

## Review article

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# Inflammation and hyponatremia: an underrecognized condition?

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Timely diagnosis of hyponatremia is important for preventing potential morbidity and mortality as it is often an indicator of underlying disease. The most common cause of euvolemic hyponatremia is the syndrome of inappropriate antidiuretic hormone (SIADH) secretion. Recent studies have demonstrated that proinflammatory cytokines such as interleukin (IL) 1 $\beta$  and IL-6 are involved in the development of hyponatremia, a condition that is associated with severe inflammation and is related to antidiuretic hormone (ADH) secretion. Serum sodium levels in hyponatremia are inversely correlated with the percentage of neutrophils, C-reactive protein, and N-terminal-pro brain type natriuretic peptide. Additionally, elevated levels of serum IL-6 and IL-1 $\beta$  are found in inflammatory diseases, and their levels are higher in patients with hyponatremia. Because it is significantly correlated with the degree of inflammation in children, hyponatremia could be used as a diagnostic marker of pediatric inflammatory diseases. Based on available evidence, we hypothesize that hyponatremia may be associated with inflammatory diseases in general. Understanding the mechanisms responsible for augmented ADH secretion during inflammation, monitoring patient sodium levels, and selecting the appropriate intravenous fluid treatment are important components that may lower the morbidity and mortality of patients in a critical condition.

**Key words:** Hyponatremia, Inappropriate ADH Syndrome, Cytokines, Inflammatory disease, Critical condition

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## Introduction

Hyponatremia, characterized by a serum sodium level that is less than 135 mEq/L, is one of the most commonly diagnosed electrolyte disorders in clinical medicine<sup>1</sup>. Although sodium deficiency leads to hyponatremia, this condition is more commonly caused by solute dilution resulting from excessive consumption of water. Severe hyponatremia, where serum sodium level falls below <125 mEq/L, occurs in approximately 3% of all hospitalized patients<sup>2</sup>. Additionally, a rapid drop in serum sodium levels to 110–120 mEq/L leads to cerebral edema and brain herniation<sup>1</sup>. Since it is often an indicator of underlying disease, timely diagnosis of hyponatremia is of great importance in preventing potential morbidity and mortality<sup>3</sup>.

Approximately one-third of all hyponatremic patients are diagnosed with euvolemic hyponatremia, a condition commonly caused by the syndrome of inappropriate antidiuretic hormone secretion (SIADH)<sup>4</sup>. Under normal physiological conditions, antidiuretic hormone (ADH; also known as vasopressin) is secreted from the posterior pituitary gland in response to hyperosmolality in a process called osmotic ADH secretion. Osmotic ADH secretion leads to lowering of serum osmolality. Nonosmotic ADH secretion, associated with hypovolemia, pain, nausea, and use of certain drugs, also leads to hyponatremia<sup>5</sup>.

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Although nonosmotic ADH secretion can be a normal biological response when caused by hypovolemia or low effective arterial blood volume, it can also be a symptom of SIADH<sup>3</sup>.

SIADH is characterized by euvolemia, high urinary sodium excretion (natriuresis), and elevated urine osmolality in the absence of diuretics. This syndrome is often associated with pituitary insufficiency, adrenal or renal dysfunctions, thyroid disorders, and edema<sup>3</sup>. ADH binds to the vasopressin-2 receptors in the renal collecting duct and stimulates a cyclic adenosine monophosphate–signaling cascade that leads to the insertion of preformed aquaporin-2 water channels into the apical plasma membrane, thereby resulting in the transcellular movement of water<sup>6</sup>.

### Inflammation and hyponatremia: pathophysiological mechanisms

The development of hyponatremia is associated with various inflammatory diseases including pneumonia, severe acute respiratory distress syndrome, tuberculosis, meningitis, encephalitis, human immunodeficiency virus infection, and malaria<sup>5</sup>. However, the pathophysiology of hyponatremia diagnosed under these inflammatory conditions remains elusive.

Recent research revealed that inflammatory cytokines such as IL-1 $\beta$  and IL-6 are involved in the development of hyponatremia associated with inflammatory conditions, and that this process is related to ADH secretion<sup>5,7,8</sup>. Landgraf et al.<sup>9</sup> reported that IL-1 $\beta$  stimulated both central and peripheral release of vasopressin in rats. In addition, Palin et al.<sup>10</sup> reported that treatment of Wistar rats with lipopolysaccharide (LPS) resulted in reduced diuresis, elevated plasma arginine-vasopressin (AVP) levels, and an increase in the activity of AVP neurons. These authors also reported that a brain injection of IL-6 increased the activity of AVP neurons in a manner similar to that observed after peripheral LPS treatment. Accordingly, a brain injection of anti-IL-6 antibodies prevented the LPS-induced activation of AVP neurons. Therefore, these authors suggested that IL-6 induces an early activation of AVP neurons in response to a LPS injection<sup>10</sup>. Most notably, Mastorakos et al.<sup>11</sup> demonstrated that AVP levels were elevated 2 hours after IL-6 injection in all the six patients studied, suggesting that IL-6 activated the magno-cellular AVP-secreting neurons and that it may be involved in the development of an inappropriate AVP secretion syndrome.

