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COMMENTARY

Hyponatremia in COVID-19 Infection - Should Only Think about SIADH?

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Abstract

SARS-CoV-2 disease (COVID-19) has dramatically increased since March 2020. There is not sufficient data to establish the risk of acquiring the hyponatremia in patient with COVID-19 infection. The prevalence, causal factors, clinical characteristics, severity, treatment and prognosis of hyponatremia in patients with pneumonia due to COVID-19 is not yet known, although several articles on kidney injury and electrolyte abnormalities have recently been reported. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is one of the most common causes of hyponatremia in hospitalized patients. The hyponatremia in COVID-19 infection is multifactorial and one of the underlying mechanisms is ADH secretion, probably as a result of the marked elevation of inflammatory cytokines (Interleukin-6). Finally, we consider that COVID-19 infection could have played a role in the severity of the symptoms of hyponatremia.

Keywords

Hyponatremia, SARS-CoV-2, COVID-19, Syndrome of inappropriate antidiuretic hormone, IL-6

Introduction

In early December 2019, a respiratory disease caused by a novel coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in Wuhan, China. This disease, which the World Health Organization (WHO) denominated coronavirus disease 2019 (COVID-19), spread rapidly throughout China and worldwide [1]. The WHO declared COVID-19 a pandemic in March 2020 [2]. SARS-CoV-2 belongs to the family of RNA beta-coronavirus, which include the virus that were responsible for the outbreaks of severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS) between 2012 and 2013 [3,4]. COVID-19 has a variable mortality rate according to each country and is expected to affect a major part of the world's population [2].

The clinical spectrum of COVID-19 infection is variable, ranging from asymptomatic carrier state, anosmia, ageusia or minor upper respiratory tract illness to severe pneumonia potentially leading to acute respiratory distress syndrome (ARDS), respiratory failure, multiple organ disfunction and even death [5]. Diarrhea and cutaneous and thrombotic manifestations were recently described [6]. SARS-CoV-2 mainly affects the respiratory system causing acute respiratory illness, with bilateral and diffuse pneumonia, but it can affect multiple organs and systems, such as the kidneys [6]. Kidney cells express receptors and enzymes required for viral entry, such as angiotensin-converting enzyme 2 (ACE2), which is also expressed in the lung, heart and intestine [7,8]. Furthermore, kidney damage may result from hemodynamic factors or dysfunctional immune response. Direct renal cell infection is possible and is supported by some studies showing viral particles within proximal tubules and podocytes [9], as indicated by presence of proteinuria and hematuria. Inflammatory cytokines have long been known to induce acute kidney injury (AKI), glomerulopathy [10], and a spectrum of

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pathologic abnormalities including acute tubular necrosis, dysfunction of the kidney proximal tubule [11] and electrolyte abnormalities.

As COVID-19 is a recently emerging disease, all of its manifestations or clinical factors related to its evolution are yet known. Our main objective was to discuss the etiology of hyponatremia in SARS-CoV-2 infection and its possible mechanisms.

Syndrome of Inappropriate Antidiuretic Hormone in COVID-19

The Hyponatremia (as defined as plasma sodium < 135 mmol/L) is the most common electrolyte disorder with a prevalence as high as 30% in inpatient settings [12] and is associated with an increased mortality [13]. It is divided into euvolemic, hypovolemic, and hypervolemic hyponatremia, each of which is treated differently [14]. In COVID-19, hyponatremia is common and its etiology is not clear, probably is multifactorial not only be associated with pneumonia but also with the gastrointestinal symptoms of this infection and could appears to be outside the kidneys, as it happens in SIADH [15,16]. The most common cause of hyponatremia is the SIADH, which accounts for up to 40-50% of cases, but the prevalence may be higher in some pathological conditions, such as subarachnoid hemorrhage, traumatic brain injury, and pneumonia. However, it can be assumed that data from other collectives with community-acquired pneumonia or from critically ill patients can be extrapolated [17].

Ata, et al. [18], report a case of a young diabetic patient with diarrhea, abdominal pain and asymptomatic hyponatremia (120 mmol/L) who turned out to be positive for COVID-19. The authors suspected a syndrome of inappropriate antidiuretic hormone secretion (SIADH) to be the most probable cause of the hyponatremia. In this case it is not clear if hyponatremia is only explained by SIADH or if the accumulation of other symptoms, such as diarrhea. In this case the treatment was only directed at SARS-CoV-2. Ravioli, et al. [15], report 2 cases of SIADH in COVID-19 pneumonia, showing a new complication of this emerging infectious disease. Also, Ho KS, et al. [16], report a first case of SARS-CoV-2 induced syndrome of SIADH manifesting as new-onset seizures. They utilized for management: A pro-active DDVAP strategy, 3% hypertonic saline infusion and fluid restriction. The patient demonstrated a radical clinical recovery with resolution and normalization of sodium on day 4 of hospitalization and the authors conclude that it were probably the inflammation cytokine levels (Interleukin-6) itself, that have been contributing directly to the impairment of osmoregulation, thus leading to hyponatremia [19]. Recently, a case series of COVID-19 pneumonia associated with SIADH was published by Yousaf, et al. [20], they described patients diagnosed with COVID-19 and that were found to have acute severe hyponatremia of SIADH after excluding other causes. The authors described that the mechanism of hyponatremia in these patients were multifactorial, including increased interleukin-6 (IL-6) levels stimulating ADH release. In this case series, all patients recovered with fluid restriction.

