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POINTS OF VIEW

Chronic hyponatremia in a patient with renal salt wasting and without cerebral disease: relationship between RSW, risk of fractures and cognitive impairment

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Abstract
Renal salt wasting syndrome (RSW) is defined as a renal loss of sodium leading to hyponatremia and a decrease in extracellular fluid volume (ECV). Differentiation of this disorder from the syndrome of inappropriate antidiuretic hormone secretion (SIADH), a common cause of hyponatremia, can be difficult because both can present with hyponatremia and concentrated urine with natriuresis. Our clinical case about a 78-year-old woman with a recent fracture of the right femur not only confirms that this syndrome can occur in patients without intracranial pathologies (CT documented), but depicts how the hyponatremia caused by RSW can show a chronic, oscillating course. This is an interesting point of view because it suggests to us to consider RSW in the differential diagnosis of patients with chronic hyponatremia.

Keywords Renal salt wasting syndrome · Cerebral salt wasting syndrome · Chronic hyponatremia · SIADH · Natriuretic peptides

Background

Cerebral salt wasting syndrome (CSW) was first described by Peters et al. in 1950 in a report of three patients with neurogenic diseases and hyponatremia [1], but the identification 7 years later of the Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) by Schwartz et al. eventually eclipsed the interest of the researchers since, given the overlap of the clinical and laboratory characteristics of the two syndromes, CSW was considered a misnomer of SIADH [2]. Indeed, some authors even doubted the existence of CSW. However, in recent years the interest of authors has returned to the study of this syndrome through the publication of case reports, reviews and other studies. In particular among neurosurgeons, CSW is considered a fairly frequent syndrome.

However, internists and nephrologists have also reevaluated this syndrome and propose to rename it Renal Salt Wasting syndrome (RSW) since cases have been described in the absence of brain diseases. We believe that the name of RSW is more correct in consideration of our clinical case [3]. Despite the recent increase in interest of researchers, this syndrome remains controversial, and many authors are sceptical towards it. The reasons for this attitude are different, starting from the uncertainty about the name to be given to the syndrome (recently the shift from CSW to RSW has been proposed), the lack of universally recognized and defined diagnostic criteria, and the lack of knowledge of pathophysiological mechanisms responsible for the onset of this syndrome (conditions that also determine a difficult understanding of the real incidence and prevalence of this pathology). However, in view of the increasing number of clinical cases described in the literature and the clinical case reported in this article that shows that only a RSW can explain a so marked polyuria with hyponatremia and renal sodium loss in an otherwise healthy patient, we believe it is right to continue with scientific efforts to shed light on this syndrome whose existence is now certain, and whose knowledge will allow us to understand further the interesting aspects of water and sodium homeostasis, and in particular, the functioning of the complex "puzzle of natriuretic peptides".

The purpose of this point of view is to further confirm the existence of this syndrome, the importance of the

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recognition of RSW, and to underline how this syndrome can determine chronic alterations of natremia and consequently neurological changes (balance changes, attention deficit, memory changes) and bone changes (osteoporosis, increased risk of fracture).

