Hyponatremia in the elderly: challenges and solutions

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Abstract: Decreased serum sodium concentration is a rather frequent electrolyte disorder in the elderly population because of the presence of factors contributing to increased antidiuretic hormone, the frequent prescription of drugs associated with hyponatremia and also because of other mechanisms such as the “tea and toast” syndrome. The aim of this review is to present certain challenges in the evaluation and treatment of hyponatremia in the elderly population and provide practical solutions. Hyponatremia in elderly subjects is mainly caused by drugs (more frequently thiazides and antidepressants), the syndrome of inappropriate antidiuretic hormone secretion (SIAD) or endocrinopathies; however, hyponatremia is multifactorial in a significant proportion of patients. Special attention is needed in the elderly population to exclude endocrinopathies as a cause of hyponatremia before establishing the diagnosis of SIAD, which then requires a stepped diagnostic approach to reveal its underlying cause. The treatment of hyponatremia depends on the type of hyponatremia. Special attention is also needed to correct serum sodium levels at the appropriate rate, especially in chronic hyponatremia, in order to avoid the osmotic demyelination syndrome. In conclusion, both the evaluation and the treatment of hyponatremia pose many challenges in the elderly population.

Keywords: sodium, prognosis, hypopituitarism, elderly, pituitary

Introduction

Hyponatremia is the most frequent electrolyte disorder both in hospitalized patients and in community subjects. Elderly patients represent a high-risk group for the occurrence of hyponatremia because age is a strong independent risk factor for hyponatremia. Furthermore, the symptomatology of acute hyponatremia (developed in <48 h) such as nausea, vomiting, headache, stupor, coma and seizures, as well as manifestations (even mild) associated with chronic hyponatremia, such as fatigue, cognitive impairment, gait deficits, falls, adverse effects on bone quality (e.g., osteoporosis) and fractures, are more frequent and severe in elderly patients. Relevant studies also indicate that hyponatremia is related with a poor prognosis in elderly subjects, because it is independently associated with an increased mortality risk.

Taking into consideration the aging of the population, the increased susceptibility of the elderly to develop electrolyte disorders and the increased morbidity associated with hyponatremia in this population, hyponatremia is of increasing importance. Herein, we present the available data with reference to hyponatremia in the geriatric population focusing mainly on practical issues regarding its diagnosis and treatment.

Prevalence of hyponatremia in the elderly

The prevalence of hyponatremia in the elderly, similar to the general population, varies considerably depending on the population at risk and the sodium concentration used.
Pathogenetic mechanisms of increased susceptibility of the elderly to develop hyponatremia

The greater propensity of the elderly to develop hyponatremia is mainly ascribed to 1) the aging-related impaired water-excretory capacity, and 2) the frequent exposure to medications and diseases associated with hyponatremia. In elderly patients, multiple factors are usually implicated in the development of hyponatremia.

Older subjects are more prone to hyponatremia because of impaired water-excretory capacity mainly attributed to aging-related reduction of glomerular filtration rate (GFR). Additionally, the decreased intrarenal generation of prostaglandins seen in advanced age may also be involved in the impaired ability of elderly individuals to excrete water. Another contributing factor in elderly patients is the age-related reduction in the percentage of total body water content, leading to greater fluctuations in serum sodium concentration, because: serum sodium levels = exchangeable total (sodium + potassium)/total body water.

Furthermore, a higher sensitivity to osmotic stimuli may be evident in geriatric population given that the relatively rare idiopathic syndrome of inappropriate antidiuretic hormone secretion (SIAD) is more frequently observed in elderly subjects.

Despite the above pathogenetic factors, the urinary diluting ability is preserved in most elderly persons, even with a low GFR, and hyponatremia develops only in the presence of increased water intake and additional precipitating or/superimposed factors. In this context, elderly individuals frequently take drugs (eg, thiazide diuretics, selective serotonin reuptake inhibitors [SSRIs], serotonin–norepinephrine reuptake inhibitors [SNRIs], nonsteroidal anti-inflammatory drugs [NSAIDs]) or/and suffer from diseases (eg, diabetes mellitus [DM], infections, heart failure, liver diseases, malignancies, endocrinopathies) that are all well-established causes of hyponatremia. Moreover, many elderly patients with hypertension or heart failure follow a low-salt diet that is associated with decreased serum sodium concentration. Additionally, in this population, the frequent reduction in protein intake (habitual or due to superimposed illness) that impairs water excretion may also play a role in the development of hyponatremia. It should also be mentioned that hyponatremia follows a seasonal variation (higher incidence during the summer) because of more frequent impairment of renal function, increased salt losses, diminished salt intake and increased water ingestion.

