Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

European Journal of Internal Medicine 103 (2022) 113–114

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Letter to the Editor

Syndrome of inappropriate antidiuresis as a maladaptive stress response shared by coronavirus disease 2019 and other cytokine storm disorders

Dear Editor,

Hyponatremia is the most common electrolyte disorder in clinical medicine and is associated with increased morbidity and mortality. The syndrome of inappropriate antidiuresis (SIAD) is an important cause of hyponatremia and has been linked to a wide variety of etiologies, including inflammatory diseases.

In this letter, we summarize current evidence on hyponatremia in coronavirus disease 2019 (COVID-19) and other cytokine storm disorders, showing that hyponatremia represents a shared feature across these conditions irrespective of pulmonary involvement, possibly as a consequence of a maladaptive, cytokine-driven, stress response.

Arginin vasopressin (AVP) is a peptide produced by the hypothalamus, mainly released in response to hyperosmolality, resulting in the reabsorption of solute-free water (antidiuresis).

The blood sodium level is tightly regulated by several brain areas, namely circumventricular organs, which detect variations of osmolality and engender behavioral (thirstiness) and endocrinological (AVP secretion) responses. Nonetheless, clinically significant hyponatremia may be caused by non-osmotic stimuli, including hypovolemia, pain, and nausea [1]. Notably, compelling laboratory and clinical evidence suggest a critical role of inflammation-related hyponatremia [1]. Indeed, proinflammatory cytokines, mainly IL-6, have been shown to activate the central magnocellular AVP-secreting neurons in the hypothalamus to produce non-osmotic, non-volume-mediated AVP release by the so-called immune-neuroendocrine interplay, that may lead to cytokine-driven SIAD [1].

COVID-19 is characterized predominantly by respiratory symptoms and encompasses a broad spectrum of severities. Severe COVID-19 is associated with cytokine storm, an acute systemic hyperinflammatory condition defined by elevated cytokine levels and secondary organ dysfunction, including acute respiratory distress syndrome and encephalopathy [2,3].

Hyponatremia was frequently reported in hospitalized COVID-19 patients, ranging from 10 to 50% [4]. Although there are limited investigations on the etiopathogenesis of hyponatremia in this population, SIAD has been proposed as a leading mechanism [4]. Increasing severity of hyponatremia was identified as an independent risk factor for in-hospital mortality and the need for invasive mechanical ventilation, as well as encephalopathy [4], a recurrent manifestation of COVID-19-associated cytokine storm [2,3]. Notably, multiple studies have shown a direct correlation between serum IL-6 level and hyponatremia severity in COVID-19, suggesting that hyponatremia may be used as a surrogate marker for the risk of cytokine storm and the need for treatment with interleukin antagonists [4,5].

In addition to COVID-19, the cytokine storm umbrella encompasses several disorders at the intersection of hematology, oncology, rheumatology, and virology. Although the *primum movens* of these conditions differs, there are several shared clinical features and laboratory abnormalities, including hyponatremia [2].

Chimeric antigen receptor T-cell (CAR-T) therapy is a novel treatment for refractory malignancies, whose most common complications are cytokine release syndrome (CRS), a framework model of cytokine storm, and immune effector cell-associated neurotoxicity syndrome (ICANS), a cytokine-mediated neuroinflammatory condition that shares several features with COVID-19-related encephalopathy [3]. Hyponatremia is common in CAR-T therapy recipients (about 60% of patients), where an inverse linear relationship between IL-6 and sodium levels has been demonstrated [6]. Interestingly, lung involvement is typically not observed in these patients, suggesting that cytokine storm is sufficient to cause hyponatremia, irrespective of respiratory distress.

Hemophagocytic lymphohistiocytosis (HLH) is a cytokine storm disorder characterized by fever, cytopenia, hepatosplenomegaly, lymphadenopathy, and abnormal liver functions, usually triggered by an infection in predisposed subjects. Laboratory findings in HLH often include IL-6-related hyponatremia, and SIAD may even represent the first manifestation [7].

Hematopoietic stem cell transplantation (HSCT) is another hematological condition in which elevated proinflammatory cytokines, notably IL-6 and TNF-α, have been implied in the pathophysiology of SIAD. Specifically, these cytokines have been reported to be elevated post HSCT from an HLA-mismatched donor or unrelated donor [7].

Mild encephalopathy with a reversible splenial lesion (MERS) is an infection-associated encephalopathy syndrome that typically occurs following a viral infection [8], including COVID-19. In MERS, elevated serum and CSF IL-6 levels represent a recurrent finding; accordingly, the pathogenesis of MERS is characterized by a cytokine-mediated neuroinflammatory process triggered by the systemic inflammation caused by a viral infection, similarly to COVID-19 and HLH-related encephalopathy [3]. There are reports of many patients with hyponatremia related to MERS, with sodium levels significantly reduced compared with those of patients with mild upper respiratory infections, other types of encephalopathy, and febrile seizures [8]. As systemic and pulmonary involvement in MERS is typically negligible, this syndrome represents a clear example of how a systemic and intracranial cytokine storm may be independently related to hyponatremia.

We acknowledge that during inflammation and, perhaps more importantly, a cytokine storm, several factors other than elevated cytokine levels, particularly hypovolemia, may contribute to AVP release and hyponatremia [1]. A contributing role of kidney injury may also be present, yet hyponatremia is frequently reported in the absence of concomitant renal impairment in cytokine storm disorders, including COVID-19 [4].

https://doi.org/10.1016/j.ejim.2022.05.031
Received 21 April 2022; Received in revised form 19 May 2022; Accepted 27 May 2022
Available online 30 May 2022

Other factors may be implied, such as hypoxic pulmonary vasoconstriction and positive pressure ventilation in COVID-19 and disorders with marked pulmonary involvement.

