Hyponatremia in children with pneumonia rarely means SIADH

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Abstract

Background: Hyponatremia (HN) < 135 mmol/L is a frequent finding in children with community-acquired pneumonia (CAP). We aimed to determine the proportion of syndrome of inappropriate antidiuretic hormone secretion (SIADH) among patients with CAP and HN. Moreover, we wished to investigate the relationship between HN and inflammatory markers, bacterial etiology and prognosis in hospitalized children with CAP.

Methods: We carried out a prospective, observational, multicentre, prospective cohort study. Eligible participants were children from 1 month to 17 years old hospitalized due to CAP from 2012 to 2015.

Results: A total of 150 children were analyzed. Forty-five (30%) patients had serum sodium levels of less than 135 mmol/L. Patients with HN had significantly higher concentrations of inflammatory biomarkers. They also had significantly lower osmolality and urine sodium. They also had longer hospitalizations and more days of fever. Only 16 out of the 45 (35%) patients with HN had confirmed calculated plasma osmolality (<275 mOsm/kg). Only 5 out of 37 (13%) patients with available measurements of plasma osmolality and urine sodium fulfilled the criteria for SIADH. Among the 16 patients with HN and hypo-osmolality, 15 had a fractional sodium excretion (EFNa) levels of less than 1%. We found a significant inverse linear correlation between serum sodium and C-reactive protein, as well as serum sodium and procalcitonin. We found a significant direct correlation between serum sodium and urine sodium.

Conclusion: HN is a common finding in hospitalized children with CAP. True SIADH is a rare event. HN has a good correlation with inflammatory biomarkers.

Keywords: Antidiuretic hormone; Children; Community-acquired pneumonia; Hyponatremia; SIADH; Vasopressin.
associated with high urinary sodium (>40 mMol/L) is usually associated with an excess of antidiuretic hormone.

A few series of cases of children with CAP have attributed HN to syndrome of inappropriate antidiuretic hormone secretion (SIADH) (2–4). SIADH is a syndrome characterized by euvolemic HN, with inadequate urinary secretion of sodium, high urine sodium concentrations and high fractional secretion of sodium. The pathophysiology of HN in several patients with CAP remains elusive (5).

HN is observed in other febrile and acute inflammatory diseases, suggesting a relationship between HN and inflammation (6–8). Inflammatory markers found in children with bacterial diseases as bacterial CAP include C-reactive protein and procalcitonin.

The aim of this study was to determine the proportion of SIADH among patients with CAP and HN. We also investigated the relationship between HN and inflammatory markers, bacterial etiology and prognosis in hospitalized children with CAP.

METHODS

Study design

This observational, multicentre, prospective cohort study was conducted at two centres in Madrid, Spain, from February, 2012, to March, 2015. This study is nested in a broader research by the name of Etiology of Pediatric Community-Acquired Pneumonia (PCAPE), approved by the Ethics Committee of Hospital Universitario Ramón y Cajal. Informed consent was obtained from the guardians of all children.

Collection of data

The main researchers from each centre recorded and collected the study data. Two authors, EO and AT, analyzed the data in this study. We ensured patient confidentiality by employing a codification system.

Participants

Eligible participants were 1-month-old to 17-year-old children hospitalized due to CAP in Hospital Universitario Ramón y Cajal, from April 2012, to March 2015, and Hospital Universitario Infanta Sofía, from February 2014, to March 2015. CAP was defined as fever and an infiltrate in the chest x-ray. Pneumonia was identified by the attending physician and confirmed after recruitment by one blinded, senior radiologist. Exclusion criteria from the study were the following: immunosuppressive conditions, chronic cardio-pulmonary disease (except asthma), hospitalization 30 days before admission, tuberculosis, malignancy, suspected foreign body aspiration, renal, thyroidal, adrenal insufficiency, and patients with medication that could alter sodium levels (except for prednisolone for asthma exacerbations).

Criteria for hospitalization were the following: infants less than 6 months old, poor feeding, clinical dehydration evaluated by the attending physician, electrolyte disturbance, respiratory or hemodynamic instability, SatO₂ ≤ 92% with FiO₂=0.21, altered state of consciousness, apnea, pulmonary complication (necrosis, abscess and significant pleural effusion), multifocal consolidation, failure of oral antimicrobials after 48 hours, or poor adherence to treatment.

