Case report

Inappropriate antidiuresis syndrome secondary to parasellar aneurysm subarachnoid hemorrhage

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José Vladimir Ángel Pérez[1]*, Melanie Rubidia Aguirre Alfaro[2], Wilber Alexander Ortiz Guerra[3], Jorge David Arbizu[4]

1-4. Rosales National Hospital, Ministry of Health, San Salvador, El Salvador.

*Correspondence
vladimirangel125@hotmail.com

1. 0009-0002-6167-7501
2. 0009-0005-9168-7809
3. 0009-0000-3645-3755
4. 0009-0007-5093-0395

Abstract
The presence of an electrolyte imbalance, primarily hyponatremia, is often a prevalent complication during patient hospitalization, caused by various factors. **Case presentation.** A 65-year-old male patient consulted for a thunderclap headache and transient altered alertness. Laboratory tests documented the presence of euvolemic hypoosmolar hyponatremia and hypokalemia. His CT scan showed a Fisher 3 subarachnoid hemorrhage, and MRI revealed a parasellar aneurysm displacing the left lobe of the pituitary gland. **Treatment.** During his hospital stay, he continued to have hyponatremia and was started on hypertonic solutions, without resolution. Given the persistence of hyponatremia despite hypertonic solutions, a high suspicion of syndrome of inappropriate antidiuretic hormone secretion (SIAD) was raised, fluid restriction was initiated with less than 1000 ml/day of daily intake. **Clinical evolution**. After four days, the patient's hyponatremia resolved, and the neurosurgery subspecialty managed the aneurysm.

Keywords
Hyponatremia, Aneurysm, Subarachnoid Hemorrhage, Inappropriate ADH Syndrome.

Resumen
La presencia de un desequilibrio hidroelectrolítico, a la cabeza la hiponatremia, suele ser una complicación muy frecuente durante la hospitalización de pacientes, ocasionada por diversas causas. **Presentación de caso.** Un hombre de 65 años, que consultó por cefalea en trueno, alteración del estado de alerta de carácter transitorio, en sus exámenes de laboratorio se documentó la presencia de hiponatremia hipoosmolar euvolémica e hipocalemia; su estudio tomográfico evidenciaba una hemorragia subaracnoidea, clasificación de Fisher 3 y la resonancia magnética demostraba la presencia de un aneurisma paraselar que desplazaba el lóbulo izquierdo de la hipófisis. **Intervención terapéutica.** Durante su estancia intrahospitalaria persistía con hiponatremia y se inició tratamiento con soluciones hipertónicas, sin presentar resolución y bajo una alta sospecha diagnóstica de un síndrome de secreción inadecuada de hormona antidiurética, se inició restricción hídrica con menos de 1000 ml/día de ingesta diaria. **Evolución clínica.** Al cabo de cuatro días, el paciente resolvió la hiponatremia y se dio manejo del aneurisma por la subespecialidad de neurocirugía.

Palabras clave
Hiponatremia, Aneurisma, Hemorragia Subaracnoidea, Síndrome de Secreción Inadecuada de ADH.

Introduction

Hyponatremia is the most common electrolyte imbalance in clinical practice (15-25 % of patients requiring hospitalization)[i]. In the population of critically ill neurological patients, hyponatremia is also the most common electrolyte imbalance, having been reported in up to 50 % of cases of severe neurological injury, with traumatic brain injury and aneurysmal subarachnoid hemorrhage showing the highest incidence.

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Síndrome de antidiuresis inapropiada secundario a hemorragia subaracnoidea de aneurisma paraselar

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Since the treatment of hyponatremia is guided by the underlying mechanism, a thorough understanding of the pathophysiology is crucial to initiating successful treatment.[ii] Subarachnoid hemorrhage (SAH) refers to the extravasation of blood into the subarachnoid space, a continuous space between the supratentorial and infratentorial compartments. This raises intracranial pressure and, as a result, acutely decreases cerebral perfusion pressure.[iii] The diagnosis of the syndrome of inappropriate antidiuresis is complicated for several reasons. [iv] Syndrome of inappropriate antidiuresis (SIAD), as a cause of euvolemic hypoosmolar hyponatremia, is due to multiple etiologies, including subarachnoid hemorrhage, parasellar masses, and other intracranial etiologies. Therefore, the present case aims to highlight the need for an adequate approach to diagnosing hyponatremia, as it is a cornerstone for treatment. Fluid restriction has been the mainstay of treatment for this disorder and is recommended as first-line therapy in two important systematic reviews.[v,vi]

Case presentation

A 65-year-old man with a medical history of chronic hypertension and type 2 diabetes *mellitus*, of unknown duration, not under medical treatment. He reported a history of headache lasting three days, for which he had consulted another medical center one week prior to his current admission. He was treated for a hypertensive crisis and discharged with unspecified oral antihypertensive medication.

