A Case Series of Acute Symptomatic Hyponatremia due to SIADH in mild COVID-19 Infection

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Short Report

Keywords: SIADH, COVID-19, hyponatremia, seizure, Interleukin-6

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A Case Series of Acute Symptomatic Hyponatremia due to SIADH in mild COVID-19 Infection

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Keyword: SIADH; COVID-19; hyponatremia; seizure; Interleukin-6

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ABSTRACT:
Syndrome of Inappropriate anti diuretic hormone (SIADH) is one of the commonest cause of hyponatremia among medical inpatients. Over recent years, the evolution of SARS-COV-2 infection has led to atypical presentations of acute symptomatic hyponatremia secondary to isolated SIADH exclusive of pneumonia. We report an unusual case series of acute symptomatic hyponatremia secondary to SIADH in Category 2 COVID-19 infection.

In our case series, all the patients presented with symptoms of acute severe hyponatremia and were incidentally screened positive for the SARS-COV-2 virus without respiratory tract symptoms and normal chest imaging. They were fully vaccinated and boosted at least three months before the presentation. Clinical and biochemical workups confirmed SIADH in all three patients. They were treated with hypertonic saline initially, followed by fluid restriction as per recommendations. It was postulated that the most likely mechanism responsible for the inappropriate ADH secretion is mediated by the increased inflammatory cytokines, especially interleukin-6 and the direct effect of the SARS-COV2 infection.

In the context of the COVID-19 pandemic, atypical presentations of acute symptomatic hyponatremia without an apparent cause could be an isolated manifestation of SARS-COV-2 infection. Awareness of this condition is essential for the early institution of the treatment protocol for this reversible and life-threatening disorder.

Main Text
Background
Hyponatremia is a prevalent electrolyte disorder, with incidences ranging from 15 to 30% among hospitalized patients. Amongst the various causes of hyponatremia, Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion accounts for at least 30-40% of the cases. The management of this disorder, especially moderate to severe hyponatremia, is vital, as it carries a high mortality rate. SIADH is characterized by euvoilemic hyponatremia, low plasma osmolality, elevated natriuresis, and hyperosmolar urine with no evidence of hypothyroidism, hypocortisolism or diuretic use. The aetiology of SIADH must be identified to exert appropriate management.

The SARS-CoV-2 virus, transmitted from human to human by droplet or contact routes, usually manifests as upper or lower respiratory tract infection in adults. However, the development of vaccines and the emergence of novel viral variants also led to an array of atypical systemic presentations.

This case series describes three acute symptomatic hyponatremia in SIADH as a solo presentation of COVID-19.

Case Presentation
Case 1
A 59-year-old lady presented with the first episode of an unprovoked generalized tonic-clonic seizure. Clinically, the patient was euvoilemic and afebrile; vitals were unremarkable, lungs clear, and no focal neurological deficit other than the postictal state. She had no respiratory symptoms, fever, vomiting, or diarrhea. However, COVID-19 Rapid Test Kit-Antigen (RTK-Ag) test was positive. Chest x-ray revealed no pneumonic changes, and Computed Tomography (CT) of the brain was normal. The patient was diagnosed with category 2 COVID-19 pneumonia and acute symptomatic euvoilemic hyponatremia. Her sodium level on arrival was 108 mmol/L. She had a normal baseline sodium and thyroid function two months before this presentation. The workup for hyponatremia confirmed SIADH. In the emergency department, 100ml of 3% sodium chloride was infused over half an hour. Her sodium gradually
increased with hydration of two liters of 0.9% sodium chloride over a day, followed by fluid restriction of one liter per day for the next four days. The sodium level upon discharge was 132 mmol/L. The patient also had thyroiditis during the same admission. She was discharged after five days well with no further fluid restriction or episode of seizure during the hospital stay.

Case 2
A 62-year-old lady presented with three days history of vomiting, four episodes per day and poor oral intake with generalized lethargy. She had no history of fever, respiratory symptoms, abdominal pain, or diarrhea. Physical examination revealed a well-hydrated patient with normal cardiorespiratory assessment and GCS of E4V4M6. COVID-19 RTK-Ag and RT-PCR was positive. Her serum sodium upon presentation was 104mmol/L. Chest x-ray and brain CT were normal. She was infused 100ml of 3% sodium chloride over one hour in the emergency department and hydrated further with 0.9% sodium chloride daily for three days. She was then fluid-restricted once confirmed to have SIADH. Her serum sodium gradually increased to 130 mmol/l in three days. She was also diagnosed with subclinical hypothyroidism during the admission, and L-thyroxine 50mcg OD was initiated. The patient had a prolonged hospital stay of 10 days due to multiple flares of gouty arthritis.

