



SIADH and severe COVID-19 pneumonia in elderly patients: a therapeutic challenge in developing countries

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Dear Editor:

We have read with great interest the article published by Sarvazad et al. [1], where they found that hyponatremia was present in 38% of patients (22/58); also it was more common in outpatients than in patients in Intensive Care Units. However, Zhang et al. found that in patients hospitalized by SARS-CoV-2 infection, hyponatremia was closely related to the severity of infection [2]. It is known that hyponatremia is an electrolyte disorder associated with high morbidity, and his correction decreases the risk of mortality regardless of the cause [3].

In this manuscript, we describe our hospital experience with the diagnosis and management of an important cause of hyponatremia in times of the COVID-19 pandemic: the syndrome of inappropriate antidiuretic hormone secretion (SIADH), which occurs in response to the continuous release of antidiuretic hormone (ADH) despite low serum osmolality and has multifactorial etiology.

The pathogenesis of SIADH in patients with COVID-19 pneumonia involves the production of proinflammatory cytokines, mainly interleukin-6 (IL-6), which directly stimulate the nonosmotic release of ADH and cause direct damage to the alveolar basement membrane; this triggers the activation of the hypoxic pulmonary vasoconstriction

pathway, leading to increased ADH production [4]. This was evidenced in a retrospective study of a case series of 52 patients with COVID-19, wherein an inverse correlation was found between sodium concentration and IL-6 levels [5].

The diagnosis is made on the basis of serum sodium levels indicating euvolemic hypoosmolar hyponatremia after ruling out renal disease, adrenal insufficiency, and hypothyroidism, as well as diuretic use. Treatment in our country, due to unavailability of vasopressin receptor antagonists (vaptans), is based on water restriction. However, this therapeutic measure involves high risk of failure due to the requirement of time to be effective; the response not being stable and varying on a daily basis; poor compliance to the indications; and the requirement of renal function monitoring [6], especially in the elderly population.

In our clinical experience in a COVID-19 Unit of a Social Security Hospital in Peru (Table 1), we identified and treated two elderly patients without contributory medical history, who were diagnosed with severe COVID-19 pneumonia confirmed via reverse transcription polymerase chain reaction and who developed euvolemic hypoosmolar hyponatremia. These patients did not respond to hydration with normal saline solution. On examining laboratory results, their biochemical findings were found to be compatible with SIADH. Both patients underwent water restriction, which was individualized and consisted of a fluid restriction of 500 ml/day less than the urinary volume of 24 h, with appropriate renal function monitoring, which contributed to the management of COVID-19, and achieved an improvement in serum sodium levels.

As in other patients with unstable hemodynamics, patients with severe COVID-19 require fluid administration as a mainstay of treatment. Extravascular volume overload is an unintended consequence of intensive fluid therapy. It makes the administration of it careful in these patients [7],

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Table 1 Demographic and laboratory characteristics of patients with COVID-19 and SIADH

