

RESEARCH ARTICLE

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Hyponatremia and anti-diuretic hormone in Legionnaires' disease

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for the ProHOSP Study Group

Abstract

Background: Medical textbooks often list Legionnaires' disease as a differential diagnosis of the syndrome of inappropriate secretion of anti-diuretic hormone (ADH) (SIADH), but evidence supporting this association is largely lacking. We tested the hypothesis whether hyponatremia in patients with Legionnaires' disease would be caused by increased CT-ProVasopressin.

Methods: We measured CT-ProVasopressin and sodium levels in a prospective cohort of 873 pneumonia patients from a previous multicentre study with 27 patients having positive antigen tests for *Legionella pneumophila*.

Results: Patients with Legionnaires' disease more frequently had low sodium levels ($\text{Na} < 130 \text{ mmol/L}$) (44.4% vs. 8.2%, $p < 0.01$), but similar mean CT-ProVasopressin levels (pmol/l) (39.4 [± 7] vs 51.2 [± 2.7], $p = 0.43$) as compared to patients with pneumonia of other etiologies. In patients with Legionnaires' disease, CT-ProVasopressin levels showed a positive correlation with sodium ($r = 0.42$, $p < 0.05$). Independent of pneumonia etiology, CT-ProVasopressin correlated significantly with the pneumonia severity index ($r = 0.56$, $p < 0.05$), ICU admission (adjusted odds ratio per decile, 95% CI) (1.6, 1.2 - 2.0), and 30-day-mortality (1.8, 1.3 - 2.4).

Conclusion: While Legionnaires' disease was associated with hyponatremia, no concurrent increase in CT-ProVasopressin levels was found, which argues against elevated ADH levels as the causal pathway to hyponatremia. Rather, Vasopressin precursors were upregulated as response to stress in severe disease, which seems to overrule the osmoregulatory regulation of ADH.

Keywords: SIADH, *Legionella*, Hyponatremia, Low sodium levels, Community-acquired pneumonia

Background

Low sodium levels are a common feature of patients with community-acquired pneumonia (CAP), particularly if caused by *Legionella pneumophila* [1-4]. In a retrospective study comparing clinical features of CAP caused by *Legionella* with CAP of other aetiology, low sodium levels ($< 131 \text{ mmol/L}$) were present in 46% of patients with Legionnaires' disease as compared to only 14% in patients with CAP of other aetiology [3]. Yet, the pathophysiological mechanisms underlying this sodium imbalance remain unclear and evidence from controlled studies is largely lacking. Previous smaller studies found evidence for dysregulation of anti-diuretic hormone (ADH)

causing the syndrome of inappropriate secretion of ADH (SIADH) in patients with tuberculosis. This was evidenced by detectable circulating levels of ADH despite low sodium levels in patients [5,6]. More recent reports linked inflammation to low blood sodium levels through an immuno-neuroendocrine pathway with non-osmotic release of vasopressin by interleukin (IL)-6 and other cytokines (reviewed in [7]). Other studies again found that changes in arterial P_aCO_2 and oxygenation stimulated hormone release from the posterior and anterior pituitary gland resulting in sodium disturbances [8]. Finally, a direct renal involvement in patients with Legionnaires' disease causing renal salt wasting has been postulated [9].

Correctly diagnosing the underlying cause of low sodium levels has important therapeutic consequences. Whereas patients with sepsis clearly benefit from early fluid resuscitation [10], free water restriction is recommended in

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