Case 3
A 63-year-old lady, hypertensive for 10 years on atenolol, presented with two days history of vomiting, five episodes per day, poor oral intake and unable to ambulate due to generalized weakness. She had no fever, respiratory symptoms, diarrhea, abdominal pain, or urinary tract infection symptoms. GCS upon arrival was E3V5M6, with normal vital signs, and her systemic examination, including neurological examination, was normal. The chest x-ray was clear, and the brain CT scan was normal. COVID-19 RTK-Ag and RT-PCR were positive. She was admitted with the diagnosis of euvolemic hyponatremia and COVID-19 category 2. Serum sodium on arrival was 100 mmol/L; hence, 100ml of 3% sodium chloride was infused over half an hour in the emergency department, followed by two litres of 0.9% sodium chloride over three days. No strict fluid restriction was imposed. Her serum sodium climbed gradually, from 100 to 133mmol/l upon discharge over seven days. She had thyroiditis post-COVID-19 infection as well. Refer Table 1 for case summary

Outcome and Follow-up
All three patients were followed up two weeks and three months later. The patients had no recurring symptoms, and their sodium levels remained stable.

Table 1: Case summary

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>CASE 1</th>
<th>CASE 2</th>
<th>CASE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59</td>
<td>62</td>
<td>63</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>Co-morbid</td>
<td>Euthyroid multinodular goitre</td>
<td>Diabetes, hypertension, dyslipidemia</td>
<td>Hypertension</td>
</tr>
<tr>
<td>COVID-19 vaccination</td>
<td>No</td>
<td>No</td>
<td>Completed primary series with one booster</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>No</td>
<td>No</td>
<td>Yes – long term</td>
</tr>
<tr>
<td>Duration of illness (days)</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Fitting and loss of consciousness, generalized lethargy</td>
<td>Vomiting, poor oral intake, generalized lethargy</td>
<td>Vomiting, lethargy, poor oral intake, generalized weakness</td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>Nil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCS on arrival</td>
<td>13</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Volume status</td>
<td>Euvolemic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest Xray</td>
<td>Clear lung fields</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT brain(plain)</td>
<td>No intracranial abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COVID-19 RT PCR</td>
<td></td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Serum sodium on admission (mmol/L)</td>
<td>103</td>
<td>104</td>
<td>100</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Serum osmolality (mOsm/kg)</td>
<td>245 (low)</td>
<td>267 (low)</td>
<td>209 (low)</td>
</tr>
<tr>
<td>Urine osmolality (mOsm/kg)</td>
<td>520 (high)</td>
<td>350 (high)</td>
<td>350 (high)</td>
</tr>
<tr>
<td>Urine sodium (mmol/L)</td>
<td>31</td>
<td>26</td>
<td>36</td>
</tr>
<tr>
<td>Serum cortisol 8am (nmol/L)</td>
<td>425</td>
<td>665</td>
<td>434</td>
</tr>
<tr>
<td>Thyroid function (reference range FT4:7.9-14.4 pmol/L, FT3:3.8-6.0 pmol/L, TSH 0.38-5.33 miu/L)</td>
<td>Thyroiditis FT4: 18, TSH 0.37, FT3 4.3</td>
<td>Subclinical hypothyroidism TSH 11.91, FT4 8.8</td>
<td>Thyroiditis TSH 0.03, FT4: 23, FT3 3.5</td>
</tr>
<tr>
<td>COVID Category</td>
<td>2B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>-100 ml of 3% saline -2 litres 0.9% saline for 1 day -fluid restriction of 1 litre per day for another 4 days</td>
<td>-100 ml of 3% saline -2 litres of 0.9% saline per day for 3 days -fluid restriction of 1 litre per day</td>
<td>-100 ml of 3% saline -2 litres of 0.9% saline over 24 hours for 3 days -No strict fluid restriction was imposed</td>
</tr>
<tr>
<td>Serum Sodium on discharge (mmol/L)</td>
<td>132</td>
<td>130</td>
<td>133</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>5 days</td>
<td>10 days</td>
<td>7 days</td>
</tr>
</tbody>
</table>

**Reference Range**
- *Serum Sodium normal range:* 135-145 mmol/L
- *Serum Osmolality normal range:* 275-295 mOsm/kg H2O
- *Urine Sodium normal range:* 40-190 mmol/L
- *Urine Osmolality normal range:* 300-900 mOsm/kg H2O
- *Free T4 normal range:* 7-14.1 pmol/L
- *Free T3 normal range:* 3.8-6.0 pmol/L
- *TSH normal range:* 0.38-5.33 mIU/L
- *Serum cortisol normal range:* 166 – 507 nmol/L