One week after discharge, he presented with a new episode of thunderclap headache, accompanied by vomiting of food, disorganized speech, coprolalia, akathisia, and psychomotor agitation. He consulted a private clinic again, where imaging studies were performed, and it he was referred to a tertiary care hospital.

On physical examination in the emergency department, his vital signs were as follows: blood pressure 140/90 mmHg, heart rate 78 bpm, respiratory rate 16 breaths per minute, temperature 36.8°C. He was clinically euvolemic. The neurological examination described the presence of dysarthria and unspecified aphasia, with no alteration in the wakefulness-sleep state, motor deficit, or sensory alterations. The fundus examination described evidence of grade 1 mixed retinopathy, with no papilledema. The rest of the physical examination was without abnormalities. The laboratory and office tests are shown in Table 1 and Table 2 and Figure 1.

In the emergency department, evidence of electrolyte imbalance was found. The cranial CT scan showed bitemporal Fisher 3 SAH. For that reason, he was admitted to the Stroke Unit, where treatment was initiated with tramadol 100 mg intravenously every eight hours, orphenadrine 60 mg intravenously every 12 hours, nimodipine 60 mg orally every four hours, and three doses of 3 % saline solution 100 mL intravenously over 15 minutes in 48 hours. The solution was prepared by combining a 20 % sodium chloride ampoule (15 mL) with 85 mL of normal saline solution; however, the electrolyte imbalance persisted.

Treatment

A SIAD study was performed, obtaining the following criteria: sodium 126 mEq/L (corrected sodium 127.6 mEq/L), glucose 232 mg/dL, urea nitrogen 14 mg/dL, serum osmolarity 264 mOsm/L (effective osmolarity = two times sodium (mEq/L + glucose [mg/dL] / 18), urinary osmolality 455 mOsm/kg (estimated by multiplying the last two digits of the urinary density of the general urine test by 35), clinically euvolemic, normally hydrated mucous membranes, no need for oxygen, no edema in lower limbs, normal heart rate, urinary sodium 46 mmol/L, TSH 0.41 uUI/mL, with use of hypertonic solutions, no resolution of hyponatremia. The diagnostic and therapeutic plan was established as a brain MRI (Figures 2A and 2B) and fluid restriction to less than 1000 mL/day.

A cerebral MRI scan, performed using Siemens MAGNETOM Avanto 1.5T equipment, revealed the presence of an aneurysmal dilatation of the supraclinoid portion of the left internal carotid artery measuring 1 cm by 1.28 cm by 0.87 cm, located suprasellar and slightly displacing the left lobe of the pituitary gland, SAH Fisher 3, pachymeningitis, Fazekas 2 leukoaraiosis.

Outcome

The patient's hyponatremia and symptoms resolved five days after the implementation of fluid restriction, with sodium levels of 135 mEq/L, potassium levels of 3.7 mEq/L, and glucose levels of 127 mg/dL. The patient's clinical course was satisfactory, and he experienced relief from symptoms related to hyponatremia. He was treated with nimodipine for 21 days, underwent angiography, and underwent endovascular coil placement by neurosurgery. Comorbidities were managed with antihypertensive and oral antidiabetic medications on an outpatient basis.

Clinical diagnosis

The primary diagnosis was SIAD, also formerly known as the syndrome of inappropriate antidiuretic hormone secretion. Other diagnoses included: Fisher 3 SAH, documented by brain CT scan; aneurysm of the supraclinoid portion of the left internal carotid artery with slight displacement of the left lobe of the pituitary gland, evidenced by MRI. In addition, the patient presented with euvolemic hypoosmolar hyponatremia and hypokalemia, and had a medical history of essential hypertension and type 2 diabetes *mellitus*.