HN was defined as serum sodium <135 mmol/L. Essential criteria for SIADH were plasma osmolality <275 mOsm/kg, urine sodium >40 mMol/L and clinical euvoilemic without edema or dehydration (9). Dehydration was evaluated attending skin turgor, urinary output, tears and mouth saliva. Additional criteria were urinary osmolality >100 mOsm/kg and fractional sodium excretion (FENa) >1%.

Laboratory methods

We measured serum sodium at admission, before administration of any intravenous solution. We used an indirect potentiometry method with Integrated Multisensor QuikLYTE (Dade Behring, Deerfield, IL, USA). Serum osmolality was calculated from the equation: Corrected Sodium = Serum Sodium + [(total proteins [mg/L]×10)-8 × 0.025] (10).

An extensive microbiological work-up was performed to determine etiology. Blood was cultured using the BacT/ALERT® 3D blood culture system (bioMérieux, Marcy L’Etoile, France) or BacTec® 9240 blood culture system (Becton, Dickinson and Company, USA). Streptococcus pneumoniae antigen in pleural fluid (BinaxNow) was added if thoracentesis was performed. Pleural fluid was cultured by standard methods. PCR for S pneumoniae was carried out in blood. PCR multiplex was performed in nasopharyngeal aspirate for 16 viruses. These viruses were respiratory syncytial virus (RSV), human metapneumovirus (hMPV), parainfluenzae (PIV; 1, 2, 3 and 4), influenza (A and B), human bocavirus (hBoV), adenovirus (ADV), enterovirus (EV), human rhinovirus (hRV), and coronavirus (CoV; 229E, OC43, NL63 y HKU12). PCR was carried out for M pneumoniae and C pneumoniae in nasopharyngeal aspirate. Serology for M pneumoniae, C pneumoniae and L pneumophila was performed throughout enzyme immunoassay.

Definition of etiological agent

We determined that the detected microorganism was the causal etiology of CAP, with a high probability in the following cases: bacterial growth in blood culture or pleural fluid, S pneumoniae antigen in pleural fluid, positive PCR in blood, a fourfold increase in the IgG serology in serial samples, positive PCR in nasopharyngeal exudate for atypical bacteria, and positive PCR in nasopharyngeal exudate for RSV, hMPV, influenza A and B and PIV.
Data collection and variables
We collected data starting from July 2015. We examined the patients’ medical records, and data were gathered into a confidential database. Basal features, laboratory values and immunization data were recorded. The principal investigator and biostatistician handled the database exclusively.

The primary endpoint was HN, defined as serum sodium <135 mmol/L. We studied the following potential predictors as independent variables: C-reactive protein (CRP), procalcitonin (PCT), white blood cell (WBC) count (× 10⁹/L), neutrophils (× 10⁹/L), lobar pneumonia, typical bacterial etiology (S pneumoniae, S aureus, S pyogenes, Haemophilus), pneumococcal etiology, days of admission, days of oxygen, days of antibiotic therapy, age, days of fever before admission, vomiting, clinically evaluated dehydration, severity of pneumonia according to WHO classification, chest x-ray pattern (consolidation end-point according to WHO classification), urea, serum sodium, urinary sodium and fraction of sodium excretion. We studied the following outcomes: complicated pneumonia, total days of fever, Paediatric Intensive Care Unit (PICU) admission, days of oxygen, high flow oxygen therapy, mechanical ventilation, severe acute respiratory syndrome (SARS), total days of antibiotics and days of hospitalization.

Statistical analysis
Categorical variables are presented with (both absolute and relative) frequency distributions. A descriptive analysis of the sample was performed. The continuous variables are expressed as the mean ± standard deviation (SD) or the median and interquartile range (IQR: Q1 to Q3) according to the Kolmogorov-Smirnov normality test. In order to compare the categorical variables, we employed a χ² test or Fisher’s exact test if there were ≤5 items of data in 20% of cells. Continuous variables were analyzed using the parametric Student’s t-test, or the non-parametric Mann–Whitney U test. All statistical tests were two-tailed. All P-values less than 0.05 were considered significant. Odds ratio (OR) with a 95% CI was used to assess association of HN with features considered as secondary variables.

Spearman’s test was performed in order to study the linear correlations. Simple regression analyses were developed, provided that the assumptions of simple linear regression were verified using graphics of residuals. Outliers were reported and included in the analyses. Goodness of fit was determined with the correlation coefficient, 95% CI and P-value, the coefficient of determination (r²) and P-value, and the residual and outlier assessment, the standard deviation of the residuals (Sy.x).

