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Case Report

Severe Hyponatremia Exacerbated by Nirmatrelvir and Ritonavir in a Coronavirus Disease 2019 (COVID-19) Patient with Chronic Hyponatremia

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Abstract

We report a case report of a 75-year-old female patient with a history of mild baseline hyponatremia who developed severe and life-threatening hyponatremia secondary to Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) following treatment with nirmatrelvir/ritonavir for coronavirus disease 2019 (COVID-19). The patient's sodium levels were stable at 133 mmol/L as of July 1, 2024, but decreased significantly to 105 mmol/L by her admission on August 7, 2024. The patient was diagnosed with COVID-19 on July 24, 2024, and received a full course of nirmatrelvir/ritonavir from July 26 to July 31, 2024. Despite the absence of fever and pneumonia, common triggers for SIADH in COVID-19, the temporal relationship between the antiviral treatment and the decline in sodium levels suggests a causative link. This case highlights the importance of vigilant monitoring of sodium levels in patients with a history of hyponatremia who are treated with Nirmatrelvir/ritonavir for COVID-19, as they may be at increased risk for severe hyponatremia.

Keywords: COVID-19; Hyponatremia; SIADH; Nirmatrelvir; Ritonavir

Introduction

Hyponatremia is a commonly feared and closely monitored electrolyte disturbance. It is classified based on serum sodium concentration levels: severe hyponatremia (<120 mEq/L), moderate hyponatremia (120 to 129 mEq/L), and mild hyponatremia (130 to 134 mEq/L). Complications from untreated hyponatremia and from overcorrection are most common among patients with severe hyponatremia [1].

Nirmatrelvir/ritonavir is an oral combination medication authorized by the Food and Drug Administration (FDA) on December 22, 2021, for the treatment of coronavirus disease 2019 (COVID-19). Nirmatrelvir is a protease inhibitor targeting the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) main protease, while ritonavir is a cytochrome P450(CYP)3A inhibitor which boosts the levels of nirmatrelvir by slowing its metabolism [2].

This case report presents a 75-year-old female with a history of chronic hyponatremia who developed severe hyponatremia following recent treatment with nirmatrelvir/ritonavir for COVID-19. Her clinical course and laboratory findings highlight the potential impact of these medications on sodium levels and underscore the importance of careful monitoring in patients with pre-existing electrolyte imbalances.

Case Presentation

A 75-year-old female with a history of hypertension and chronic hyponatremia (baseline sodium levels of 126-133 mmol/L) was brought to the emergency department by her family on August 7, 2024, due to altered mental status, general malaise, fatigue, and headache. On admission, her blood pressure was 159/74 mmHg, heart rate 86 beats per minute, temperature 97.88°F, and oxygen saturation 98% on room air. Physical examination revealed a

euvolemic, lethargic patient with no focal neurologic deficits. Cardiac and pulmonary examinations were unremarkable with no oedema or signs of hyperlipidaemia or jaundice. Her chest X-ray on 8/7/24 showed no acute disease, including the absence of pneumonia.

The patient had been taking a low-dose regimen of spironolactone (6.25 mg three times weekly) for over a year. On June 6, 2024, her sodium level was measured at 126 mmol/L, which was lower than her baseline of 133 mmol/L on January 12, 2024. This led to the discontinuation of spironolactone, after which her sodium level returned to her baseline of 133 mmol/L by July 1, 2024.

On July 24, 2024, she was diagnosed with COVID-19. On July 26, she initiated treatment with nirmatrelvir/ritonavir and completed the course by July 31. Following treatment, she experienced progressive weakness, mild diarrhoea, nausea, and reduced appetite. Her water intake was approximately 45 ounces per day.

Upon admission on August 7, 2024, initial laboratory evaluation revealed critically low sodium (105 mmol/L), serum osmolality 218 mOsm/kg, blood glucose 99 mg/dL, glomerular filtration rate (GFR) 94 mL/min/1.73m², normal White Blood Cell (WBC) count (7×10^9/L), normal cortisol (13.75 mcg/dL), elevated Thyroid-Stimulating Hormone (TSH) (7.82 µIU/mL), and normal Thyroxine (T4) (8.1 ng/dL). She was admitted to the intensive care unit (ICU) for management of severe hyponatremia, and treated ICU protocol with 3% sodium chloride infusion (Table 1). The following day (August 8), her urine sodium was within the reference range (20 mEq/L) and her urine osmolality was 187 mOsm/kg. The patient reported improvement and by August 11 her sodium level had risen to 127 mmol/L, leading to discharge. At her follow-up appointment (August 26) the patient was feeling well and her sodium level was stable at her baseline of 133 mmol/L.

Date	Sodium Level
08/07/24 (*admission date*)	105 mmol/L
08-08-2024	112 mmol/L
08-09-2024	114 mmol/L
08-10-2024	120 mmol/L
08/11/24 (*discharge date*)	127 mmol/L

Table 1: Patient sodium levels from admission through discharge date. Patient's baseline level is 126-133 mmol/L.

Discussion

The patient's clinical presentation suggests that the Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) was likely exacerbated by her recent treatment with nirmatrelvir/ritonavir for COVID-19. Her sodium levels were stable at her baseline of 133 mmol/L as of July 1, 2024, but had significantly decreased to 105 mmol/L by her admission on August 7, 2024, indicating severe and life-threatening hyponatremia [1].

The key event during this period was her diagnosis of COVID-19 on July 24, 2024, followed by a full course of nirmatrelvir/ritonavir from July 26 to July 31, 2024. Although COVID-19 itself can cause SIADH through mechanisms such as the induction of inflammatory cytokines [3], these are often associated with fever or pneumonia [4], which were not present in our patient; she was afebrile and had no evidence of pneumonia on chest X-ray.

Nirmatrelvir/ritonavir have been associated with SIADH in the literature, potentially due to direct effects on antidiuretic hormone regulation or interactions with other medications [5]. However, in this case, the patient was not taking any other medications, making it less likely that medication interactions played a role. The temporal relationship between the initiation of nirmatrelvir/ritonavir and the decline in sodium levels, along with the absence of other identifiable causes, strongly suggests that the combination of COVID-19 and the antiviral treatment were key contributors to the progression of her mild baseline hyponatremia to a severe and potentially fatal level.

Conclusion

While cases of both nirmatrelvir/ritonavir-exacerbated hyponatremia and COVID-19-induced SIADH have been documented, this case is unique due to the patient's pre-existing history of chronic hyponatremia, which may have predisposed her to a more severe response. This highlights the importance of vigilant monitoring of sodium levels in patients with a history of hyponatremia who are diagnosed with COVID-19 and are treated with nirmatrelvir/ritonavir, as they may be at increased risk for exacerbation of their condition. Clinicians should be aware of this potential risk and consider alternative therapies or close monitoring in similar patients to prevent severe complications.

Consent

Informed consent was obtained from the patient and all identifying information has been removed.

Conflicts of Interest

The author(s) declare(s) that they have no conflicts of interest.

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