Causes of hyponatremia of special interest in the elderly

Drugs

Diuretics make up one of the most common causes of hyponatremia in the elderly. Thiazide diuretics are usually associated with hyponatremia, while loop diuretics only occasionally induce hyponatremia. The incidence of thiazide-induced hyponatremia has not been clearly determined, because additional risk factors for low serum sodium levels are usually present. A study reported that ~14% of thiazide-treated outpatients had hyponatremia (serum sodium concentration <135 mmol/L), whereas age >70 years was associated with a fourfold increase in the risk of hyponatremia. Thiazide-associated hyponatremia is more frequent in patients with heart failure, liver disease or malignancy, and in those taking large doses of thiazides or several medications, such as NSAIDs, SSRIs or tricyclic antidepressants. Clues for the diagnosis of thiazide diuretics-associated hyponatremia are given below in the “Challenges” section.

A wide array of psychotropic medications, including antipsychotic drugs (phenothiazines, butyrophenones), benzodiazepines and more frequently antidepressants, is associated with hyponatremia. It has recently been reported that SSRIs, SNRIs and mirtazapine account for the majority of hyponatremia cases related to antidepressants in adults 60 years of age or older, while bupropion, trazodone and tricyclic antidepressants are implicated less often.
Main implicating mechanism is the development of SIAD (see below for details). Female gender, low body mass index, low baseline serum sodium, concomitant nonpsychiatric medication use, such as diuretics, NSAIDs, proton-pump inhibitors, angiotensin-converting enzyme inhibitors, as well as the presence of heart failure, malignancy, liver disease or adrenal insufficiency are important factors that contribute to the development of psychotropic medications-associated hyponatremia in the elderly. Carbamazepine and oxcarbazepine are the most common anti-epileptic drugs (AEDs) associated with hyponatremia. Recently, other AEDs, such as eslicarbazepine, sodium valproate, lamotrigine, levetiracetam and gabapentin, have also been reported to induce hyponatremia. In fact, older adults on valproic acid, phenytoin or topiramate have a higher risk of being hospitalized with hyponatremia compared with those who do not receive AEDs.

**SIAD**

SIAD is one of the more frequent causes of hyponatremia especially in the elderly. Although direct comparisons of the prevalence of SIAD between elderly and younger matched controls are missing, it has been found that aging is accompanied by an increase in plasma vasopressin concentrations. In a prospective study that included patients >65 years, SIAD was the main factor in half of the patients with hyponatremia (serum sodium <135 mmol/L). SIAD was also the leading cause of hyponatremia in elderly hospitalized patients with severe hyponatremia (serum sodium ≤125 mmol/L). Of note, even the relatively rare idiopathic SIAD is more common among the elderly. Indeed, in two relevant studies the underlying etiology of SIAD was not identified in 54% and 60% of cases, respectively. Clues for the diagnosis of SIAD are given below in the “Challenges” section.

**Endocrinopathies**

Hypopituitarism should not be considered as a rare cause of hyponatremia especially in patients aged 65 years or older. Indeed, Ishikawa et al reported that 40% of patients aged 65 years or older presenting with hyponatremia have pituitary adrenal dysfunction. Thus, secondary adrenal insufficiency is frequently an overlooked cause of hyponatremia. Hypopituitarism is more difficult to be diagnosed in the elderly patients in whom symptoms such as weakness or easy fatigability may be ascribed either to aging per se or to associated comorbidities.