Endothelial cells, smooth muscle cells, and blood brain barrier (BBB) pericytes secrete IL-6 in response to IL-1 $\beta$  and LPS stimulation<sup>12,13</sup>. Circulating IL-6 can be transported across the BBB or may simply diffuse across the BBB in the circumventricular organs<sup>5</sup>. Taken together, these findings suggest that inflammatory cytokines may regulate ADH secretion.

### Inflammation and hyponatremia: clinical conditions

A number of studies have demonstrated that hyponatremia is associated with various inflammatory conditions<sup>7,14–18</sup>. Very frequently, meningitis has been identified to be a cause of SIADH<sup>15</sup>. Patwari et al.<sup>15</sup> reported that SIADH was diagnosed in 22 of 60 patients (36.7%) with bacterial meningitis on admission, and found that SIADH is significantly correlated with the severity of meningeal inflammation. Although there are no reports that address the possible mechanisms underlying the relationship between SIADH and meningitis, we speculate that elevated levels of inflammatory cytokines such as IL-1 $\beta$  or IL-6, as observed in this disease, may lead to hyponatremia by augmenting ADH secretion.

Riikonen et al.<sup>16</sup> showed that high C-reactive protein (CRP) levels were associated with low serum sodium concentrations and that an elevation in CRP levels is an early indicator of bacteremia in neutropenic children. Ohta and Ito<sup>7</sup> also reported four cases of hyponatremia arising from SIADH that appeared to be related to inflammation. These authors reported the presence of increased concentrations of AVP and IL-6 in patients, and found that intravenous administration of IL-1 $\beta$  increased AVP and urinary sodium excretion. Therefore, IL-1 $\beta$  may have a significant role in the development of SIADH and hyponatremia associated with inflammation<sup>7</sup>.

Watanabe et al.<sup>17</sup> reported that coronary artery lesions and increased serum CRP levels were significantly more common in patients diagnosed with both Kawasaki disease and hyponatremia. In the light of their findings, these authors suggested that hyponatremia occurs in Kawasaki disease patients having severe inflammation. The precise mechanisms leading to hyponatremia in Kawasaki disease is not known. We hypothesize that IL-1 $\beta$  and IL-6 are involved in the development of hyponatremia that is associated with SIADH in Kawasaki disease<sup>18</sup>.

Recently, Lim et al.<sup>14</sup> conducted a study that supported our hypothesis regarding the consequences of inflammation in Kawasaki disease patients. These authors found that the serum sodium concentrations were inversely correlated with the percentage of neutrophils, CRP, and N-terminal-pro brain type natriuretic peptide levels. Additionally, serum IL-6 and IL-1 $\beta$  levels were higher in a section of Kawasaki disease patients who were also diagnosed with hyponatremia<sup>14</sup>. Increased levels of plasma ADH are found in Kawasaki disease patients diagnosed with SIADH<sup>14</sup>. Further, the increase in ADH concentrations positively correlated with the levels of IL-6 and IL-1 $\beta$ , suggesting that these cytokines may augment ADH secretion, leading to SIADH and hyponatremia in Kawasaki disease<sup>14</sup>.

Recently, we extended this hypothesis to a febrile urinary tract infection (UTI) model, and identified that hyponatremia was associated with renal cortical defects. Using 99m-Techne-

dimercaptosuccinic acid scintigraphy, we determined the serum sodium concentrations. The results showed that serum sodium concentration was negatively correlated with the white blood cell count ( $r=-0.156$ ,  $P=0.011$ ) and CRP levels ( $r=-0.160$ ,  $P=0.028$ ). Our results showed that hyponatremia is significantly correlated with the degree of inflammation in children with febrile UTIs<sup>19</sup>. Based on our findings, we suggest that hyponatremia may be a potential marker of severe inflammation in general<sup>19</sup>. Hyponatremia in febrile UTI can occur in association with other underlying disorders including pseudohypoaldosteronism (renal tubular unresponsiveness to aldosterone) and proximal tubular dysfunction<sup>19</sup>. SIADH also leads to hyponatremia under conditions 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 via the action of proinflammatory cytokines such as IL-1 $\beta$  and tumor necrosis factor- $\alpha$ <sup>19</sup>.

It was suggested that patients who may be producing ADH due to acute inflammatory diseases or subtle volume depletion may be more safely treated by administering fluids that contain higher concentrations of sodium, by a decrease in fluid rate, or by employing a combination of these strategies<sup>20,21</sup>. It was also suggested that patients who are at risk for producing persistent ADH (SIADH) should receive smaller quantities of maintenance fluid to avoid hyponatremia. Patients with possible subtle volume depletion may receive 20 mL/kg (maximum of 1 L) of isotonic fluid (normal saline or Ringer lactate) over 1–2 hours to restore their intravascular volume<sup>22</sup>. The patient can then be switched to a 5% Dextrose solution in half-normal saline (0.45% NaCl)+20 mEq/L KCl as a standard maintenance fluid regimen, rather than routinely receiving fluids with 0.2% NaCl<sup>22</sup>.

## Conclusions

In conclusion, available data indicate that inflammatory cytokines such as IL-1 $\beta$  and IL-6 have an important role in the nonosmotic release of ADH. Under inflammatory conditions, this mechanism may be responsible for the development of hyponatremia. Understanding the physiological mechanisms of ADH release and antidiuresis during inflammation, monitoring patient sodium levels, and selecting the appropriate intravenous fluid regimen with a suitable infusion rate will all be important aspects of future patient care.

## Conflict of interest

No potential conflict of interest relevant to this article was reported.

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