To predict the occurrence of HN, we performed a univariate and a multivariate, conditional logistic regression analysis model. We included all variables associated with an increased likelihood of HN in the univariate analysis. A significance level of 0.1 was used. An intro, simultaneous regression model was built, and then checked with forward and backward models. Explanatory variables were assessed for interaction and co-linearity, and goodness of fit was calculated. The statistical analysis was performed with SPSS 19.1 (SAS Institute, IBM Inc, USA).

RESULTS
A total of 240 eligible children were admitted to the hospital during the study period, and 169 of these children were recruited for the study. In the end, a total of 150 children were analyzed (Figure 1). Median levels of serum sodium were 136 (IQR: 134 to 138) mmol/L, median plasma osmolality was 281 (IQR: 279 to 285) mOsm/kg, median CRP was 59 (IQR: 30 to 151) mg/L and median PCT was 0.32 (IQR: 0.11 to 1.82) ng/mL.

A total of 45 (30%) of 150 patients had HN with serum sodium <135 mmol/L. Among them, 5 (3%) of 150 patients had serum sodium <130 mmol/L. No patient had symptoms attributable to HN.

Features of children with and without HN can be found in Table 1. Patients with HN showed significantly higher levels of CRP, PCT, WBC and neutrophils and significantly lower levels of plasma osmolality and urine sodium. They had a significantly worse outcome, longer hospitalization and more days of fever. Moderate to severe HN (<130 mmol/L) was associated with typical bacteria (P<0.001, OR 25 [95% CI 3.5 to 184]).

Of the 45 patients with serum sodium levels <135 mmol/L, we wanted to determine the number of patients who had true, hypo-osmolar HN. We excluded 10 patients who lacked serum proteins data. Of the remaining 35 patients with HN, we corrected for hyperglycemia and protein levels, and only 22 (62%) of these 35 patients had true HN. Thirteen patients (29% of the initial 45 patients with HN) had true, hypo-osmolar HN (Figure 1, flowchart).

Eventually, only 5 (11%) out of 45 patients fulfilled criteria for SIADH, among those with plasma osmolality data. Three patients with HN and hypo-osmolality had urine sodium <40 mmol/L, but had a urine osmolality of >100 mOsm/kg. Consequently, they were not classified as SIADH. Features of patients with probable or confirmed SIADH are depicted in Table 2. No significant differences were found in terms of hospitalization, compared with the rest of patients with HN (data available on request).

In regards to urine sodium, 15 out of 16 patients with HN and hypo-osmolality had excretion fraction of sodium (EFNa) less than 1%. A total of 19 (51%) out of 37 patients with HN and available measurements of urine sodium had urine sodium <20 mmol/L. We did not find significant differences in age (P=0.66), hemoglobin (P=1), creatinine (P=0.64), temperature (P=0.75), respiratory rate (P=0.54), days of fever (P=0.75) or urea (P=0.87) between patients with urine sodium levels <20 mmol/L and patients with urine sodium levels >20 mmol/L.

We found a significant, negative, linear correlation between serum sodium (after correcting protein levels) and CRP (P<0.001, Spearman r=−0.48, 95% CI: −0.61 to −0.32. We also
found a negative linear correlation between serum sodium and PCT (P<0.001, Spearman r=−0.53, 95% CI: −0.66 to −0.37). The Spearman rho for the linear correlation between CRP and PCT is 0.56 (95% CI: 0.40 to 0.69, P<0.001), between CRP and WBC is 0.32 (95% CI: 0.17 to 0.47, P<0.001) and between CRP and neutrophils is 0.38 (95% CI: 0.21 to 0.52, P<0.001).

We also found a significant linear correlation between urine sodium and serum sodium (P<0.01, Spearman r=0.3, 95% CI: 0.13 to 0.46).

CRP and PCT tend to increase as serum sodium decreases (Figures 2 and 3). Urine sodium tends to decrease as serum sodium decreases (Figure 4). The correlation of determination and p values

Figure 1. Flowchart of the study. Only 5 out of 150 (3%) patients with community acquired pneumonia (CAP) had probable or possible syndrome of inappropriate antidiuretic hormone secretion.
are shown in the figures. In the conditional, multivariate logistic regression model, only gender (being male) and CRP > 100 mg/L remained as independent, significant risk factors for HN (Table 3).

**DISCUSSION**

In this study, HN at admission was closely related to inflammatory markers, hospitalization and fever, but rarely with true SIADH. Children admitted with CAP have a tendency for renal sodium avidity.

