Syndrome of inappropriate antidiuretic hormone secretion induced by the phytotherapy Harpagophytum procumbers: case report

Síndrome da secreção inapropriada do hormônio antidiurético induzida pelo fitoterápico *Harpagophytum procumbers*: relato de caso

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Abstract

Introduction: The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the inability of antidiuretic hormone (ADH) suppression, compromising the mechanisms of water excretion and urinary concentration. It manifests as hyponatremia and its symptoms, especially neurological. There are many causes that trigger such disease, notably: central nervous system disorders, malignant neoplasm, drugs and others. **Case Report:** A 65 years female hypertensive patient presented clinical and laboratory manifestations of hyponatremia due to SIADH. It happened twice under use of herbal medication for osteoarthritis treatment. **Discussion:** The drug-related hyponatremia can be triggered by direct effect of the drug or by association with SIADH. The clinical manifestations presented could have been related to psychiatric condition and may have severe outcome if not properly diagnosed. The association of an herbal medicine to SIADH could be confirmed after a new episode of hyponatremia related to Harpagophytum procumbers reintroduction. Our literature review did not find this herbal medicine associated with SIADH, so far. **Conclusion:** SIADH may be caused by herbal medicine described from now on their association in the literature.

Keywords: hyponatremia; inappropriate ADH syndrome; phytotherapy; psychomotor agitation.

Resumo

Introdução: A síndrome da secreção inapropriada do hormônio antidiurético (SIADH) consiste na incapacidade de supressão do hormônio antidiurético (ADH), comprometendo os mecanismos de excreção da água e concentração urinária. Possui como manifestações a hiponatremia e seus sintomas, sobretudo neurológicos. Há variadas causas que desencadeiam tal distúrbio, a se destacarem: distúrbios do sistema nervoso central, neoplasias malignas e drogas, dentre outros. **Relato de Caso:** Paciente feminina, 65 anos, hipertensa, apresentando manifestações clínicas e laboratoriais correspondentes à hiponatremia. O fato ocorreu em duas ocasiões em vigência de medicação fitoterápica para tratamento de osteoartrite. **Discussão:** A hiponatremia relacionada às drogas pode ser provocada pelo efeito direto do medicamento ou por desencadear SIADH. As manifestações clínicas apresentadas poderiam ter sido atribuídas a um quadro psiquiátrico, o que poderia ter desfecho grave, caso não diagnosticada corretamente. A associação de um fitoterápico à SIADH pôde ser confirmada após novo episódio de hiponatremia relacionado à reintrodução do *Harpagophytum procumbers*. Nossa revisão da literatura não encontrou este fitoterápico associado à SIADH, até o momento. **Conclusão:** SIADH pode ser ocasionada por medicamento fitoterápico doravante descrita sua associação na literatura.

Palavras-chave: agitação psicomotora; fitoterapia; hiponatremia; síndrome de secreção inadequada de HAD.

Introduction

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a condition introduced by a multitude of mechanisms characterized by impaired water excretion caused by the inability to suppress the secretion of antidiuretic hormone (ADH).[1]

Increased ADH or vasopressin causes water retention and fluid overload.

However, increased fluid volume stimulates the secretion of the atrial natriuretic peptide, which leads to increased renal excretion of sodium and water. In addition, proximal tubular transport is inhibited, leading to greater urinary excretion of uric acid.[1]

Patients with normovolemic hyponatremia, serum hypo-osmolarity, hypouricemia, urinary osmolarity above 100 mOsmol/kg, and natriuresis increased by more than 40 mEq/L should be suspected for SIADH.[2,3]

Medications are among the main causes of SIADH. These include: chlorpropamide, carbamazepine, oxcarbazepine, cyclophosphamide, and selective serotonin reuptake inhibitors.[4]

This is the first report of a case of SIADH related to an herbal agent made with *Harpagophytum procumbers*.

Case report

A 65-year-old white female patient residing in Rio de Janeiro sought treatment at the Gaffrée and Guinle University Hospital complaining of 'distress.' She reported psychomotor agitation, nausea, and a feeling of imminent death. She had no complaints of headache, fever, chest pain, weight loss, hallucinations or other symptoms.

She had been seen in an emergency unit, where she was diagnosed with a psychotic outbreak, which led to a referral for psychiatric care. The patient suffered from systemic hypertension and took losartan, clonidine, omeprazole, and simvastatin regularly. She had started taking the *Harpagophytum procumbers* agent a month earlier for osteoarthritis.

