Review Article

Inflammation and hyponatremia: an underrecognized condition?

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Abstract

Recognizing hyponatremia is important for preventing potential morbidity and mortality and also because it can be an indicator of an underlying disease. The most common cause of euvolemic hyponatremia is the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Recent research has demonstrated that inflammatory cytokines such as interleukin (IL)-1β and IL-6 are involved in the development of hyponatremia, which is associated with inflammatory conditions and is related to ADH secretion. Serum sodium levels are inversely correlated with the percentage of neutrophils, CRP, and NT-proBNP. Additionally, serum IL-6 and IL-1β levels increased in inflammatory diseases and were higher in patients with hyponatremia. Therefore, because hyponatremia is significantly associated with the degree of inflammation in children with inflammatory diseases, hyponatremia could be used diagnostically as a marker of inflammation. Finally, understanding ADH secretion during inflammation, monitoring patient sodium levels, and selecting the appropriate intravenous fluid treatment are important components that can reduce potential morbidity and mortality, particularly for hospitalized patients in critical condition.

Key words: hyponatremia, syndrome of inappropriate antidiuretic hormone secretion, inflammatory cytokines, inflammatory disease, critical patients.
**Introduction**

Hyponatremia is defined by a serum sodium level less than 135 mEq/L and is the most common electrolyte disorder in clinical medicine\(^1\). Hyponatremia can develop from a sodium deficit, but usually results from excessive water consumption leading to solute dilution. Severe hyponatremia (serum sodium, <125 mEq/L) occurs in approximately 3% of all hospitalized patients\(^2\). In addition, if serum sodium rapidly falls to 110-120 mEq/L, it can cause acute cerebral edema and brain herniation\(^1\). Timely diagnosis of hyponatremia is important not only because of the potential for morbidity and mortality but also because it can be an indicator of underlying disease\(^3\).

Approximately one-third of hyponatremic patients have euvolemic hyponatremia, which is most commonly caused by the syndrome of inappropriate antidiuretic hormone secretion (SIADH)\(^4\). In normal physiologic conditions, antidiuretic hormone (ADH, vasopressin) is secreted from the posterior pituitary gland in response to hyperosmolality, termed osmotic ADH secretion, which lowers serum osmolality. Non-osmotic ADH secretion associated with hypovolemia, pain, nausea, and certain drugs can also cause hyponatremia\(^5\). Non-osmotic ADH secretion can be a normal biological response when caused by hypovolemia or a low effective arterial blood volume, but can also be a symptom SIADH\(^6\).

SIADH is characterized by euvolemia and high urinary sodium excretion (natriuresis), and osmolality in the absence of diuretics, pituitary insufficiency, adrenal or renal dysfunctions, thyroid disorders or edema\(^6\). ADH binds to the vasopressin-2 receptor in the renal collecting duct and stimulates a cyclic AMP-dependent cascade, which leads to preformed aquaporin-2 water channel insertion into the apical plasma membrane\(^7\) and the transcellular movement of water.

**Inflammation and hyponatremia: pathophysiologic mechanisms**
Various inflammatory diseases including pneumonia, severe acute respiratory distress syndrome, tuberculosis, meningitis, encephalitis, human immunodeficiency virus infections and malaria are associated with the development of hyponatremia\(^5\). However, the pathophysiology of hyponatremia with these conditions remains elusive.

Recent research has demonstrated that inflammatory cytokines, such as interleukin (IL)-1\(\beta\) and IL-6, are involved in the development of hyponatremia and associated with inflammatory conditions by ADH secretion\(^4,8,9\)\(^\)\(^\). Landgraf et al. reported that IL-1\(\beta\) stimulated both central and peripheral release of vasopressin in rats\(^10\). In addition, Palin et al. revealed that lipopolysaccharide (LPS) treatment in male Wistar rats decreased diuresis and increased plasma arginin-vasopressin (AVP) as well as AVP neuron activity, and that a brain injection of IL-6 increased AVP neuron activity in a similar manner as peripheral LPS treatment\(^11\). In contrast, Palin et al. also demonstrated that a brain injection of anti-IL-6 antibodies prevented LPS-induced AVP neuron activation. Therefore, they suggested that brain IL-6 induces the early activation of AVP neurons in response to an LPS injection\(^11\). Most notably, Mastorakos et al. demonstrated that AVP levels were elevated 2 h after an IL-6 injection in all six of the patients in the study, which suggested that IL-6 activated the magnocellular AVP-secreting neurons and that it could be involved in inappropriate AVP secretion syndrome\(^12\).

Furthermore, studies demonstrated that endothelial cells, smooth muscle cells, and blood brain barrier (BBB) pericytes secrete IL-6 in response to IL-1\(\beta\) and LPS\(^13,14\), and circulating IL-6 can also be transported across the BBB or can simply diffuse across the BBB in the circumventricular organs\(^5\). These mechanisms all suggest that inflammatory cytokines could cause ADH secretion.