The prevalence of DM is high among the elderly population. In cases of marked hyperglycemia, serum osmolality (Posm) is increased, because glucose is an osmotic active substance, leading to movement of water out of cells and subsequently to a reduction of serum sodium levels by dilution. Uncontrolled DM can also induce osmotic diuresis and hypovolemic hyponatremia. In this setting of uncontrolled DM, hypovolemia is an almost invariable finding because of osmotic diuresis and hypotonic fluid losses (losses of water in excess of electrolytes), which when accompanied with large intake of water (without solutes) or administration of more hypotonic solutions may lead to hyponatremia. Noteworthy, DM per se is associated with hyponatremia, independent of the presence of hyperglycemia.

**“Tea and toast” hyponatremia**

This type of hyponatremia may occur in elderly individuals with a low GFR who follow a diet poor in salt and protein but drink a large amount of water. In these cases, there is a low distal delivery of filtrate (due to low GFR and possibly chronic sodium deficit) and increased water reabsorption due to the low rate of osmoles excretion; thus, when water consumption exceeds the renal water excretion capacity, hyponatremia occurs.

**Challenges in diagnosing hyponatremia in the elderly**

**Possible pseudohyponatremia or hyperglycemia-induced hyponatremia**

Pseudohyponatremia is observed in patients with hyperproteinemia (as seen in multiple myeloma and other monoclonal gammapathies or with intravenous immunoglobulin administration) and severe hyperlipidemia (hypertriglyceridemia and hypercholesterolemia). The opposite phenomenon of spurious higher serum sodium levels (pseudohyponatremia, pseudonormonatremia in cases of true normo/or hyponatremia, respectively) may also occur when sodium is measured with methods requiring a predilution step, as a result of severe hypoproteinemia that is not infrequently observed in the elderly. In clinical settings predisposing to unreliable serum sodium concentrations (severe hyperproteinemina, hypoalbuminemia, hypertriglyceridemia or hypercholesterolemia), measurement of the effective serum osmolality (tonicity), that is: effective serum osmolality = measured serum osmolality – serum urea (mmol/L) differentiates between true hyponatremia (hypotonicity), pseudohyponatremia (normal tonicity) and hyponatremia due to increased concentrations of osmotically active substances, such as glucose and mannitol (increased tonicity). Alternatively, measurement of serum sodium levels with a direct potentiometer (using one of the most modern blood gas analyzers) can reliably detect the true serum sodium concentration.
In patients with hyperglycemia, sodium concentration should be corrected for the degree of hyperglycemia. Corrected serum sodium is calculated by adding to measured serum sodium 1.6 mmol/L for every 100 mg/dL (5.55 mmol/L) increment of serum glucose above normal up to 400 mg/dL and by adding to measured serum sodium 2.4 mmol/L when serum glucose concentrations are higher than 400 mg/dL (22.2 mmol/L).

Evaluation of the cause of hypotonic hyponatremia

Clinicians should follow a diagnostic algorithm in patients with hyponatremia in order to avoid certain pitfalls.\(^{59}\) Hyponatremia evaluation requires a diagnostic workup of hypopituitarism (secondary adrenal insufficiency) especially in the elderly.\(^{60}\) Hypopituitarism and, to a lesser degree, primary adrenal insufficiency (ie, Addison’s disease) are causes of hyponatremia that are not straightforwardly discriminated from SIAD by routine laboratory studies and volume status assessment; thus, the measurement of associated laboratory parameters is mandatory for the diagnosis of hypothalamic–pituitary–adrenal axis disorders.\(^{22}\)

Hypothyroidism is more frequently observed among elderly persons because of the increasing incidence and prevalence of autoimmune thyroiditis.\(^{61}\) Hypothyroidism is among the causes of hyponatremia, and the exclusion of this endocrine disease is a prerequisite for the diagnosis of SIAD. However, hypothyroidism-induced hyponatremia is rather rare and probably occurs only in severe hypothyroidism.\(^{62}\) Thus, in a euvolemic hypothryoid elderly patient with thyroid-stimulating hormone <50 mIU/mL, after a comprehensive diagnostic workup (including primary and secondary adrenal insufficiency), idiopathic SIAD is the most possible diagnosis if normonatremia has not been achieved with thyroid hormone replacement. It should be emphasized than even in myxedema coma, other probable causes and superimposed factors of hyponatremia (eg, drugs, infections, adrenal insufficiency) should be thoroughly investigated.\(^{62}\)

