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Hyponatremia and Encephalopathy in a 55-Year-old Woman with Syndrome of Inappropriate Antidiuretic Hormone Secretion as an Isolated Presentation of SARS-CoV-2 Infection

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Female, 55-year-old
Final Diagnosis: COVID-19 • SIADH
Symptoms: AMS • seizure
Medication: —
Clinical Procedure: —
Specialty: Critical Care Medicine • Nephrology

Objective: Unknown ethiology

Background: During the coronavirus disease 2019 (COVID-19) pandemic of 2020, varied presentations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been reported. The present report is of a case of hyponatremia and encephalopathy due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) as the main presentation of SARS-CoV-2 infection in a 55-year-old woman.

Case Report: A 55-year-old woman with type II diabetes mellitus presented with confusion and slurring of speech, with a temperature of 38.5°C, heart rate of 120 bpm, blood pressure of 159/81 mmHg, and oxygen saturation of 98% on room air. She did not have edema on examination. Laboratory testing showed a low sodium level of 116 mEq/L (reference range, 135-145 mEq/L) with urine osmolarity of 364 mOsm/kg, urinary sodium of 69 mEq/L, urinary potassium of 15.6 mEq/L, and serum osmolarity of 251 mOsm/kg. The patient had normal serum thyroid-stimulating hormone and cortisol levels. A chest X-ray should no pulmonary infiltrates nor did a lumbar puncture reveal signs of infection. A real-time SARS-CoV-2 polymerase chain reaction assay was positive for COVID-19. Brain imaging with computed tomography was negative for acute infarct, intracranial hemorrhage, and mass effect. Based on findings from laboratory testing and physical examination, a diagnosis of SIADH was made. The patient was treated with 3% hypertonic saline, followed by salt tablets and fluid restriction, with improvement in her clinical symptoms and serum sodium level.

Conclusions: The present report is of a rare but previously reported association with SARS-CoV-2 infection. Encephalopathy and hyponatremia associated with SIADH without pneumonia or other symptoms of infection should be an indication for testing for SARS-CoV-2 infection.

Keywords: COVID-19 • Hyponatremia • Inappropriate ADH Syndrome • Seizures

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/930135

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Background

Infections of the lung and central nervous system (CNS) disorders are well-established causes of the syndrome of inappropriate antidiuretic hormone release (SIADH) [1,2]. Coronavirus-19 disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) primarily affects the respiratory tract and can lead to severe respiratory illness [1,2]. SARS-CoV-2 virus encephalitis also has been described [3,4]. Unsurprisingly, SIADH-related hyponatremia has been identified in patients hospitalized for COVID-19 [5-7]. Observational studies have noted an association between interleukin (IL)-6 levels and hyponatremia and suggest that IL-6-mediated inflammation and non-osmotic antidiuretic hormone (ADH) release is the underlying pathophysiology [7,8]. Given that brain imaging was normal in our patient, we ruled out direct CNS involvement with SARS-CoV-2 as a cause of encephalopathy. Therefore, the present report is of a case of hyponatremia and encephalopathy due to SIADH as the main presentation of SARS-CoV-2 Infection in a 55-year-old woman.