Discussion

The patient met all the diagnostic criteria for SIAD: effective serum osmolality less than 275 mOsm/kg, urinary osmolality greater than 100 mOsm/kg with decreased effective osmolality, evidence of clinical euvolemia, urinary sodium excretion greater than 30 mmol/L with normal salt and water intake, absence of other potential causes of euvolemic hypoosmolality (glucocorticoid insufficiency, severe hypothyroidism), no recent use of diuretic drugs, and normal renal function.

Central nervous system diseases are a relatively common cause of SIAD, especially head trauma, hemorrhages, tumors, and sphenoid surgery. Thirty-five percent of patients with SAH have hyponatremia during the first week, 70 % of whom have SIAD.[vii] The patient attends the emergency unit with a history of thunderclap headache, which led to investigation and diagnosis, documenting SAH. From the beginning of his admission, his paraclinical tests show the presence of hyponatremia and hypokalemia.

Table 1. Complete blood count results on admission

Name	Result	Unit	Min Value	Max Value
Hemoglobin	14.4	g/dL	12	16
Hematocrit	36.6	%	36	48
Platelets	264	10^3/µL	150	400
White blood cells	9.69	10^3/µL	5	10
Neutrophils %	75.8	%	55	65

Table 2. Blood chemistry results on admission

Name	Result	Unit	Min Value	Max Value
Sodium	126	mEq/L	135	150
Corrected Sodium	127.6	mEq/L		
Potassium	2.4	mEq/L	3.5	5.5
Chloride	86	mEq/L	100	115
Blood Urea Nitrogen (BUN)	14	mg/dL	5	18
Creatinine	0.63	mg/dL	0.4	1.5
Albumin	4.16	g/dL	3.5	5
Glucose	232	mg/dL	70	100
Calcium	8.39	mg/dL	8.5	10.5
Total Cholesterol	166	mg/dL	140	200
LDL	96	UI/L	30	125
Triglycerides	84	mg/dL	12	8
Hb A1c	7.82	%	Menor de 5.7 %	-

Table 3. Special test results on admission

Name	Result	Unit
Urinary Sodium	46.0	mmol/L
Morning Cortisol	27.43	µg/dL
TSH	0.41	uUI/mL
Free T4	1.12	ng/dL

Table 4. Comparative chart

Name	Chronological Results						
Hospital Stay (Days)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Sodium	126mEq/L	132mEq/L	128mEq/L	130mEq/L	133mEq/L	135mEq/L	137mEq/L
Potassium	2.4mEq/L	2.2mEq/L	3.5 mEq/L		3.7mEq/L	5 mEq/L	4.2mEq/L
Chloride	86 mEq/L	90 mEq/L	92 mEq/L	91 mEq/L	96 mEq/L	98 mEq/L	102mEq/L
Blood Urea Nitrogen	14mg/dL	21mg/dL			24mg/dL		11 mg/dL
Creatinine	0.63 mg/dL	0.67mg/dL		0.45mg/dL			0.59 mg/dL
Magnesium		2.33 mg/dL	2.3 mg/dL			2.2 mg/dL	2.33 mg/dL
Glucose	232 mg/dL	135 mg/dL		70 mg/dL	128 mg/dL	117 mg/dL	125 mg/dL