Index case

On July 27, a 78-year-old woman suffered a pertrochanteric fracture of the right femur following an accidental fall, and was treated with osteosynthesis. She was discharged from the orthopaedics ward on August 3 and later, on August 27, admitted to a neuromotor rehabilitation centre. During this hospitalization she was found to have a hyponatremia poorly responsive to NaCl supplementation, so it was the thiazide diuretic therapy with which the patient was being treated, was withdrawn. She was discharged on September 29, but, the next day, alteration of the state of consciousness occurred associated with three episodes of nausea and vomiting. For this reason, the patient was admitted to our Department on October 1. The past medical history revealed that the patient suffered from arterial hypertension treated with angiotensin receptor blockers/hydrochlorothiazide (ARB/HCT), Paroxysmal Atrial Fibrillation treated with beta-blocker and gastroesophageal reflux disease (GERD) treated with proton pump inhibitor (PPI). Moreover, during the prior year relatives recount episodes of amnesia, attention deficit and postural instability that were revealed after an accidental fall with consequent fracture of the left humerus that was treated conservatively. Physical examination showed that the patient was confused with a tendency to fall asleep, but reawakening with verbal stimuli (Glasgow coma scale 14), mild hypotension (100/68 mmHg) and no peripheral edema, body weight was about 50 kg and she was 1.50 m high. The blood chemistry tests revealed the presence of severe hyponatraemia (120 mEq/l), potassium 4.5 mEq/l, uricemia 1.9 mg/dl, calcium 9.58 mg/dl, normal indices of renal function (Creatinine 0.4 mg/dl, eGFR 85 ml/min with CKD-EPI, Azotemia 24 mg/dl), Plasma osmolarity 263 mOsm/KgH_2O, NT-proBNP 834 pg/ml. Arterial blood gas analysis was normal (pH 7.427, pCO2 37.7 mmHg, pO_2 82.9 mmHg, HCO_3–24.4 mmol/l, Lac 1.2 mmol/l). Urine chemistry showed Urine Na (UNa) 44 mEq/l, Urine osmolarity 468.93 mOsm/KgH_2O, absence of proteinuria. Cerebral CT performed in the emergency department before arriving at our department showed no noteworthy alterations. Her medications during hospitalization included pantoprazole, bisoprolol, and enoxaparin. In light of the clinical picture, the study for the classification of hyponatremia was started (serum TSH, ACTH and cortisol were measured), and, despite laboratory values suggesting a diagnosis of the syndrome of inappropriate antidiuretic hormone secretion (SIADH), (hyponatremia associated with plasma hyposmolarity, urinary hyperosmolarity and UNa > 40 mEq/l), the presence of mild hypotension and alteration of the state of consciousness leading to the administration of NaCl associated with commensurate volumes of water to maintain an adequate hydration of the patient through the administration of isotonic saline solution at about 42 ml/h (approximately 1000 ml/day). The subsequent laboratory tests showed no endocrine abnormalities: TSH 2.33 µU/ml (r.r. 0.27–4.2), ACTH at 08:00 a.m. 12.4 pg/ml (r.r. 7.9–66.1), Cortisol at 08:00 a.m. 11.75 µg/dl (r.r. 7–28). At this point, the diagnosis of SIADH seemed the most probable, but, unexpectedly, in the days following entry into our ward an intense polyuria was observed (from a minimum of 3200 ml/day up to a maximum of 8200 ml/day, with an average of 5400 ml/day) (Fig. 1). It caused dehydration of the patient, and required an increase of isotonic saline infusion up to 150 ml/h. Such infusion therapy has allowed the progressive even if slow increase of natremia values (about 3 mEq/day), and the rapid improvement of the patient's awareness in that she was able to start drinking again, thus reinstating the urinary losses together with the infusive therapy. It should be noted that an accurate fluid balance was made every day by assessing water intake and loss according to the common methods used in clinical practice, which indicate when we are faced with a frankly positive or negative balance as in this case. So what can explain a so marked diuresis with a frankly negative fluid balance in a hyponatremic patient with the laboratory values mentioned above, without alterations of the GFR, absent diuretics and without other obvious causes of polyuria? The answer can only be a renal salt wasting syndrome (RSW).

Outcome and clinical follow-up

The patient was discharged after 9 days of hospitalization in good clinical condition, with a salt-based therapy (1 g NaCl tablets twice a day), and with the instruction to drink at least 1.5 l of water per day. Laboratory tests 2 weeks and 2 months after discharge showed, respectively, a sodium of 135 mEq/l and 142 mEq/l. However, whenever we tried to stop treatment with NaCl, natremia again tended to shrink, so the patient continued to take the 1 g NaCl tablets twice a day. About 4 months later from the last control, hyponatremia was found again (127 mEq/l), so an increase in salt-therapy was recommended (1 g NaCl tablets three times a day). The patient was lost in subsequent follow-up.

Clinical case discussion

Our clinical case not only confirms that RSW can occur in patients without intracranial pathologies, but highlights how this syndrome can take a sub-acute or chronic course that