The association between hyponatremia and IL-6 levels in the COVID-19 infection was recently described by Berni A, et al. [21], to evaluate the clinical impact of hyponatremia and its correlation with IL-6 levels, they retrospectively evaluated data from 52 laboratory-confirmed COVID-19 patients. Among the 52 patients, they excluded those who were pregnant (n = 1) or had, at admission, diarrhea (n = 4), acute renal failure (n = 8) or malignancy (n = 10). Overall, 29 patients were included and divided into two groups: Patients with a serum IL-6 level ≤ 10 pg/mL (n = 12, group 1) and patients with serum IL-6 level > 10 pg/mL (n = 17, group 2). They compared median age, gender, serum sodium concentration ($[Na^+]$), and PaO_2/FiO_2 (P/F) ratio at admission. IL-6 was inversely correlated with $[Na^+]$, whereas $[Na^+]$ was directly correlated with P/F ratio (Pearson's correlation test). The bivariate linear regression analysis showed that IL-6 and $[Na^+]$ were independently related to the P/F ratio (respectively, Beta = -0.45, p = 0.016; Beta = 0.33, p = 0.048). Although the series of cases is limited, they suggest that $[Na^+]$ might represent a readily available biomarker to be considered in the clinical protocols designed for COVID-19 patients. Low $[Na^+]$ appears to be inversely related to IL-6 and directly related to P/F ratio, an important index of respiratory performance. Low $[Na^+]$ appears to be associated with a more unfavorable outcome and it may be hypothesized that $[Na^+]$ decrease indicates the presence of a more advanced disease. $[Na^+]$ is not currently considered among the inclusion criteria for initiating tocilizumab treatment. However, the right timing of administration might be of pivotal importance in determining the effectiveness of tocilizumab and $[Na^+]$ might be of help in decision-making strategies.

It is unclear whether hyponatremia due to SIADH is common in this population. Probably, hyponatremia is a direct consequence of glucocorticoid deficiency caused by insufficient hypothalamic-pituitary stimulation. Furthermore, it may be related to an inappropriate antidiuresis resulting from non-suppressible arginine vasopressin release (despite hypoosmolality) and, probably, to a direct renal water excretion defect, both being consequences of cortisol deficiency, but with an intact renin-angiotensin-aldosterone system [22]. In the vast majority of reported cases, the hyponatremia appeared after a digestive episode and respiratory infection. We do not know if the glucocorticoid decompensation caused by stress has been triggered by this infection [23]. De La Flor, et al. [24], report the case of a patient with severe hyponatremia secondary to pituitary macroadenoma with COVID-19 pneumonia, hardly explained by the emetic episode and /or diuretic treatment with thi-

azides. It is known that hyponatremia occurs in patients with hypopituitarism, but infrequently as first presenting feature of a pituitary tumor in the context of a respiratory infection by COVID-19 [25], which has probably exacerbated its presentation. The association between the hypothalamo-pituitary-adrenal axis and a type of coronavirus (SARS), was first reported by Leow, et al. in 2005 [26]. Sixty-one survivors of SARS were evaluated at 3 months post-recovery and thereafter periodically. Forty percent of patients had evidence of central hypocortisolism, most of them (62.5%) were resolved within a year. The authors had proposed the possibility of a reversible hypophysitis or a direct hypothalamic damage that could have led to a state of hypothalamo-pituitary dysfunction [27]. The association of hyponatremia and COVID-19 infection with endocrine disorders has been described in recent studies, although the possible underlying pathophysiological mechanisms are not known currently, we do not have any such data on cortisol dynamics in patients with COVID-19. Other factors also probably contribute to hyponatremia are the hypothyroidism secondary to thyrotropic, nausea, vomiting and hypoglycemia (related to both ACTH/cortisol and GH/IGF-1 deficiency) since these are non-osmotic stimuli of arginine vasopressin release [28,29].

Conclusions

The relationship between the electrolyte abnormalities and COVID-19 infection is not clear. Hyponatremia is the most common electrolyte disorder in patients with COVID-19, but it is not yet known the mechanism that would cause it entirely understood. It can be caused by systemic inflammation due to non-osmotic stimuli for vasopressin production. Interferon-6 has been associated with the cytokine storm involved in the pathogenesis of severe COVID-19 complications and may play a role in the inappropriately higher secretion of antidiuretic hormone leading to hyponatremia. It is important to emphasize the need for early clinical judgment of volume status to decide between fluid restriction and fluid replacement strategy, because patients with COVID-19 require cautious and conservative fluid resuscitation to avoid pulmonary edema and exacerbating underlying respiratory distress and pulmonary inflammation. The use of serum osmolality, urine osmolality, and urine sodium is crucial to establish a correct diagnosis of hyponatremia. Therefore, it is necessary to carry out comparative studies to elucidate the causality of the hyponatremia, as well as to estimate its real prevalence.

We conclude that COVID-19 can present with symptomatic hyponatremia. This electrolyte disorder is likely multifactorial and can vary among between different patient presentations, we should not only think about SIADH.

Conflict of Interest

The author declares no conflict of interest and no financial support for this study.

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