Urine osmolality (Uosm) is a useful tool in the evaluation of the hyponatremic patient because it can establish the diagnosis of psychogenic polydipsia.\(^{57}\) Accordingly, Uosm <100 mosmol/kg (or a specific gravity ≤1.003) is usually found in patients with psychogenic polydipsia. However, hyponatremia with reduced Uosm has been also reported in ill-nourished heavy drinkers (beer potomania syndrome), in reset osmostat syndrome (eg, in patients with quadriplegia, malignant disorders or chronic malnutrition) but also in elderly patients with increased water and low solute intake (for example, tea and toast diet).

The assessment of the extracellular volume status is of vital importance in the evaluation of hyponatremia, because it helps to differentiate between hypovolemic, euvoemic and hypervolemic hyponatremia. A drop in systolic pressure of greater than 10–20 mmHg or an increase in heart rate greater than 15 beats/minute after 3 minutes of standing suggests orthostatic hypotension (a major sign of hypovolemia especially in case of a greater than 30 beats/minute increase in heart rate).\(^{63}\) However, postural changes in blood pressure and nonhypovolemic orthostatic hypotension are frequently encountered in non-volume-depleted elderly subjects due mainly to autonomic dysfunction (a failure of the heart rate to increase may indicate autonomic dysfunction), medications or other systemic diseases; thus, it is often difficult to differentiate between hypovolemic and euvoemic hyponatremia based solely on clinical grounds in elderly patients.\(^{64}\)

Urine sodium concentration should be measured in patients with hyponatremia, because in patients with according clinical findings a level <30 mmol/L strongly indicates hypovolemia.\(^{65}\) However, a low urine sodium concentration may not be observed in elderly people who may have slower adaptive mechanisms to retain sodium in the context of hypovolemia.

Certain laboratory clues that suggest SIAD are urine sodium levels >30 mmol/L, hypouricemia (≤4 mg/dL) and urea levels ≤20 mg/dL.\(^{59}\) However, these biochemical parameters should be interpreted critically especially in the elderly. As aforementioned, elderly people are usually on a low-salt diet or suffer from anorexia. Under these circumstances, urine sodium levels <30 mmol/L can be found in patients with chronic SIAD. Moreover, there is an increase in plasma urea level attributed to an age-related reduction in fractional urea excretion.\(^{66}\) Additionally, hypouricemia accompanied by a high fractional excretion (FE) of uric acid (>12% in the general population; >16% in the elderly) is observed not only in SIAD but also in other conditions, such as hypocortisolism, diuretics, potomania and renal salt wasting.\(^{59,67-69}\)

Therefore, the differentiation between hypovolemic hyponatremia and SIAD is often difficult in elderly subjects. In such cases, the administration of normal saline (1–2 L/day for 2 days) provides important clues, because an increase of >5 mmol/L in serum sodium level combined with an increase of <0.5% in FE of sodium (FENa) is highly suggestive of hypovolemic hyponatremia. In contrast, an increase of >0.5% in FENa and an increase of <5 mmol/L
Thiazide diuretics are among the most common causes of drug-induced hyponatremia. An increased potassium excretion (FE of K⁺ >13%) is a useful marker for the diagnosis of thiazide-induced hyponatremia. Clinicians should be aware that there are two groups of patients with thiazide-induced hyponatremia, one with a biochemical profile that is consistent with extracellular volume depletion and another that simulates the SIAD. Regarding the latter group, recent investigations have identified a phenotype resembling SIAD, with intravascular volume expansion, low plasma osmolarity, inappropriately concentrated urine and more than minimal urinary sodium excretion but with low/normal ADH levels.

In this phenotype, the SLCO2A1 A396T gene variant (that encodes the solute carrier organic anion transporter family member 2A1 [SLCO2A1], also known as the prostaglandin transporter), which is associated with increased urinary excretion of prostaglandin E2 and aquaporin-2-mediated water reabsorption, has been identified to contribute to thiazide-induced hyponatremia. Serum uric acid level can differentiate between the extracellular volume depletion-associated and the SIAD-like thiazide-induced hyponatremia. Specifically, serum uric acid concentration <4 mg/dL points to an SIAD-like state, whereas serum uric acid concentration >4 mg/dL points to extracellular volume depletion.