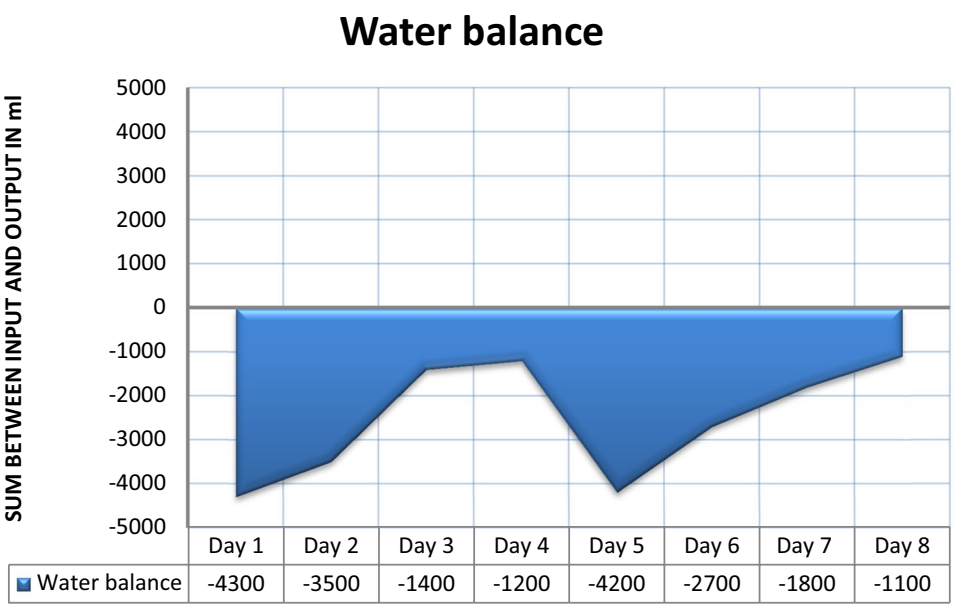

Fig. 1 Water balance of our patient during hospitalization

can evolve into episodes of acuteness with rapidly worsening of hyponatremia and consequent alteration of the state of conscience if the disorder is not treated properly. Our patient suffered a fracture of the femoral neck 2 months before reaching our attention, so it took 2 months from the acute event to the development of an evident RSW. In this regard, it is interesting to note that the first case of RSW in the absence of intracranial disorders described in the literature concerns a 76-year-old woman with a femoral neck fracture [3]. The cases described in the literature, especially concerning patients with intracranial diseases, describe the development of RSW usually within 10 days of the acute event. In our case, however, not only did 2 months pass from the acute event to the development of evident RSW with severe hyponatraemia, but the negative alteration of sodium balance lasted for at least other 6 months from discharge. The documentation presented by the patient showed that already during the admission to a neuromotor rehabilitation centre (which took place about a month after the fracture), a treatment-resistant hyponatraemia emerged that was imputed to the HCT therapy hitherto being followed by the patient. However, despite the suspension of this drug, hyponatremia persisted and even got worse reaching very low levels (120 mEq/l), and causing alteration of the state of consciousness. Even after discharge from our internal medicine department, the patient continued to have low serum levels that required additional oral NaCl therapy, which could not be stopped due to rebound hyponatremia. Moreover, about 6 months after discharge (a period during which the patient has always taken a 1 g supplement of NaCl two times a day) there was a new reduction of the natremia that required an increase in additional therapy with NaCl. This alteration of sodium homeostasis that has been going on for several months is reasonably attributable to a RSW syndrome, and we can state this as a consequence of the considerations described below (it is also to underline that ours is not the first case of RSW described in the literature in which the alteration of sodium balance is maintained for several months after the discharge of the patient [4, 5]). We have documented that our patient had suffered from hyponatremia for at least 7 months, although this condition could have existed for a long time considering the related humerus fracture following accidental fall a year before the current hospitalization, and the recently described association described in the literature between chronic hyponatremia and increased risk of falls and fractures. During hospitalization it was shown that, at that time, hyponatremia was due to a RSW. Thus, it is logical to assume that, in the absence of additional external factors (such as the appearance of other acute pathologies or the introduction of new drugs), the same mechanism has been responsible for the hyponatremia in the period between the fracture of the femur and the hospitalization (the period during which the Patient took HCT but the suspension of the latter not only did not resolve hyponatremia, but also did not avoid the reduction of sodium up to 120 mEq/l), and in the period subsequent to admission.

Chronic hyponatremia in renal salt wasting syndrome

The report of our clinical case explains that it is possible to think that in addition to presenting itself in an "acute" form (the cases described in the literature usually resolve within a month), RSW may present in a subacute or chronic form with possible oscillations over time. Among the main

causes of RSW are the alteration of sympathetic renal afferents and an increase in the production of natriuretic peptides [6]. The increased production of these peptides is balanced by adequate secretion of antidiuretic hormone (ADH) under the hypovolemic stimulus (which is stronger than the hypoosmolar stimulus that would tend to inhibit the secretion of ADH), resulting in a condition of chronic hyponatremia. If extracellular volume (ECV) is decreased due to RSW, the baroreceptors are triggered, and ADH is secreted to restore intravascular volume. The stimulus for ADH secretion by the reduced ECV is more potent than the osmolar effect on ADH secretion, so the patient remains hyponatremic despite the hypoosmolality. This defines the appropriateness of ADH secretion in RSW, and why saline can remove the volume stimulus for ADH secretion and allow the hypoosmolarity to inhibit ADH secretion, increase free water excretion and correct the hyponatremia [7].