**Inflammation and hyponatremia: clinical conditions**

A few reports have demonstrated that hyponatremia is associated with various
inflammatory conditions \(^8,15-19\); most frequently, meningitis has been identified as a cause of SIADH\(^{16}\). Patwari et al. reported that SIADH was diagnosed in 22 (36.7\%) of 60 cases with bacterial meningitis on admission and found a significant correlation between SIADH with severe meningeal inflammation\(^{16}\). Although there are currently no reports that address the possible interactions between SIADH and meningitis, we speculate that increased inflammatory cytokines such as IL-1 \(\beta\) or IL-6 might cause hyponatremia by increasing ADH secretion.

Riikonen et al. showed that high C-reactive protein (CRP) levels were associated with low serum sodium concentration and that these levels were early indicators of bacteremia in neutropenic children\(^{17}\). Ohta and Ito also reported four cases of hyponatremia due to SIADH, which appeared to be related to inflammation\(^8\). They demonstrated that both the plasma AVP and IL-6 concentrations increased in patients, and their experiments showed that intravenous administrations of IL-1\(\beta\) increased AVP and urinary sodium excretion, which suggested that IL-1\(\beta\) might play an important role in the development of SIADH which is associated with inflammation\(^8\).

Watanabe et al. reported that coronary artery lesions and increased serum CRP levels were significantly more common in patients with Kawasaki disease and hyponatremia and suggested that hyponatremia in Kawasaki disease occurs in patients that exhibit severe inflammation\(^{18}\). However, their study did not elucidate the pathogenic mechanisms, and the results of this review suggest that IL-1\(\beta\) and IL-6 are involved in the hyponatremia pathogenesis that is associated with SIADH in Kawasaki disease\(^{19}\).

Recently, Lim et al. performed a study that supports our hypothesis about the effects of inflammation in Kawasaki disease\(^{15}\). Lim et al. found that serum sodium concentrations were inversely correlated with the percentage of neutrophils, CRP, and NT-proBNP. In addition, increased serum IL-6 and IL-1\(\beta\) levels in patients with Kawasaki disease were higher in
patients with hyponatremia\textsuperscript{15).} They also showed that plasma ADH levels increased in patients with SIADH, which were positively correlated with IL-6 and IL-1\(\beta\) levels, suggesting that increased IL-6 and IL-1\(\beta\) may activate ADH secretion, leading to SIADH and hyponatremia in Kawasaki disease\textsuperscript{15).}

Recently, we applied this hypothesis to a febrile urinary tract infection (UTI) model and determined that hyponatremia was associated with renal cortical defects. The study used 99m-Technetium-dimercaptosuccinic acid scintigraphy and measured the serum sodium concentration which indicated that serum sodium concentration was negatively correlated with the white blood cell count \((r=-0.156, P=0.011)\) and CRP levels \((r=-0.160, P=0.028)\), which indicated that hyponatremia may be a substantial inflammatory marker and is significantly associated with the degree of inflammation in children with febrile urinary tract (UTI) infections\textsuperscript{20).} Although hyponatremia in febrile UTI can occur in association with other underlying disorders such as pseudohypoaldosteronism (renal tubular unresponsiveness to aldosterone), proximal tubular dysfunction, and increased levels of serum atrial and brain natriuretic peptide, SIADH is also considered to lead hyponatremia in the condition of more severe inflammation by reducing the expression and inhibiting the function of the apical epithelial sodium channel and/or sodium potassium adenosine triphosphatase at the basolateral membrane of renal epithelial cells through inflammatory cytokines such as IL-1\(\beta\) and tumor necrosis factor\textsuperscript{20).}

Therefore, it is suggested that patients who may be producing ADH due to acute inflammatory diseases or subtle volume depletion may be more safely treated with fluids that have a higher sodium concentration, with a decrease in fluid rate, or with a combination of these strategies\textsuperscript{21, 22)\). Patients who are at risk for producing persistent ADH (SIADH) should receive less than maintenance fluid to avoid hyponatremia. Patients with possible subtle volume depletion should receive 20 mL/kg (maximum of 1 L) of isotonic fluid (normal saline
or Ringer lactate) over 1-2 hr to restore their intravascular volume\textsuperscript{23}). The patient can then be switched to Dextrose 5% half-normal saline (0.45\% NaCl) + 20 mEq/L KCl for a standard maintenance fluid regimen instead of routinely receiving fluids with 0.2\% NaCl\textsuperscript{23}).

**Conclusions**

In conclusion, there is an increasing amount of data that indicates that inflammatory cytokines such as IL-1\(\beta\) and IL-6 have an important role in the non-osmotic release of ADH. Additionally, this mechanism may be involved in the development of hyponatremia, which can be associated with numerous inflammatory conditions. Understanding the physiological mechanisms of antidiuresis during inflammation as well as monitoring patient sodium levels, and selecting the appropriate intravenous fluid regimen and infusion rate will be important aspects of patient care in the future.
References


