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Review Article

Hyponatremia in COVID-19 infection: possible causal factors and management

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Abstract

SARS-CoV-2 disease (COVID-19) has dramatically increased since March 2020. There is no 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 described. The management of hyponatremia will continue to be treated according to well established guidelines, and the treatment will depend on the volume status, etiology and tonicity. 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, Management

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 but spread rapidly throughout China. This disease, which the World Health Organization (WHO) denominated coronavirus disease-2019 (COVID-19), spread rapidly throughout China and worldwide [1]. The World Health Organization (WHO) declared COVID-19 a pandemic in March 2020 [2]. SARS-CoV-2 belongs to the family of RNA beta-coronavirus, which include the viruses 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, 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 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 pathologic abnormalities including acute tubular necrosis, dysfunction of the kidney proximal tubule [11] and electrolyte abnormalities.

As COVID-19 is a recently emerging disease, its manifestations or clinical factors related to its evolution are not yet known. Our main objective was to describe the prevalence, main causal factors and management of hyponatremia in patients with COVID-19 pneumonia.

Hyponatremia: Most Frequent Electrolytic Disorder in COVID-19

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]. The presence of hyponatremia has been described in more than 35% of patients with pneumonia, observing a higher mortality in these patients [15]. Furthermore, hypoxemia has been shown to be the leading added risk factor for mortality in hyponatremic patients [16]; for this reason, early diagnosis and treatment are important to improve its prognosis [17].

As an association between COVID-19 and hyponatremia has been shown in the literature and since the main manifestation of these patients is pneumonia, a high frequency of hyponatremia should be suspected [18,19]. However, its prevalence, characteristics, and clinical implications are unknown. Of note, 60% of SARS-CoV-1 patients with watery diarrhea were reported to have mild hyponatremia secondary to virus replication within the intestinal cells [20]. Lippi et al. [21], following an electronic search on MEDLINE (PubMed), Scopus, and Web of Science, using the keywords sodium, potassium, chlorine and calcium in patients with COVID-19 disease, identified five studies with a total of 1,415 patients. Sodium was significantly lower in patients with severe disease compared to patients with mild disease due to COVID-19 (weighted mean difference: -0.91 mmol/L, 95% CI: -1.33–0.5 mmol/L). However, it is not yet known whether there is a greater risk of hyponatremia in patients with COVID-19, nor its the mechanism.

The etiology of hyponatremia is multifactorial and variable among patients with COVID-19. Different reports show that hyponatremia should not only be associated with pneumonia but also with the gastrointestinal symptoms of this infection. Ata et al. [22], 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.

Syndrome of Inappropriate Antidiuretic Hormone in COVID-19

In COVID-19, hyponatremia is common, and its etiology is not clear, probably could appears to be outside the kidneys, as it happens in SIADH [23,24]. 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 [15]. Ravioli et al. [23] reported 2 cases of SIADH in COVID-19 pneumonia, showing a new complication of this emerging infectious disease. Also, Ho KS et al. [24] reported a first case of SARS-CoV-2 induced syndrome of SIADH manifesting as new-onset seizures. The authors utilized for the 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 [25]. Recently, a case series of COVID-19 pneumonia associated with SIADH was published by Yousaf et al. [26]; 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 (cytokine storm) in the COVID-19 infection was recently described by Berni A et al. (27); 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) and patients with serum IL-6 level >10 pg/mL (n=17). 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 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. In addition, they observed a statistically significant improvement in [Na] levels 48 hours after initiation of treatment with tocilizumab, as compared to the control group. 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 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, a direct renal water excretion defect, both being consequences of cortisol deficiency, but with an intact renin-angiotensin-aldosterone system [28]. In most of the 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 [29]. De La Flor et al. [30], 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 thiazides. 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 [31], 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 [32]. 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 [33]. 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 that 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 [34,35].

Management of Hyponatremia with COVID-19 Infection

Currently there is no consensus nor clinical guidelines for the management of hyponatremia in COVID-19. The hyponatremia is most likely multifactorial and not only secondary to SIADH. Other etiologies, as for example gastrointestinal (GI) loss as symptoms of COVID-19 may play and important role in the development of hyponatremia in these patients. The management of hyponatremia will depend on the etiology, tonicity and volume status, according to the recommendations of the current clinical guidelines [14]. 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. In COVID-19 patients with hypotonic hyponatremia and volume depletion due to gastrointestinal fluid loss, including vomiting, diarrhea, poor oral intake or use of diuretic therapy; the use of replacement fluids should be initiated.

Alternatively, if hypotonic hyponatremia is due to SIADH, management with volume restriction, urea, or hypertonic boluses will depend on the severity of the neurological symptoms. In patients with severe hyponatremia complicated by symptoms of cerebral irritation, the guidelines recommend treatment with hypertonic saline to rapidly elevate plasma sodium concentration [14,36].

Conclusions

The relationship between the electrolyte abnormalities, acute kidney injury and multiorgan failure in COVID-19 is unclear. Hyponatremia is the most common electrolyte disorder, but it is not yet known whether there is a greater risk of hyponatremia in patients with COVID-19, nor is 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.

Therefore, it is necessary to carry out comparative studies to elucidate the causality of the hyponatremia, as well as to estimate its real prevalence. However, we must pay more attention to the elderly population who are particularly susceptible due to impaired free water excretion and late recognition of symptoms and consider that COVID-19 infection could have played a role in the severity of the symptoms of hyponatremia.

We conclude that COVID-19 can present with symptomatic hyponatremia. This electrolyte disorder is likely multifactorial and can vary among between different patient presentations. Additional studies are required to explore its response to treatment, morbidity and mortality in COVID-19.

Conflict of Interest

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

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