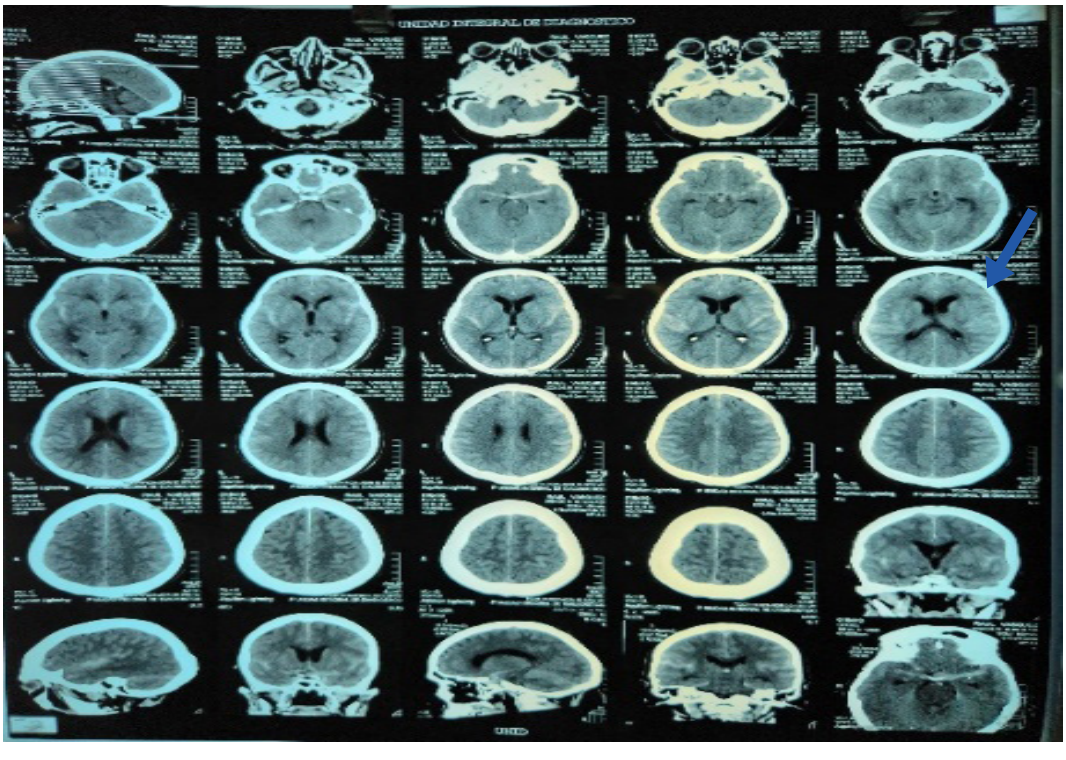

Figure 1. Fisher 3 subarachnoid hemorrhage, indicated by the blue arrow.

Figure 2A. Aneurysmal dilation, coronal section.

Figure 2B Aneurysmal dilation.

Two studies on hyponatremia and subarachnoid hemorrhage (SAH) show results that point to the high prevalence of this complication, but differ in the specific cause. In the presence of subarachnoid hemorrhage, the first study reported that 85 % of patients had hyponatremia due to SIAD. In the second study, 32.7 % had hyponatremia at some point during their hospital stay.[viii,ix]

The patient was admitted to the Neurology Unit for adequate monitoring of the complications of Fisher 3 SAH, which is a serious and often fatal condition. Prehospital and in-hospital mortality rates have been reported to be 22 % to 26 % and 19 % to 20 %, respectively.[x] Hyponatremia is one of the most common sequelae after an acute episode of aneurysmal SAH; the presence of hypokalemia can also be attributed to this condition.[xi] The patient's clinical picture is consistent with most symptoms associated with hyponatremia *per se*. During his hospital stay, he received medical treatment with drugs to prevent vasospasm of the aneurysmal rupture, analgesia, and initiation of normal saline and hypertonic saline solution, which failed to correct the sodium level.

The hormone arginine vasopressin, or antidiuretic hormone, is synthesized in the paraventricular and supraoptic nuclei of the hypothalamus and transported to the posterior pituitary gland (neurohypophysis), where it is stored and released. Its main function is to maintain plasma osmolarity in the face of any fluctuations in water balance.[xii] In SIAD, an increase in the hormone arginine vasopressin, produced by a non-physiological stimulus, results in hyponatremia and decreased serum osmolarity.[xiii] During his hospital stay, the patient presented with hypoosmolar hyponatremia.

Clinical manifestations depend on the magnitude and rate of development of hyponatremia, which may or may not be accompanied by symptoms. Prominent physical findings may be observed in people with acute and/or severe hyponatremia, including confusion, disorientation, delirium, generalized muscle weakness, myoclonus, tremor, asterixis, hyporeflexia, ataxia, dysarthria, Cheyne-Stokes respiration, pathological reflexes, and generalized seizures or coma.[xiv] The patient did not present all the symptoms described in the literature, but several clinical manifestations generally documented in cases of acute and severe onset were reported.