A significant number of patients with HN had pseudohyponatremia, with normal osmolality. When the laboratory uses indirect potentiometry, it is necessary to correct protein levels. For clinical conditions such as hyperproteinemia, in which the water content of plasma is decreased, indirect potentiometric
techniques may give values lower than a technique that does not involve fixed-volume aliquots (direct potentiometry) (11). Inflammation can be one of these situations.

Low levels of urine sodium (<20 to 40 mmol/L, or FENa <1%) suggest a nonrenal cause of HN. Low urine sodium levels also involve an appropriate compensating mechanism through the activation of the renin-angiotensin-aldosterone system. This is the normal response to hypo-osmolar HN with extracellular fluid depletion. Some of our patients with HN and urine sodium <20 mmol/L may have had sodium loss and volume depletion through vomiting. Most patients with HN and hypo-osmolality had low urine sodium and FENa <1%, which is at odds with SIADH. Volume depletion in our hyponatremic patients seemed to be mild, and was not reflected in laboratory values, in agreement with other reports (2).

Vomiting is a well-known cause of vasopressin release, along with pain and stress (12). Also, there is increasing evidence that IL-6 and ADH release are related. ADH has been shown to be released after injection of lipopolysaccharides, IL-1B and IL-6 (12–14). HN and high levels of ADH have been found in other entities with significant inflammation (6).

Inflammation seems clearly associated with HN (15,16). We confirm this association and provide a quantification of the linear correlation between corrected sodium levels, CRP and PCT. We found a negative, linear correlation between serum sodium levels at admission and inflammatory markers in children hospitalized with CAP. Serum sodium decreased significantly with increasing levels of markers of inflammation. The multiple logistic regression analysis demonstrates the strength of the relationship between HN and CRP. However, the models

### Table 2. Features of the five hyponatremic patients with possible or probable syndrome of inappropriate antidiuretic hormone secretion

| Patient #70 | Patient #35 | Patient #80 | Patient #84 | Patient #36 |
|-------------|-------------|-------------|-------------|-------------|
| Serum sodium (mmol/L) | 132 | 131 | 132 | 133 | 125 |
| Serum sodium after correction for proteins (mEq/L) | 133 | N/A | 133 | 134 | 126 |
| Serum glucose (mg/dL) | 42 | 124 | 82 | 142 | 87 |
| Plasma Osmolality (mOsmol/kg) | 271 | 273 | 274 | 274 | 266 |
| Urine Sodium (mmol/L) | 60 | 140 | 88 | 43 | 46 |
| Urea (mg/dL) | 26 | 15 | 23 | 18 | N/A |

**Figure 2.** Scatter plot of the regression analysis between serum sodium and C-reactive protein. The slope of the regression line was significantly greater than zero, indicating that PCR levels tend to increase as serum sodium levels decrease (slope = −18.66, 95% CI, −25.07 to −12.25).

**Figure 3.** Scatter plot of the regression analysis between serum sodium and procalcitonin. The slope of the regression line was significantly greater than zero, indicating that Procalcitonin (PCT) levels tend to increase as serum sodium levels decrease (slope = −1.26, 95% CI, −2.22 to −0.31).
were not good enough to predict HN alone. HN variations should be explained for further factors.

In situations of inflammation and infections, IL-6 is an endogenous pyrogen. IL-6 stimulates prostaglandin E2, which attaches to the prostaglandin receptors in the hypothalamus to produce the new temperature set point. IL-6 could also set a new osmolality set point, stimulating ADH liberation before reaching the physiological threshold of 290 mOsm/kg or 10% loss of blood volume. Our interpretation for patients with HN, hypo-osmolality and low urine sodium is that vomiting, inflammation and IL-6 may displace the ADH curve to the left. They would increase ADH liberation, leading to hypo-osmolality. On the other hand, the loss of water and sodium from vomiting lead to physiological renal sodium avidity and low urine excretion of sodium.

Only five patients in our study had clinical and laboratory criteria for SIADH. Urine sodium and FENa are usually low in children with HN and hypo-osmolality, which is incongruous with SIADH. In fact, the lower the serum sodium levels, the lower the urine sodium levels. None of the five most relevant papers about CAP-associated HN provided sodium levels in urine, preventing us from making a comparison with our study (2–4,16).

This study has some limitations. The main shortcoming is the lack of data for all the patients, especially urine osmolality and total proteins. The number of patients with full data was lower than expected. However, we believe that the data gathered are enough to derive conclusions.

