PARTICULARITIES OF THE ETIOLOGY OF HYPONATEREMIA IN THE FRAIL ELDERLY PATIENT

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PARTICULARITIES OF THE ETIOLOGY OF HYPONATEREMIA IN THE FRAIL ELDERLY PATIENT (Abstract). Hyponatremia is the most common electrolyte disorder in medical practice, and its prevalence is increasing in frail elderly patients. There are many reasons behind this phenomenon: the changes induced by aging itself, the presence of comorbidities and polypharmacy, the increased risk of dehydration, increased frequency of iatrogenesis and therapeutic noncompliance. Of the iatrogenic causes, we will refer to hyponatremia induced by thiazide-type and thiazide-like diuretics (1) due to 4-fold increase in prevalence in the frail elderly patients. Hyponatremia is a disease that benefits from prompt and appropriate treatment with excellent results, but the key to therapeutic success is the determination of its cause - which can be difficult in the elderly, and of patient’s volume status for a correct classification of the disease. Hyponatremia in frail elderly patients may be asymptomatic or mimic other diseases. These are due to the almost constant association of varying degrees of geriatric syndromes, the most often responsible for symptom mystification being the cognitive impairment, the presence of comorbidities that have similar symptoms, the overlapping of acute events - fractures resulting from same-level falls that distort the diagnosis. We report 3 cases of hyponatremia characterized by atypical symptoms that was induced by indapamide treatment. Hospitalization for thiazide-induced hyponatremia is frequent, suggesting suboptimal monitoring, especially during the treatment initiation phase. Literature data suggest that the ionogram should be obtained 7 to 14 days after treatment initiation to detect the early onset of hyponatremia. There are reports of hyponatremia occurring after years of treatment, suggesting the need for constant monitoring of a patient treated with long-acting thiazide diuretics. Considering an iatrogenic cause (most commonly induced by thiazide-type or thiazide-like diuretics) should be in the forefront of physician’s mind, but it requires a thorough medical history, assessment of patient compliance and cognitive status as well as support from patient’s family. Identification of the cause of hyponatremia should prevent recurrences and provide adequate patient education to prevent secondary complications. Keywords: HYONATREMIA, FRAIL ELDERLY PATIENTS, INDAPAMIDE TREATMENT.

Hyponatremia is the most common electrolyte disorder in medical practice, and its prevalence is even greater in frail elderly patients due to the addition of some particularities of this age segment: changes induced by aging per se, presence of comorbidities and polypharmacy, increased risk of dehydration (both by a natural predisposition to low daily fluid intake of the elderly and by the existence of such conditions that favor dehydration as prolonged and repeated hospitalizations, perioperative hydrological
restrictions), increased frequency of iatrogenesis and therapeutic noncompliance. Among the iatrogenic causes, we draw attention to hyponatremia induced by thiazide-type and thiazide-like diuretics (1) due to the up to 4-fold increase in prevalence in the frail elderly patient (2). Most elderly patients have varying degrees of hyponatremia. The severe form (Na < 125 mmol/l) is usually characterized by obvious clinical symptoms: altered general state, marked physical asthenia, seizures, nausea and vomiting culminating with the severe forms: hyponatremic encephalopathy, non-cardiogenic pulmonary edema, coma and death (3). Moderate forms of hyponatremia have more attenuated and polymorphic symptoms, and in frail elderly patients they may be asymptomatic or mimic other pathologies. These are due to the almost constant association of varying degrees of geriatric syndromes, the most frequently responsible for symptom mystification being cognitive impairment, the presence of comorbidities with similar symptoms, the overlapping of acute events - fractures resulting from same-level falls that distort the diagnosis (3,4). Hyponatremia is a disorder that benefits from prompt and appropriate treatment (1), but the key to therapeutic success is the determination of its cause - which can be difficult in the elderly, and of patient's volume status for a correct classification of the disease.

To exemplify, we report three cases with various forms of hyponatremia who shared the advanced age, presence of comorbidities and polymedication, the common element being the treatment with thiazide-like diuretic (indapamide).

