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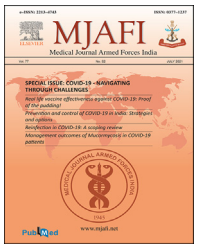

Correspondence/Letter to the Editor

Hyponatremia in COVID-19 infection: One should think beyond SIADH

Dear Editor,

Hyponatremia, defined as serum sodium less than 135mEq/L, is a common problem in clinical settings. It may be hypervolemic, euvolemic, or hypovolemic, with different underlying pathophysiological mechanisms. A proper interpretation of the various clinical and laboratory parameters is necessary to differentiate between the various causes of hyponatremia. As the causes in a given patient may be multiple, a proper understanding of the same is crucial in order to initiate effective therapy. The association of hyponatremia with coronavirus disease 2019 (COVID-19) has been described in recent studies, and it was found to be euvolemic hyponatremia due to syndrome of inappropriate antidiuretic hormone (SIADH).[1,2] In COVID-19 patients, SIADH can occur in response to numerous factors, including pneumonia, stroke, and respiratory failure. We report here three interesting cases of hyponatremia in patients with COVID-19 and discuss the underlying pathophysiological mechanisms. The diagnosis of COVID-19 was established by nasopharyngeal RT-PCR in all three cases. Based on surrogate clinical markers of extracellular fluid volume, all three patients were euvolemic. A detailed clinical and laboratory characteristic of all three patients is described in Table 1.

Case 1: A 46-year-old male patient with well-controlled hypertension, hypothyroidism, and type-2 diabetes mellitus (DM). He presented with fever, cough, and sore throat. On investigation (Table 1), his serum sodium level was found to be 120mEq/L at presentation. He was clinically euvolemic, and bilateral lung infiltrates were revealed in his chest X-ray. His urine osmolality was elevated at 798mOsm/kg, along with increased urine sodium. However, his serum osmolality level fell within the normal range (293mOsm/kg). His hypothyroidism was well controlled, but there was an elevated level of blood glucose (274 mg/dl).

Case 2: A 47-year-old male patient, without any comorbidity, who had a four-day history of fever, cough, and mild breathlessness. He had bilateral lung infiltration on the chest X-ray and elevated levels of inflammatory markers in the serum (Table 1). At presentation, his serum sodium level was 116mEq/L, and he was also euvolemic. Similar to case 1, his urine osmolality was also elevated (1006mOsm/kg) without a decline in the level of serum osmolality (297mOsm/kg). He was nondiabetic, but his blood glucose level was found to have increased (266 mg/dl).

Case 3: A 59-year-old male patient with controlled hypertension, who presented with febrile illness, anorexia, fatigue and abdominal pain. He had euvolemic hyponatremia (serum sodium 110 mEq/L) with urine and serum osmolarity levels of 100mOsm/kg and 258mOsm/kg, respectively. He did not have significant hyperglycemia (blood glucose: 129 mg/dl), but his serum cortisol level was found to be reduced (2.05 μg/dL).

Based on the presence of euvolemic hyponatremia with concurrent high urine osmolality (>100mOsm/kg) and high urine sodium (>40mEq/L), a diagnosis of SIADH was considered in all three patients. The absence of low serum osmolality in the first and second cases was attributed to coexistent hyperglycemia. No underlying medications commonly associated with SIADH were identified in any of the three patients. Fluid restriction was initially done in all three patients; however, hypertonic saline had to be used in view of acute hyponatremia and the presence of severe weakness and fatigue. The 3% saline infusion was started at a rate of 1 ml/kg/hr with the aim to correct serum sodium by not more than 8mEq/L to 10mEq/L within the first 24 h. Patients with coexistent hyperglycemia were given plain insulin to maintain normoglycemia. The first and second patients clinically improved within three days. However, the third patient, with low serum cortisol, showed improvement only after initiation of dexamethasone. Along with resolution of hyponatremia, the clinical symptoms of patients, including general fatigue and anorexia, improved.