However, the recurrence of SIAD across cytokine storm disorders, irrespective of lung involvement, and the presence of a correlation between cytokine storm intensity and hyponatremia, argue for a primary pathogenic role of cytokine-driven AVP release in cytokine storm-associated hyponatremia.

The human stress response has evolved to maintain homeostasis under conditions of stress, and the hypothalamic-pituitary-adrenal axis represents a key regulatory pathway of this response [9]. External or interoceptive stressors, including systemic inflammation, are signaled to the hypothalamus by cytokines, which act as potent neuromodulators. Sickness behavior is an innate adaptive stress response orchestrated by the hypothalamus, which leads an individual to display a general disengagement from the environment and decreased motivation to engage in rewarding activities, limiting the exposure to potential threats and the risk of infecting relatives [10]. These evolutionarily conserved changes also include reduced food and, notably, water intake. In this context, inflammation-related AVP release leads to finalistic water retention. Interestingly, AVP circuits in the central nervous system also promote depressive behaviors and passive coping, consistently with the anhedonia characteristic of sickness behavior [9,10]. These coordinated responses reflect immune activation and may become maladaptive and dangerous under particular conditions, similarly to other evolutionary conserved responses meant to restore homeostasis [10]. This has already been proposed for delirium, which represents a framework model of a maladaptive sickness behavioral response following an inflammatory stimulus [10]. Cytokine storm is characterized by a dysregulated immune response to various triggers, leading to a release of more abundant cytokines than expected in an organized, homeostatic response to a stressor [2]. This excessive cytokine release may activate the hypothalamic AVP-secreting neurons to produce a likewise disproportionate non-osmotic, non-volume-mediated AVP release. In this biobehavioral perspective, the excessive water retention leading to hyponatremia in cytokine storm-related SIAD may represent a maladaptive response of the hypothalamic-pituitary-adrenal axis to inflammation. This viewpoint provides deeper insight into the pathophysiology of cytokine-driven SIAD and may be applied to other manifestations associated with cytokine storm.

Concluding, hyponatremia is a common, clinically relevant, yet poorly examined feature of COVID-19 and other cytokine storm disorders, that may develop irrespective of pulmonary involvement. According to the consistently observed direct correlation between serum IL-6 levels and hyponatremia, the excessive cytokine-mediated AVP release likely plays a major pathogenic role and might represent a maladaptive response to the dysregulated immune activation. As the only definitive treatment of SIAD is the elimination of its underlying cause, immunotherapies arguably have a critical role in the management of cytokine storm-associated hyponatremia.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

None of the authors has any conflict of interest to disclose.

References

[1] Swart RM, Hoorn EJ, Betjes MG, Zietse R. Hyponatremia and inflammation: the emerging role of interleukin-6 in osmoregulation. Nephron Physiol 2011;118:45–51.
[2] Fajgenbaum DC, June CH. Cytokine Storm. The New England Journal of Medicine 2020;383:2255–73.
[3] Pensato U, Muccioli L, Cani I, et al. Brain dysfunction in COVID-19 and CAR-T therapy: cytokine storm-associated encephalopathy. Ann Clin Transl Neurol 2021;8(4):968–79. https://doi.org/10.1002/acn3.51348.
[4] Tzoulis P, Grossman AB, Baldeweg SE, Bouloux P, Kaltsas G. Management of endocrine disease: Dysnatraemia in COVID-19: Prevalence, prognostic impact, pathophysiology and management. Eur J Endocrinol 2021;185(4):R103–11. https://doi.org/10.1530/EJE-21-0281.
[5] Ayus JC, Negri AL, Moritz ML, et al. Hyponatremia, Inflammation at Admission, and Mortality in Hospitalized COVID-19 Patients: A Prospective Cohort Study. Front Med (Lausanne) 2021;8:748364.
[6] Dixon BN, Daley RJ, Buie LW, et al. Correlation of IL-6 secretion and hyponatremia with the use of CD19+ chimeric antigen receptor T-cells. Clin Nephrol 2020;93:42–6.
[7] Koumpis E, Florentin M, Hatzimichael E, Liamis G. Hyponatremia in Patients with Hematologic Diseases. J Clin Med 2020;9.
[8] Takanashi J, Tada H, Maeda M, Suzuki M, Terada H, Barkovich AJ. Encephalopathy with a reversible splenial lesion is associated with hyponatremia. Brain Dev 2009;31:217–20.
[9] Beurel E, Nemeroff CB. Interaction of stress, corticotropin-releasing factor, arginine vasopressin and behaviour. Curr Top Behav Neurosci 2014;18:67–80.
[10] Cunningham C, Maclullich AM. At the extreme end of the psychoneuroimmunological spectrum: delirium as a maladaptive sickness behaviour response. Brain Behav Immun 2013;28:1–13.

Lorenzo Muccioli[a,#,*], Umberto Pensato[b,#], Maria Guarino[c], Francesca Bisulli[a,c], Marco Faustini Fustini[c]

[a] *Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy*

[b] *Department of Neurology, IRCCS Humanitas Research Hospital, Milan, Italy*

[c] *IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy*

[*] Corresponding author at: Department of Biomedical and Neuromotor Sciences, University of Bologna, Address: IRCCS Istituto delle Scienze Neurologiche di Bologna, Bellaria Hospital, Via Altura 3, Bologna, Italy.
E-mail address: lorenzo.muccioli@gmail.com (L. Muccioli).

[#] these authors contributed equally to this work.