Relationship between RSW, risk of fractures and cognitive impairment: a possible role for natriuretic peptides

Chronic hyponatremia in RSW may have important implications considering that there is a growing awareness that mild hyponatremia is associated with mental dysfunction, unsteady gait, osteoporosis, increased falls and bone fractures [8–10]. Moreover, some authors have investigated the direct effects of chronic hyponatremia on bone and brain metabolism [11, 12]. However, in addition to the direct effects of hyponatremia on the bone and brain, we must consider that the relationship between natremia, cognitive functions and bone metabolism could be even closer than what has been described so far, and the trait d'union could be the complex natriuretic peptide system. Consider for example the role of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) in brain metabolism. ANP and BNP can be used as markers for Alzheimer's disease as well as stroke, and are possibly involved in the pathophysiological mechanisms of these diseases [13, 14]. CNP, which acts unlike ANP and BNP locally in an autocrine or paracrine manner, appears to be the natriuretic peptide with a prominent role in the brain physiology. Indeed, though all natriuretic peptides (NPs) and their receptors can be found in the brain, natriuretic peptide receptor-B and it's binding hormone CNP are the most abundant in the brain. For example in the hypothalamus, CNP expression is 50 times higher compared to ANP and BNP [15]. There are three known natriuretic peptide binding proteins: natriuretic peptide receptor-A, natriuretic peptide receptor-B and natriuretic peptide receptor-C (NPR-A, NPR-B and NPR-C). Whereas NPR-C primarily controls local natriuretic peptide concentrations via receptor-mediated internalization and degradation, NPR-A and NPR-B are the main mediators of the effects of natriuretic peptides on natremia and on tissue metabolism. They are guanylate cyclase receptors, so they signal by catalyzing the synthesis of the intracellular signalling molecule cyclic guanosine monophosphate (cGMP) [16]. cGMP, regardless of its source (NO, and soluble guanylate cyclase or NPs and their receptors) plays an important role in brain physiology. Its actions are of particular importance regarding modulations of long-term changes of synaptic activity in the hippocampus, amygdala, cerebellum (by pre-synaptic transmitter release [17]) and post-synaptic functions via activation of different protein kinase G (PKG) isoforms [18]. Recent studies show a neuroprotective role of NPs and the cGMP signalling pathway. An increase of intracellular cGMP concentration protects neurons against excitotoxic, metabolic, oxidative damages as well as *N*-methyl D-aspartate (NMDA)-induced neurotoxicity [19]. Despite the abundance of the evidence suggesting that NPs play an important physiological role in certain pathophysiological conditions such as stroke and brain trauma, there still remain many unanswered questions.

But NPs, and in particular the CNP, possess other important properties, and also come into play in the modulation of the bone metabolism. Our case is the second clinical case described in the RSW literature diagnosed following femoral fracture [7]. Maesaka et al. describe a similar case, also in that case concerning an elderly patient without the evidence of intracerebral pathology [7]. CNP plays an important role in bone metabolism as it stimulates endochondral ossification and elongates bones, as evidenced by the skeletal phenotypes of transgenic and knockout [20].

Therefore, summing up, the neurological and bone changes observed in patients with RSW and chronic hyponatremia may be mediated not only by the hyponatremia itself, but by an "impairment" of the NPs system in which a relative increase in the activity of properly natriuretics peptides is determined (with consequent establishment of chronic hyponatraemia) to the detriment of a reduction in CNP activity with possible metabolic repercussions at bone and brain level.

Conclusions

RSW is a syndrome whose existence is now certain, however, it still has many aspects on which it is necessary to shed light. Our clinical case not only confirms that this syndrome can occur in patients without intracranial pathologies (CT documented), but shows how the hyponatremia caused by RSW can take a chronic, oscillating course. This is an interesting aspect because it suggests the consideration of RSW in the differential diagnosis of patients with chronic hyponatremia, a condition that must be treated to prevent

neurological changes (balance changes, attention deficit, memory changes) and bone changes (osteoporosis, increased risk of fracture).

Compliance with ethical standards

Conflict of interest The authors declare they have no conflicts of interest with the publication of this article.

Statement of human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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