Discussion:
COVID-19 presentations can vary from asymptomatic to severe pneumonia with multisystem involvement. Symptomatic hyponatremia due to SIADH in Category 3 COVID-19 patients with pneumonia has been reported over the past two years [1-3]. This is attributed to low intravascular fluid volume and low extracellular fluid osmolality due to hypoxic pulmonary vasoconstriction, which causes baroreceptors in the carotid sinus, carotid body and aorta to activate the renin-angiotensin system [1]. The RAS triggers a non-osmotic ADH secretion. However, in our case series, all three patients presented to the hospital with a complaint of symptoms related to the underlying hyponatremia without fever or respiratory symptoms, with normal chest imaging. Hence, we postulate that SARS-CoV-2 infection is the cause of SIADH with the presentation of acute severe euvolemic hyponatremia in all three patients. There is only one similar case reported in Category 2 COVID-19 disease [4].
There are a few postulated mechanisms related to our case series, with the most likely rationale being interleukin-6 (IL-6) mediated SIADH in SARS-CoV-2 infection. Virus depends primarily on the host’s immune system to replicate and cause insults. Cytokines, specifically IL-6 released by monocytes and macrophages in COVID-19 infection, are the prime mediators of inflammation. It plays a pathogenic role leading to electrolyte impairment by inducing the non-osmotic release of vasopressin. A study by Berni et al. among 52 COVID-19 positive patients demonstrated an inverse relationship between sodium and IL-6 levels. Tocilizumab, a human monoclonal antibody against the IL-6 receptor, reported a positive response with a rise of serum sodium within 48 hours [2,5]. Hyperactivation of the immune system and cytokine storm in COVID-19 is known to manifest as acute respiratory distress syndrome and myocarditis. However, the hypothesis regarding a milder form of hypercytokinemia could result in less pronounced atypical presentations, including SIADH [3]. Other proposed etiologies of euvolemic hyponatremia in COVID-19 patients without pneumonia exist. Among them is a renal injury in this illness caused directly by the virus via ACE-2 receptors. Cytokine-induced renal impairment can lead to a renal pathological change, including electrolyte imbalance [5].

Apart from the above, poor oral intake and gastrointestinal losses among COVID-19 patients can result in SIADH. More frequently, watery diarrhea due to viral replication in the gastrointestinal epithelial cells via the ACE-2 receptor leads to hypovolemic hyponatremia. However, occasionally volume depletion leads to a secondary elevation in ADH secretion, which results in euvolemic hyponatremia [5]. The patient in the second case had subclinical hypothyroidism with serum TSH of 11 miU/L, which was not significant enough to cause hyponatremia. Current available literature suggests that only severe hypothyroidism is capable of causing significant reductions in GFR that result in large enough disturbances in renal tubular function to cause clinically significant hyponatremia [6]. Thyroiditis, as observed in two of our patients, is common in SARS-COV2 infection, conceivably due to the virus’s direct infection of the endocrine glands and cell damage induced by the immune response [7].

Treatment recommendation for SIADH are principally fluid restriction, management of underlying disease, hypertonic saline in the initial phase, urea powder, oral salt, demeclocycline and occasionally low-dose loop diuretics. Moreover, the introduction of renal vasopressin V2 receptor antagonist, the Vaptans, in 2006 has been superseded other treatment options [8,9]. All three patients mentioned above were treated with hypertonic saline upon presentation, thereafter hydrated with isotonic saline for at least two days prior to fluid restriction of 800ml to 1000ml per day. These patients had an increment of serum sodium to normal levels within an average of seven days without strict fluid restriction or Vaptans. Observation of these three cases implies that SIADH in Category 2 COVID-19 infection does not needs aggressive treatment methods, and a rise in serum sodium can be expected to occur swiftly. More research is required to ascertain the incidence, pathogenesis, and prognosis of patients with SIADH secondary to COVID-19 to devise specific treatment protocols for managing hyponatremia in these cases.

Conclusion:
In the context of the COVID-19 pandemic, SARS-CoV-2 infection could result in acute symptomatic hyponatremia due to SIADH, even in the mild category of COVID. It could be the first and only manifestation of COVID-19 that requires a high index of suspicion among clinicians. Monitoring inflammatory markers such as IL-6 may assist in determining the relationship between hyponatremia and COVID-19

Abbreviation:
Syndrome of Inappropriate Antidiuretic Hormone (SIADH), Rapid Test Kit-Antigen (RTK-Ag), Computed Tomography (CT), interleukin-6 (IL-6)

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REFERENCES

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Competing Interests
The authors have no relevant financial or non-financial interests to disclose.

AUTHORS CONTRIBUTORS
VD involved in clinical care, conceptualization and drafting of the manuscript. FSH involved in clinical care, revision of manuscript for intellectual content and approval of the manuscript. JM involved in writing, reviewing and editing. All the authors read and approved the final manuscript.

Ethics Approval
This manuscript is in line with local ethics protocol.

Consent to Publish
Written consent was obtained from patient for publication of their clinical details.