In our clinical case series, the analytical parameters were initially interpreted as SIADH in all three cases, but there were inconsistencies in certain parameters and clinical response, which could be attributed to other coexistent abnormalities. Urine osmolality is helpful in establishing the diagnosis of SIADH. Typically, patients with SIADH have inappropriately concentrated urine with high urine sodium and urine osmolality in excess of 100mOsm/kg. In SIADH, the serum should be hypotonic, whereas it was hypertonic in one of our cases and isotonic in the other. This can be explained by the presence of coexistent hyperglycemia. Under normal conditions, glucose contributes very little to the serum osmolality. But in hyperglycemia, the entry of glucose into cells is limited, which leads to a rise in serum osmolality. Studies have found that hyperglycemia is quite common in patients with COVID-19 and is

Table 1 – Clinical and laboratory characteristics of all three cases.

Characteristics	Case 1	Case 2	Case 3
Age (years)	46	47	59
Sex	Male	Male	Male
Comorbidity	DM, HTN	None	HTN
Symptoms	Fever, weakness, cough, loss of appetite	Chest pain, cough, weakness, shortness of breath	Fever, fatigue, anorexia, pain abdomen
Chest X-ray	Bilateral perihilar infiltrates	Bilateral diffuse patchy infiltrates	Bilateral perihilar infiltrates
Volume status	Euvolemic	Euvolemic	Euvolemic
Hemoglobin, g/dL	13.2	14.2	13.3
White blood cells, per μL	6940	12,360	10,180
Platelet count, per μL	199,000	183,000	146,000
d -Dimer, μg/Ml	0.44	1.1	0.5
Serum Procalcitonin, ng/mL	0.56	0.56	0.74
Serum CRP, mg/L	2.8	61.47	6.5
Serum Ferritin, ng/mL	827.24	791.96	596.65
Serum Albumin, g/dL	3.67	3.85	3.48
Serum Alanine aminotransferase, U/L	31.9	41.8	100.8
Serum Aspartate aminotransferase, U/L	33.3	90.4	136.6
Blood Glucose, mg/dL	274	266	129
Blood Urea, mg/dL	23.2	65.7	31.8
Serum Creatinine, mg/dL	0.86	1	0.83
Serum Uric acid, mg/dL	1.83	4.3	3.89
Serum Potassium, mEq/L	3.88	4.89	3.11
Serum Chloride, mEq/L	83.51	94.53	70.8
Serum Calcium, mEq/L	8.47	9.61	8
Serum Sodium, mEq/L	120	116	110
Serum osmolality, mOsm/kg	293	297	258
Urine osmolality, mOsm/kg	798	1006	100
Urine sodium, mEq/L	125	238	224
Serum Cortisol level, μg/dL	8.25	16.84	2.05
Serum Triglyceride mg/dL	212.9	245.2	66
TSH level, IU/mL	0.32	2.15	1.13

DM (Diabetes Mellitus).
HTN (Hypertension).

associated with poor outcomes.[3] The association between the hypothalamo–pituitary–adrenal axis and a type of coronavirus was first reported by Leow et al, in 2005.[4] There are reports of suppression of hypothalamo–pituitary axis secondary to stress induced by a viral infection, resulting in failure of an increase in the serum ACTH despite the increased demand for cortisol.[5] In the third case, the patient had persistent hyponatremia despite initial replacement therapy with hypertonic saline. The administration of dexamethasone, despite its lack of mineralocorticoid activity, quickly restored his serum sodium level; hence, glucocorticoid deficiency was thought to have contributed to hyponatremia. Cortisol deficiency suppresses the pituitary release of ADH, and the resulting water retention leads to a low serum sodium concentration. In the other two cases, correction of hyperglycemia rapidly led to clinical improvement. Although, a diagnosis of SIADH requires exclusion of cortisol deficiency and hyperglycemia, in a given clinical setting where a single mechanism may not explain all the findings, the coexistence of these two conditions contributing to hyponatremia should be considered.

In conclusion, the hyponatremia in COVID-19 patients can be multifactorial. A proper clinical evaluation and interpretation of laboratory parameters are important. This will help to identify the multiple contributing factors so that a targeted treatment strategy can be instituted in order to avoid serious consequences.

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