	Case 01	Case 02
Age (years)	89	70
Gender	Female	Male
Chronic disease	none	None
Symptoms	Cough, shortness of breath, and drowsiness	Cough, fever, and shortness of breath
Chest CT without contrast on admission	Ground-glass pattern involving 50% of both lungs	Ground-glass pattern involving 45% of both lungs
CBC on admission		
Hemoglobin (Hb): 12.9–18.4 g/dl	Hb: 12.5	Hb: 14.1
Platelets (PLT): 150–450×10 ³ /ul	PLT: 269	PLT: 548
White blood cells (WBC): 5–10×10 ³ /ul	WBC: 8540	WBC: 12,060
Band neutrophils (AB): 0–5%	AB: 0	AB: 2
Lymphocytes (LT): 20–40%	LT: 6	LT:4
Ferritin level on admission		
Male: 28–365 ng/ml	1664	951
Female: 5–148 ng/ml		
C-reactive protein on admission		
Normal < 10 mg/l	39	112
Serum electrolyte on admission		
Na: 135–145 mEq/L	Na: 128	Na: 124
K: 3.5–5 mEq/L	K: 3.7	K:5.1
Serum osmolarity		
Normal range: 285–295 mmol/kg	262	254
Biochemical profile		
Glucose (Glu): 70–100 mg/dl	Glu: 122	Glu: 119
Creatinine (Cr): 0.5–1.2 mg/dl	Cr:0.5	Cr: 0.6
ALT: 10–49 U/l	ALT:57	ALT:66
AST: 0–34 U/l	AST:54	AST:65
GGT: 0–38 U/l	GGT:56	GGT:43
ALP: 45–129 U/l	ALP: 115	ALP: 80
Volemia	Euvolemia	Euvolemia
Use of diuretics	No	No
Response to normal saline	No	No
Initial diagnostic	Euvolemic hyposmolar hyponatremia. Severe COVID-19 pneumonia	Euvolemic hyposmolar hyponatremia. Severe COVID-19 pneumonia
Basal cortisol-8:00 h		
Normal range: 5–25 ug/dl	26	15
Thyroid profile		
TSH: 0.55–4.78 uIU/ml	TSH:2.06	TSH: 2.30
fT4: 0.89–1.76 ng/dl	fT4: 1.09	fT4: 1.4
Serum uric acid		
Male: 3.7–9.2 mg/dl	1.8	1.4
Female: 3.1–7.8 mg/dl		
Urine specific gravity		
Normal range: 1.005–1.030	1.010	1.010
Urine sodium level		
Normal range: 40–220 mEq/day	165	175
FENa (%)	> 0.5	> 0.5
Urinary osmolality		
Normal range: 50–1200 mOsm/Kg	350	372
Treatment	Initially hypertonic saline, after water restriction. Management of COVID-19 infection	Initially hypertonic saline, after water restriction. Management of COVID-19 infection
Final serum electrolytes		
Na (mEq/L), K (mEq/L)	23 days after admission: Na:132, K:4.3	25 days after admission: Na: 136, K:3.8

Data obtained from the Division of Neumology of Hospital Nacional Guillermo Almenara Irigoyen

ALT Alanine transaminase, *ALP* Alkaline phosphatase, *AST* Aspartate transaminase, *CBC* Complete blood count, *FENa* fractional excretion of sodium, *fT4* free thyroxine, *GGT* Gamma-glutamyltransferase, *TSH* thyroid-stimulating hormone

especially in patients with advanced age. During the treatment of COVID-19 infection, it is important to highlight the effects of corticosteroid use in these patients, such as water and sodium retention, especially those with mineralocorticoid action and when high doses are administered [8]. Some corticoids have minimal mineralocorticoid effects, such as dexamethasone, which it's used in patients who require mechanical ventilation or oxygen because it showed a decrease in mortality according to the RECOVERY study [9]. The indirect effects of glucocorticoids in the proximal tubule increase the cellular response of angiotensin II-stimulated sodium transporters; in the distal tubule, their effect appears to be related to cross-binding to mineralocorticoid receptors. As a result, there is an increase in sodium and water retention, and circulating volume increases [10].

Additionally, some patients may require positive pressure ventilation, which can contribute to fluid retention, because it raises intrathoracic pressure, which in turn leads to a decrease in central arterial blood volume. Finally, the activation of baroreceptors increases vasomotor tone and the reabsorption of sodium and water destined to increase blood volume [11].

In conclusion, we highlight the importance of identifying the underlying etiological hyponatremia in patients with COVID-19, with SIADH being a diagnostic and therapeutic challenge, especially in the elderly population, as well as emphasizing appropriate clinical judgment when deciding between fluid restriction and fluid therapy to avoid complications.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Consent for publication Written informed consent was obtained from study participants for participation in the study and for publication of this report. Consent and approval for publication was also obtained from the Ethics Committee of the Guillermo Almenara Irigoyen Hospital-Lima, Peru.

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