In patients with diuretic-related hyponatremia and an SIAD-like profile, unless there is strong evidence to suggest an underlying cause for SIAD, a thorough diagnostic evaluation of SIAD (see below) should be delayed for 2–3 weeks to see if serum sodium levels are fully corrected with diuretic discontinuation. However, taking into account that thiazides may worsen the hyponatremia induced by SIAD, this evaluation should be undertaken if even mild hyponatremia persists after this diagnostic waiting period.

Finally, one of the most challenging issues in the evaluation of elderly persons with SIAD is to reveal the underlying cause given that this syndrome can be seen in a wide variety of clinical states (eg, numerous drugs, malignancies, pulmonary and neuropsychiatric diseases) and simultaneously in a considerable fraction of patients is idiopathic. It should be emphasized that a clinically driven-through approach for the identification of the underlying cause of SIAD before the diagnosis of idiopathic SIAD is of paramount importance. A detailed medical history with emphasis in drugs and diseases affecting water homeostasis including infections and malignancies, a complete physical examination and appropriate investigations depending on the cause identified by the clinical features are necessary. Furthermore, rare causes of the syndrome such as temporal arteritis or Waldenstrom macroglobulinemia can be considered in suspected cases. In case of SIAD with no evident cause, careful and repeated monitoring for the presence of an occult tumor (particularly pulmonary) is of vital importance.

**Solutions**

**Prevention strategies of hyponatremia in the elderly**

Clinicians should prescribe drugs with caution in elderly patients, especially in those with risk factors to develop SIAD. The avoidance of polypharmacy, especially with drugs implicated in the development of hyponatremia, should be a priority in elderly people. Additionally, the use of low doses of suspected drugs or alternative therapies may be preferable in many cases. For example, low doses of thiazide diuretics (equivalent to 12.5 mg of hydrochlorothiazide) should be prescribed in high-risk patients for hyponatremia or alternative antihypertensive treatment not associated with hyponatremia (eg, a calcium-channel blocker or beta-blockers) should be selected. In fact, a population-based study (n=13,325 individuals, age >45 years old), thiazide diuretic exposure was associated with an almost 5 times higher risk of hyponatremia than nonexposure (hazard ratio [HR] 4.95, 95% CI 4.12–5.96). Moreover, exposure with an equal or greater than 1 standardized defined daily thiazide dose was associated with a significantly higher risk of hyponatremia than exposure below 1 standardized defined daily thiazide dose (HR 5.72 [95% CI 4.67–7.00] and 3.42 [95% CI 2.46–4.77], respectively). In another study in hypertensive patients with hyponatremia (average daily dose of the hydrochlorothiazide 35±18 mg), 44% of the patients used a dose greater than 50 mg daily, whereas only 10% of the patients received a low thiazide dose (12.5 mg daily). Especially in patients with thiazide-induced hyponatremia, furosemide
or torsemide may be alternatively prescribed without risk of recurrent hyponatremia.28

In patients at risk for or with a history of antidepressant-induced hyponatremia, bupropion may be the most appropriate antidepressant treatment.41 Mirtzapine could be also used alternatively because the associated risk of hyponatremia is moderate.77

Generally, discontinuation of treatment with agents implicated in the development of hyponatremia and avoidance of readministration is fully warranted. However, given that chronic hyponatremia is frequently multifactorial in the elderly,19 there is increased risk of unnecessary discontinuation of treatments, especially if patients have responded favorably to therapy (eg, a patient on antidepressants with well-controlled symptoms). In such cases, the discontinuation of the most recent suspected medication(s) is a useful strategy.