Case Report

A 55-year-old woman with a history of type II diabetes mellitus treated with metformin, glipizide, and insulin glargine was brought to our Emergency Department (ED) after being found on the bathroom floor, confused and with slurred speech. As per her daughter, the patient was in her usual state of health before this event. There was no prior history of headache, nausea, vomiting, diarrhea, shortness of breath, or chest pain, nor any recent change in medications or current diuretic use. On arrival at the ED, the patient was febrile with a temperature of 38.5°C and tachycardic with a regular heart rate of 120 bpm. Her blood pressure was 159/81 mmHg, respiratory rate 20 breaths per minute, and oxygen saturation 98% on room air. Physical examination revealed no focal neurological deficits. There was no edema or orthostatic hypotension, the patient's mucous membranes were moist, and she was found to be euvolemic. Laboratory findings were significant for a low sodium level of 116 mEq/L (reference range, 135-145 mEq/L), normal blood urea nitrogen level of 15.0 mg/dL (reference range, 7-20 mg/dL), and normal creatinine level of 0.6 mg/dL (reference range, 0.5-1.2 mg/dL). A random blood glucose level was 324 mg/dL (reference range, 70-90 mg/dL). The serum uric acid level was decreased to 1.6 mg/dL (reference range, 2.5-6.2 mg/dL). Urine osmolarity was 364 mOsm/kg, urinary sodium was 69 mEq/L (reference range, 30.0-90.0 mEq/L), urinary potassium was 15.6 mEq/L, and serum osmolarity was 251 mOsm/kg (reference range, 285-295 mOsm/kg). The patient's thyroid-stimulating hormone level was normal at 1.1 mIU/L (reference range, 0.465-4.680 mIU/L) and her morning cortisol level was normal at 16.7 µg/dL (reference range, 4.46-22.70 µg/dL). **Table 1** lists the initial laboratory values.

A portable chest X-ray and chest tomography scan revealed no pulmonary pathology. Brain imaging with computed tomography (CT), CT angiography, and brain magnetic resonance imaging without gadolinium was negative for acute infarct, intracranial hemorrhage, and mass effect. Specifically, there was no leptomeningeal enhancement, cortical signal abnormalities, or cortical diffusion restriction, findings that have been described in COVID-19 with CNS involvement.

As part of the hospital surveillance protocol for all patients admitted during the COVID-19 pandemic, we performed testing for COVID-19. SARS-CoV-2 infection was confirmed from a nasopharyngeal sample with a reverse transcription-polymerase chain reaction (RT-PCR) test (Abbott, Brooklyn, New York, United States) performed in an accredited LabCorp laboratory in Brooklyn, New York. Because the patient was febrile, a lumbar puncture (LP) was performed. The cerebrospinal fluid (CSF) was clear. Other than an elevated opening pressure of 26 mmHg, biochemical and cellular analysis of the CSF was noted to be within normal limits, including a protein level of 44 mg/dL (reference range, 12-60 mg/dL) and a white blood cell count of 1 cell/µL (reference range, 0.0-5.0 cells/µL). CSF cultures and PCR testing to identify bacterial or viral infections were negative. Based on the previous data, we concluded that the patient had SIADH associated with COVID-19. Because of the altered sensorium, initial management was administration of 3% hypertonic saline on Day 1, which led to improvement in

Table 1. Initial laboratory values in our patient.

Serum sodium	116 mEq/L	Normal range 135-145 mEq/L
Serum osmolarity	251 mOsm/kg	Normal reference range 285-295 mOsm/kg
Urine osmolarity	364 mOsm/kg	Normal range varies
Urine sodium	69 mEq/L	Normal reference range 30.0-90.0 mEq/L
Thyroid-stimulating hormone	1.1 mIU/L	Normal reference 0.465-4.680 mIU/L
Cortisol	16.7 mcg/dL	Normal range 4.46-22.70 mcg/dL
Glucose	324 mg/dL	Normal reference 70-90mg/dL

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the serum sodium level to 120 mEq/L over the first 24 hours, followed by salt tablets and fluid restriction. We did not use urea or tolvaptan. The patient's neurological symptoms started to improve within 24 hours of presentation, in parallel with her improving serum sodium levels. She did not require any specific treatment for COVID-19. The patient was discharged home on a regular salt diet, no fluid restriction, and previous home medications. Her sodium level was 131 mEq/L at discharge and 136 mEq/L at the 2-week follow-up visit.

Discussion

Non-osmotic ADH release that is inappropriate to the clinical circumstance is termed SIADH [9]. The diagnosis requires the presence of decreased plasma osmolality, inappropriate urine concentration (usually >100 mosm/kg), a urinary sodium concentration usually >30 mEq/L under conditions of regular salt and water intake, and euvolemic status [9,10]. An SIADH diagnosis also requires ruling out adrenal, thyroid, and pituitary diseases; renal insufficiency; and current diuretic use [9,10]. Our patient fulfilled these criteria; therefore, the diagnosis of SIADH was established. Current treatment for SIADH includes hypertonic saline, urea, vaptans, and fluid restriction, depending on the severity of symptoms [11].