**CASE REPORTS**

**Case 1**: a 68-year-old woman with polymedication due to polypathology: digestive (gastroesophageal reflux disease, chronic gastritis and hepatitis C for 11 years treated with 3 different drugs) and cardiovascular (AHT and heart failure for which she received a 10-day treatment with 4 different drugs - a fixed combination of perindopril 10 mg and indapamide 2.5 mg, trimetazidine, platelet antiaggregant and statin). Five days before the doctor's appointment, the patient became symptomatic, presenting vertigo, headache, nausea and vomiting, and presented to the Gastroenterology department. Routine biological screening revealed severe hyponatremia (Na = 121 mmol/L) and hypokalemia (K = 3.28 mmol/L). A digestive cause was ruled out and she was referred to the Geriatrics Clinic. The thorough history confirmed the compliance with treatment and low-salt diet and a normal neurocognitive status (MMSE = 29/30). The volume status was assessed using echocardiography, which revealed normal diameter and almost complete inspiratory collapse of the inferior vena cava, suggestive of a diagnosis of iatrogenic euvolemic hyponatremia (indapamide). Slow correction of ionic imbalance was initiated by the discontinuation of the thiazide-like diuretic and normal dietary salt intake followed by oral and parenteral hydration with isotonic saline for 8 days. The course was slowly favorable, with the remission of symptoms and correction of ionic imbalance, on discharge the Na level being within normal ranges (143 mmol/L).

**Case 2**: an 83-year-old male patient with difficult to take history and without medical documents, with cardiovascular and rheumatic polypathology (according to his daughter who also mentioned the home treatment with indapamide) and who had sustained a craniocephalic trauma from same-level fall, for which he was urgently investigated at the Neurosurgery department. Routine biological screening revealed
severe hyponatremia (Na = 118 mmol/L) and hypokalemia (K = 3.2 mmol/L) and he was referred to the Geriatrics Clinic. The assessment of volume, clinical and echocardiographic status oriented the diagnosis towards hypovolemic hyponatremia possibly of multiple etiology: iatrogenic (indapamide) and secondary to dehydration by insufficient fluid intake. Geriatric assessment revealed impaired neurocognitive status (MMSE = 19/30) and malnutrition risk. The conservative correction of hypovolemic hyponatremia was initiated by discontinuing the thiazide-like diuretic and replacing it with a nondihydropyridine calcium blocker to control blood pressure levels. The patients received parenteral hydration for 5 days with 500 mL of isotonic serum enhanced with 20 mL micro perfusions of 5.85% NaCl with dynamic ionogram monitoring and slow correction of hyponatremia to prevent osmotic demyelination with serious neurological consequences (5). For the correction of hypokalemia, 10 mL intravenous KCl was added to the treatment schedule on admission day, followed by oral administration in doses adapted according to the ionogram.

**Case 3**: a 69-year-old female patient polymedicated and with polypathology (cardiovascular, receiving treatment with 5 different drugs/day, metabolic, insulin-dependent diabetes mellitus for which she was on treatment with 2 oral antidiabetic drugs and insulin, dyslipidemic syndrome and morbid obesity, and cerebral pathology for which she took 3 other drugs/day); the patient reported the onset of symptoms a few days earlier by progressively increased leg edema, dyspnea at increasingly smaller efforts, physical asthenia and vertigo, for which she presents to the Cardiology Department where, in addition to the existing diagnoses, altered renal function (CI creatinine = 39 mL/min) and severe hyponatremia (Na = 124 mmol/l) were detected and the patient was referred to the Geriatrics Clinic. Clinical assessment (leg edema, moderate dyspnea) and echocardiography (slight inferior vena cava inspiratory collapse) suggest hypervolemic hyponatremia of multiple etiology, the main causes being the lack of therapeutic compliance (chaotic treatment, especially in case of indapamide) and diet with inadequate fluid intake (polydipsia). Geriatric evaluation revealed mild cognitive impairment (MMSE = 25/30) and depressed status (GDS = 8/15). Correction of electrolyte and volume disturbances was initiated: discontinuation of indapamide and replacing it with intravenous furosemide, water restriction (500 mL/day), correction of diabetes. The course was slowly favorable at the same time with the correction of hyponatremia being obtained the correction of renal dysfunction (CI creatinine at discharge = 76 mL/min). In all cases, the Schellong test was negative, ruling out orthostatic hypotension.

**DISCUSSION**

Hyponatremia usually occurs within the first few days of treatment with thiazide diuretics but may also occur after months of treatment (6). Although thiazide-type and thiazide-like diuretics differ in chemical structure, they share the same mechanism of action, namely the inhibition of the Na–Cl co-transporter in the distal convoluted tubule (7). Currently, thiazide diuretics are a class of first-line drugs in the treatment of high blood pressure in the elderly.