HN is a common finding in hospitalized children with CAP. HN is associated with longer hospitalizations and more days of fever, but SIADH is a rare event. Often, HN is an epiphemeron related to hyperproteinemia, inflammation, restricted sodium excretion, and probably osmostate readjustment, rather than a true electrolyte misbalance. Clinicians should be cautious and investigate urinary sodium levels before diagnosing SIADH in patients with CAP.

**Table 3.** Report of the multiple logistic regression model with the two explanatory variables. A total of 72% of patients are explained by the model. The model’s goodness of fit: $R^2$ (Cox and Snell) was 0.2 and $R^2$ (Nagelkerke) was 0.27.

| Variable     | Coefficient ($\beta$) | Standard error | Wald X2 | P value  | Odds ratio | 95% CI     |
|--------------|-----------------------|----------------|---------|----------|------------|------------|
| Male         | 1.02                  | 0.38           | 7.02    | 0.008    | 2.7        | 1.3–5.9    |
| PCR > 100 mg/L | 1.8                   | 0.38           | 22.9    | <0.001   | 6.4        | 3.0–13.7   |

Figure 4. Scatter plot of the regression analysis between serum sodium and urine sodium. The slope of the regression line was significantly greater than zero, indicating that urine sodium levels tend to decrease as serum sodium levels decrease (slope=5.12, 95% CI, 1.66 to 8.58).

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References
1. Wrotek A, Jackowska T. Hyponatremia in children hospitalized due to pneumonia. Adv Exp Med Biol 2013;788:103–8.
2. Don M, Valerio G, Korppi M, Cancan M. HN in pediatric community-acquired pneumonia. Pediatr Nephrol 2008;23:2247–53.
3. Shann F, Germer S. Hyponatraemia associated with pneumonia or bacterial meningitis. Arch Dis Child 1985;60(10):963–6.
4. Singhi S, Dhawan A: Frequency and significance of electrolyte abnormalities in pneumonia. Indian Pediatr 1992;29:725–40.
5. Feldman BJ, Rosenthal SM, Vargas GA, et al. Nephrogenic syndrome of inappropriate antidiuresis. N Engl J Med 2005;352(18):1884–90.
6. Hasegawa H, Okubo S, Ikezumi Y, et al. Hyponatremia due to an excess of arginine vasopressin is common in children with febrile disease. Pediatr Nephrol 2009;24(3):507–11.
7. Watanabe T, Abe Y, Sato S, Uehara Y, Ikeno K, Abe T. Hyponatremia in Kawasaki disease. Pediatr Nephrol 2006;21(6):778–81.
8. Park SJ, Shin JI. Inflammation and hyponatremia: An under recognized condition? Korean J Pediatr 2013;56:519–522.
9. Ellison DH, Berl T. Clinical practice. The syndrome of inappropriate antidiuresis. N Engl J Med 2007;356(20):2064–72.
10. Thomas CP. Syndrome of Inappropriate Antidiuretic Hormone Secretion. In: Medscape. 2017; emedicine.medscape.com. Last consulted, September 13, 2016.
11. Kim G. Pseudohyponatremia: Does it matter in current clinical practice? Electrolyte Blood Press 2006;4(2):77–82.
12. Landgraf R, Neumann I, Holsboer F, Pittman QJ. Interleukin-1 beta stimulates both central and peripheral release of vasopressin and oxytocin in the rat. Eur J Neurosci 1995;7(4):592–8.
13. Palin K, Moreau ML, Sauvant J, et al. Interleukin-6 activates arginine vasopressin neurons in the supraoptic nucleus during immune challenge in rats. Am J Physiol Endocrinol Metab 2009;296(6):E1289–99.
14. Mastorakos G, Weber JS, Magiakou MA, Gunn H, Chrousos GP. Hypothalamic-pituitary-adrenal axis activation and stimulation of systemic vasopressin secretion by recombinant interleukin-6 in humans: Potential implications for the syndrome of inappropriate vasopressin secretion. J Clin Endocrinol Metab 1994;79(4):934–9.
15. Swart RM, Hoorn EJ, Betjes MG, Zietse R. Hyponatremia and inflammation: The emerging role of interleukin-6 in osmoregulation. Nephron Physiol 2011;118(2):45–51.
16. Sakellaropoulou A, Hatzistilianou M, Aboriadou M, Athanasiadou-Piperopoulou F. Hyponatraemia in cases of children with pneumonia. Arch Med Sci 2010; 6(4):478–583.