At admission, the patient was disoriented, pale (1+/4+), hydrated, acyanotic, anicteric, afebrile, eupneic in ambient air with no signs of respiratory effort, and presented psychomotor agitation. Blood pressure (BP) in dorsal decubitus: 140x90 mmHg; BP in a quiet stance after three minutes: 140x90 mmHg; heart rate: 78 bpm; respiratory rate: 20 breaths per minute; axillary temperature: 36 °C; skin turgor and elasticity were preserved. Examination of her respiratory, cardiovascular, and neurological apparatuses, abdomen, limbs, bones and joints revealed no alterations (no focal neurological deficits, signs of meningeal irritation, edema or any other significant changes).

Urinalysis showed increased levels of urinary sodium (56 mEq/l) and uric acid (57.75 mg/dl). Serum tests revealed hyponatremia (serum sodium: 121 mEq/L, RV: 134 - 149 mEq/L) and hypouricemia (1.79 mg/dL, RV: 2.5 - 5.6 mg/dL). Plasma and urine osmolarity was 255.1 mOsm/L and 483.44 mOsm/L, respectively.

Additional tests were performed to rule out specific causes of SIADH such as thyroid disease (TSH: 1.8 mcIU/ml, RV: 0.3-5 mcIU/ml and free T4: 1.1 ng/dL; RV: 0.8 - 1.9 ng.dl), adrenal dysfunction (baseline serum cortisol: 14 mcg/dL; RV: 5 - 23 mcg/dl), HIV (anti-HIV negative), pulmonary diseases (chest X-ray showing normal lung transparency, heart and base vessels with normal appearance, and free costophrenic angles), and central nervous system diseases (normal head CT scans).

The patient was started on sodium replacement therapy (450 ml SS 0.9% + 50 ml 20% NaCl, 147 ml on an infusion pump for the first three hours + 343 ml in the following 21 hours), water restriction (800 ml/day), a loop diuretic (IV furosemide 20 mg twice daily) to deal with her symptomatic hyponatremia, but the recently introduced drug was discontinued. She progressed well and after five days in hospital the clinical manifestations and workup alterations were resolved (Table 1).

Table 1 Serum sodium levels since treatment introduction

Time	0 h	3 h	24 h	48 h	72 h	96 h
Na	121	124	131	134	137	138

Source: author.

However, two months after discharge the patient decided on her own to resume the therapy with the herbal agent and was once again diagnosed with hyponatremia secondary to SIADH, with laboratory tests showing hypo-osmolarity. The patient was normovolemic and had no complains on physical examination. Therefore, a diagnosis of SIADH induced by an herbal agent may be suggested.

Discussion

According to the literature and once other causes of normovolemic hyponatremia were ruled out, the findings in this case were indicative of SIADH.

The differential diagnosis of severe hyponatremia with psychiatric and neurological symptoms includes a wide array of signs and symptoms: seizures, psychomotor agitation, disorientation, sleepiness, and coma.[5,6] Other symptoms connected to severe hyponatremia, such as nausea and vomiting, may also induce dehydration and thus exacerbate hyponatremia.[6]

A limiting factor in diagnosing a patient with SIADH is the inexistence of a test to identify the disease beyond doubt. Diagnosis is indicated by the described manifestations and by ruling out other conditions, such as thyroid and adrenal dysfunction.[1,2]

Individuals with osteoarthritis often take herbal agents made with *Harpagophytum procumbers* - a.k.a. devil's claw - (Figure 1) for its anti-inflammatory and analgesic properties. Such agents may also be used as an adjuvant element in the treatment of severe osteoarthrosis as a replacement for glucosamine sulfate and chondroitin. Few adverse events have been reported, the most common of which being systemic hypertension.[7,8]

Figure 1. Harpagophytum procumbers (devil's claw).

SIADH may be caused by a number of conditions, such as central nervous system disorders; tumors; pneumonia caused by *Legionella pneumophilla;* medication; surgery; HIV infection; and inherited diseases. The association between certain drugs and SIADH has been extensively described in the literature. Many are the examples, ranging from anti-inflammatory medication to antibiotics.[4] However, the association between the syndrome and herbal agents was yet to be described.

The causal relationship at hand was suggested by the reintroduction of the *H. procumbers* agent by the patient and the ruling out of other causes of hyponatremia for a second time.

So-called natural medications - deemed safe by the patients - are often used without a prescription. This report described a proven complication caused by the use of an herbal agent made with *H. procumbers* that led to the development of symptomatic hyponatremia in an individual. Since this is the first of its kind, more studies are required to describe the cause and effect relationships pertaining to this herbal agent and the caution required when prescribing this and other herbal agents.

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