Hospital admission for hyponatremia induced using thiazide diuretics is frequent, suggesting suboptimal monitoring, especially at the time of treatment initiation. According to the literature the ionogram should be obtained 7 to 14 days after thiazide initiation to detect the early onset of hypo-
Particularities of the etiology of hyponatremia in the frail elderly patient

There are case reports of hyponatremia occurring after years of treatment, suggesting the need for constant monitoring of patients on long-term treatment with thiazide diuretics (7). Our three cases exemplify these situations - early or late occurrence of hyponatremia after indapamide treatment. Previous values for electrolytes were not available until hospital admission.

There are numerous studies aimed at identifying the causes of hyponatremia in the elderly. The most common cause is the syndrome of inappropriate antidiuretic hormone (SIADH) (8, 9), closely followed by the treatment with thiazide-type and thiazide-like diuretics (7, 10). However, the accurate determination of the etiology of hyponatremia in a frail elderly patient should also consider other causes more rarely encountered in other age groups.

The presence of comorbidities may play an independent role in triggering hyponatremia, with attention being paid to neoplasia. There are studies that associate the presence of hyponatremia (especially the euvolemic and hypovolemic forms) with a significantly increased mortality among patients diagnosed with lymphoma, breast cancer, colorectal and pancreatic cancer, bronchopulmonary cancer, and hepatocellular carcinoma (11, 12, 13, 14).

The presence of comorbidities is always associated with polymedication (> 5 different drugs per day) (3, 15), which is a known risk factor for iatrogenic hyponatremia, the most commonly incriminated being the thiazide-type and thiazide-like diuretics. Angiotensin converting enzyme inhibitors are among the most prescribed drugs together with thiazide diuretics (2), followed by sartans, non-steroidal anti-inflammatory drugs and antidepressants (which affect water homeostasis), raising the hypothesis of drug interaction as a possible cause of hyponatremia. It should be noted that the presence of hypokalemia is frequent in patients with thiazide-induced hyponatremia (1).

Older age (1), female gender and low body mass index (10) are other risk factors for hyponatremia in patients treated with thiazide diuretics (6); to these must be added the non-compliance with drug therapy, often associated with varying degrees of cognitive disturbance, and the phenomenon of self-neglect, elements that will interfere with the rate of administration and the doses of recommended drugs (16).

Finally, we should make a special mention of the frail elderly patients requiring surgery, most commonly hemiarthroplasty for hip fracture, who frequently develop moderate hyponatremia perioperatively mainly due to the recommendations for preoperative water restriction (4, 5).

Symptoms of hyponatremia in frail elderly patients are polymorphic, represented by same-level fall preceded or not by vertigo, fatigue, confusion, nausea, vomiting, and neurological symptoms (7). In patients with acute hyponatremia, nausea, vomiting and headache due to cerebral edema (1) are more common, as in our Case 1. Unfortunately, these symptoms are commonly attributed to other concomitant diseases or other overlapping acute events, with a delayed detection of hyponatremia and an often incorrectly identified etiology. Iatrogenic pathology and dehydration should be the main causal lines given the increased thiazide-type and thiazide-like diuretic prescription for in the elderly and the hypovolemic status of the elderly. Thus, in the management of hyponatremia the first gesture is discontinuing the thiazide (if present in the therapeutic regimen), which is both diagnostic and therapeutic test. Attention should be paid to the slow cor-
rejection of the imbalance in order not to induce osmotic demyelination, with severe neurological consequences (5).

CONCLUSIONS
With these cases we underlined the fact that treatment with thiazide-type or thiazide-like diuretics in the elderly requires frequent monitoring of electrolytes given the high risk of severe hyponatremia, clinical condition with atypical or less symptomatic clinical picture which delays (sometimes with fatal outcomes) the diagnosis. Considering an iatrogenic cause (most commonly induced by thiazide-type or thiazide-like diuretics) should be in the forefront of physician’s mind, but it requires a thorough medical history, assessment of patient compliance and cognitive status as well as support from patient’s family. Identification of the cause of hyponatremia should prevent recurrences and provide adequate patient education to prevent secondary, severe complications.

REFERENCES