Case reports and case series have identified an association between COVID-19 pneumonia and SIADH-related hyponatremia [5,6]. Also, a large, retrospective study reported a 30% incidence of hyponatremia, with 1% of the cases being severe, in 4452 hospitalized patients who were SARS-CoV-2 PCR-positive [7]. Among the patients with severe hyponatremia, the cause of low serum sodium was identified to be equally divided between hypovolemia and SIADH [7]. However, the study did not provide specific data regarding the presence or absence of clinical symptomatology in the lungs or CNS, or from related imaging. The study found an inverse association between IL-6 and sodium levels and implicated inflammation-associated non-osmotic ADH release as the cause of SIADH in COVID-19. This association of elevated IL6 and ADH levels has been previously described [8,12]. Although we did not obtain IL-6 levels in our patient, her ferritin level was noted to be elevated at 332 ng/mL (reference range, 11.10-264 ng/mL). However, no features of "cytokine storm," including endothelial damage and multiorgan failure, were seen [13]. Moreover, our patient had no pulmonary symptoms, and chest imaging was negative. Her presenting symptoms were solely neurological in the setting of acute hyponatremia.

Acute and subacute infarcts, microhemorrhages, and leptomeningeal contrast enhancement have been commonly identified among patients with COVID-19 [14,15]. Coagulopathy associated with COVID-19 also has been implicated as a cause of ischemic and hemorrhagic strokes [4]. Brain imaging, including MRI and CT angiography, revealed no such changes in our patient. LP, done to evaluate the cause of encephalopathy, revealed elevated opening pressures, but CSF studies, including cell counts, cultures, and PCR tests to identify bacterial or viral infections, were negative. These results essentially ruled out direct CNS involvement by SARS-CoV-2. Hence, we concluded that the encephalopathy was related to hyponatremia, rather than CNS disease or a CNS complication of COVID-19. We did not repeat brain imaging because there was rapid improvement in the patient's neurological symptoms that corresponded with the correction in serum sodium levels. Patients with severe hyponatremia (<120 mEq/L) can present with manifestations of cerebral edema, including obtundation, seizures, coma, respiratory arrest, and death [16]. Numerous published case reports about SARS-CoV-2-related neurological manifestations describe findings such as altered mental status, seizures, and cerebrovascular events [17]. These findings are not specific to COVID-19 infection and the real impact of SARS-CoV-2 on the CNS is unclear [17].

We report a unique case of severe encephalopathy and severe hyponatremia in a patient with COVID-19 that occurred in the absence of lung and CNS involvement. Habib et al reported a similar case, but the patient had only mild dizziness [18]. That case report did not comment on findings about inflammatory markers or from LP.

Previous studies in hospitalized patients and experimental studies in animals have identified a positive association between elevated intracranial pressure (ICP) and increased ADH release [19-22]. In our patient, we could not establish whether the hyponatremia raised the ICP or the elevated ICP caused non-osmotic ADH release and secondary hyponatremia. We suspect it was the former because even though a classic cytokine storm was not observed in our patient, she was febrile and had an elevated ferritin level on presentation, findings compatible with systemic inflammation. In line with the current literature, we believe that systemic inflammation and IL-6-mediated, non-osmotic ADH release caused hyponatremia, and that the acute hyponatremia, in turn, raised the ICP.

Conclusions

The present report is of a rare but previously reported association with SARS-CoV-2 infection. Encephalopathy and hyponatremia associated with SIADH without pneumonia or other symptoms of infection should be an indication for testing for SARS-CoV-2 infection. Systemic inflammation and IL-6-mediated, non-osmotic ADH release is the likely pathophysiology of SIADH in COVID-19, although yet unknown factors cannot be ruled out.

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Conflict of Interest

None.

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