All laboratory tests recommended for the diagnosis of SIAD were performed. SIAD and salt-wasting cerebral syndrome are similar clinical entities that can occur in patients with neurological diseases. Hypovolemia may help differentiate between the two conditions.[xv] The phosphorus excretion fraction is normal in SIAD but elevated in salt-wasting cerebral syndrome.[xvi]

SIAD has been classified into several distinct pathophysiological categories based on the evaluation of arginine vasopressin (AVP) concentrations. This was initiated by Zerbe *et al.*, who measured AVP concentration before and after raising serum osmolality with hypertonic saline in patients with SIAD and identified four AVP response patterns, known as types A and D. These phenotypes correlate with specific etiologies; however, it is less clear whether the categories are clinically significant or simply a vehicle for better understanding pathophysiology. Type A refers to a persistently elevated AVP concentration, regardless of an increase in serum osmolality, which occurs in the most common forms of SIAD due to continuous "inappropriate" AVP secretion, either from the pituitary or from a paraneoplastic source. Type B is characterized by a lower osmotic threshold for AVP secretion (reset osmostat), with serum sodium typically maintained stably at a lower level of 125 to 135 mmol/L, at which AVP will still be suppressed at osmolarities lower than this (unless another intercurrent pathology occurs). This pattern may be more common in older age. Rarer patterns include type C, characterized by an abnormal AVP response only to low osmolarities, possibly due to dysfunction of inhibitory neurons in the hypothalamus, and type D, in which AVP is undetectable, either due to the secretion of an unidentified antidiuretic substance from tumor cells or a gain-of-function mutation in the V2 receptor (i.e., nephrogenic SIAD).[xvii]

Among the causes of SIAD are: the presence of malignancy, infectious diseases, medications, rare causes such as receptor mutations, and central nervous system disorders. An international multicenter study reported that 8.5 % were attributed to central nervous system diseases.[xvii] It is important to determine the origin of SIAD, as the patient presented two possible causes, the presence of a parasellar mass (aneurysm) and SAH, it was not possible to determine the etiology with certainty. Similarly, therapeutic intervention is performed because hyponatremia is deleterious in any condition. The patient was managed with fluid restriction, the recommended first-line treatment, and sodium normalized five days after this measure was initiated.

It is always important to avoid correcting sodium levels too abruptly, as excessively

rapid correction of chronic hyponatremia means that extracellular tonicity increases faster than the intracellular tonicity of the brain can increase. This leads to osmotic water shift out of hypotonic brain cells, resulting in neuronal dehydration and cell crenation. This, in turn, leads to disruption of cell junctions and the blood-brain barrier, resulting in oligodendrocyte damage and neuronal demyelination.[xvii]

The myelin sheath that protects axons is composed of oligodendrocytes, supported by astrocytes that maintain homeostasis and form the blood-brain barrier. These astrocytes and oligodendrocytes are believed to be most susceptible to osmotic damage due to rapid sodium correction. This may also mean that they become relatively more depleted of osmolytes. Another factor in the vulnerability of glial cells is that hyponatremia has been shown to downregulate an amino acid transporter, which is important for osmolarity adaptation. Approximately 24 hours after the sudden osmotic change, astrocytes and oligodendrocytes begin to die. Myelin damage is classically most apparent in the pons (hence it was previously known as central pontine myelinolysis), but extrapontine myelinolysis can affect other areas in about 10 % of cases.[xvii]

Treatment strategies include vasopressin receptor antagonists, sodium-glucose cotransporter two inhibitors, urea, demeclocycline, and loop diuretics, which could be used if the patient does not respond to the initial measure.[xvii]

Salt-wasting brain syndrome is a differential diagnosis of SIAD. The patient had a non-traumatic brain injury, and both conditions can share similar findings, with fluid volume status being the key to diagnosis.[xviii] There is no documented information suggesting that salt-wasting brain syndrome can transform into SIAD, nor is there any evidence of a transient association between the two.[xix]

The inexorable administration of fluids in SIAD is a topic of intense discussion and has been reviewed in the international literature. Although fluid restriction remains the cornerstone and first-line therapy, its use is not without controversy and is not always sufficient or effective. Aspects such as efficacy and response rate, adherence, and risk of worsening hyponatremia are taken into account.

Ethical aspects

Informed consent was obtained from the patient, and all aspects of confidentiality were safeguarded in accordance with the Declaration of Helsinki.

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