The administration of hypotonic fluids as maintenance therapy, for the avoidance of volume overload, is common clinical practice in hospitalized elderly patients. However, this procedure, especially in cases accompanied by elevated antidiuretic hormone (ADH) levels (eg, central nervous system disturbances, pulmonary disease, cancer), may lead to hyponatremia and should be avoided. It has been proposed that isotonic fluids are the most suitable maintenance fluid in most circumstances including compensated heart failure.78 For example, in an elderly hospitalized individual with well-controlled congestive heart failure, 5% dextrose in a solution of 0.9% saline at a rate of 60 mL per hour could be an appropriate maintenance fluid therapy.65,79

Treatment of hyponatremia in the elderly

Although there is no concrete evidence that the restoration of hyponatremia is associated with improved outcome, it is prudent to correct low sodium concentration even in “asymptomatic elderly individuals” because it is related to increased mortality and morbidity (eg, gait disturbances, falls, cognition impairment). The indication for treatment is stronger in subjects having disorders that could be attributed to the decreased sodium concentration.

In acute symptomatic hyponatremia, hypertonic saline solution (3%) is commonly used to acutely increase serum sodium levels and prevent severe neurologic symptoms (eg, seizures). Hypovolemic hyponatremia is treated with adequate fluid resuscitation to decrease the stimulus for ADH secretion. Normal saline is usually used to suppress the hypovolemic stimulus for ADH release.65,80 In patients with SIAD, along with discontinuation of suspected drugs and decrease of water consumption, careful administration of hypertonic fluids may be needed. In these cases, furosemide (20–40 mg intravenously) can also be administered to avoid circulatory overload, particularly if there is concomitant cardiac dysfunction in elderly persons. Furosemide increases free water excretion and contributes to serum sodium elevation. Vaptans (vasopressin-2 antagonists) are a class of drugs that selectively antagonize the antiuretic effect of vasopressin leading to increased water diuresis (aquaresis).81,82 These drugs can be used in hospitalized patients with chronic symptomatic euolemic hyponatremia (mainly in patients with SIAD) and in some countries in patients with hypervolemic hyponatremia.82–88 A retrospective study (n=37, aged median 77 years) reported that lower starting doses of tolvaptan (7.5 mg/day) are effective and possibly safer to correct hyponatremia in elderly individuals with SIAD.89 However, the use of these drugs in elderly population needs more investigation.

The proper correction rate of serum sodium levels in patients with hyponatremia is of great importance. Over-correction of serum sodium concentration may lead to the osmotic demyelination syndrome (ODS), especially in alcoholic individuals and patients with hypokalemia, malnutrition or advanced liver disease.90–95 In cases of acute symptomatic hyponatremia, an acute elevation of serum sodium concentration by 4–6 mEq/L within the first 4–6 h is recommended in order to reverse the symptoms.12 In chronic hyponatremia, even symptomatic, the rate of the correction of serum sodium concentration should be restricted at <10 mEq/L/24 h and more safely at <6–8 mEq/L/24 h.96,97 Frequent determination of serum sodium concentration (every 4–6 h) and appropriate tailoring of the correction rate is strongly recommended in patients with high risk of developing the ODS.98 A number of formulas can be used to predict the change of serum sodium levels during treatment and to calculate the initial infusion rates.99 Special attention is needed in patients with hypovolemic hyponatremia for a rapid increase in serum sodium levels when volume depletion is restored because of the abrupt decrease in ADH secretion.65,98

It has been mentioned above that it is difficult to distinguish between hyponatremia due to disorders of pituitary–adrenal axis and SIAD in elderly individuals. It has been proposed that in cases of hyponatremic elderly individuals with such diagnostic uncertainty, the administration of low-dose hydrocortisone (10 mg/day or less) may be of value. Indeed, Takei et al reported five cases of severe hyponatremia in the elderly successfully treated with low doses of hydrocortisone suggesting adrenal insufficiency as the
underlying cause for the low serum sodium concentration. However, replacement with hydrocortisone may require many days to restore serum sodium levels (in the cases by Takei et al up to 179 days was needed); thus, it can be used as a diagnostic tool only in cases of relatively rapid treatment of hyponatremia.

Conclusion
Decreased serum sodium concentration is a rather common finding in the elderly population because of the presence of factors contributing to increased ADH and the frequent prescription of drugs associated with hyponatremia such as thiazides or antidepressants. Both the evaluation and the treatment of hyponatremia pose many challenges in the elderly population.

Disclosure
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