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ORIGINAL RESEARCH

Hyponatremia in patients with respiratory syncytial virus bronchiolitis

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Abstract: Children with pulmonary diseases are at risk of developing hyponatremia (serum sodium concentrations <136 mEq/L). The aim of this study was to define the clinical and laboratory characteristics of respiratory syncytial virus (RSV) bronchiolitis in patients with hyponatremia and determine the associated risk factors. Medical data of 105 children (56 boys, 49 girls; mean age ± standard deviation: 9.1 ± 8.9 months) with RSV bronchiolitis were retrospectively analyzed. At admission, 35.2% of all patients, 13% of the <12-month-old patients, and 58.8% of the 12–35-month-old patients had hyponatremia. The results show that the development of hyponatremia in inpatients with RSV bronchiolitis is associated with age (12–35 months), body temperature, high fever (≥38.5°C), duration of fever until hospitalization, and high C-reactive protein level at admission. These results indicate that hyponatremia occurs in patients with RSV bronchiolitis exhibiting severe inflammation assessed by fever severity and C-reactive protein level. The use of isotonic fluids is recommended for parenteral therapy of patients with RSV bronchiolitis with risk of developing hyponatremia.

Keywords: respiratory syncytial virus, bronchiolitis, hyponatremia, fever, C-reactive protein

Introduction

Bronchiolitis is the most common lower respiratory infection in infants,[1] and its most common etiologic agent is respiratory syncytial virus (RSV). RSV bronchiolitis generally has a low mortality rate and only slight morbidity. However, complications such as syndrome of inappropriate secretion of antidiuretic hormone (SIADH) can lead to hyponatremia.

Hyponatremia often develops in acute inflammatory diseases such as meningitis, respiratory tract infections, febrile convulsions, and Kawasaki disease in children.[2–5] Patients with pneumonia and bronchiolitis, the most common diseases encountered in pediatric general practice, are at particular risk of developing hyponatremia due to antidiuretic hormone (ADH) oversecretion.[6–9] Some researchers have recently investigated the association between pneumonia and hyponatremia in detail,[10–12] but there are few reports on the relationship between RSV bronchiolitis and hyponatremia.[7,9,13] In particular, the risk factors for developing hyponatremia in RSV bronchiolitis are not well understood.

The aims of this retrospective study were to define the clinical and laboratory characteristics of RSV bronchiolitis in patients with hyponatremia and to determine the risk factors of its development.

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Patients and methods

Patients

The medical records of 107 previously healthy <36-month-old children with RSV bronchiolitis – who were admitted to the authors' medical center between October 2008 and January 2011 because their respiratory status had worsened; their intake of breast milk, diet, or fluid had decreased; and parenteral therapy was required – were retrospectively analyzed. The diagnosis of RSV bronchiolitis was based on an episode of coughing, wheezing, and crackles with RSV positivity in nasopharyngeal secretions using a rapid immunoassay (ImmunoCard STAT® RSV Plus; TFB Inc, Tokyo, Japan). No patient had any underlying disease including renal, thyroidal, hypophyseal, or cardiac insufficiency. Two of the 107 children were excluded due to a partial lack of serum samples at admission.

Clinical data

The patients' clinical data including age, gender, the duration of fever until hospitalization, respiratory rate, oxygen saturation, and resting body temperature were noted. Fever and high fever were defined as a body temperature of ≥37.5°C and ≥38.0°C, respectively. Tachypnea was defined as a respiratory rate of >60 breaths/minute and >40 breaths/minute in patients <12 months old and 12–35 months old, respectively.[14] All patients received hypotonic fluids for at least 24 hours after admission.

Laboratory data

Laboratory tests included white blood cell count, serum sodium concentration, creatinine level, and C-reactive protein (CRP) level. Blood sampling was performed at admission before the insertion of any intravenous catheters. As there is currently no consensus on the definition of hyponatremia, it was defined in the current study as a serum sodium concentration of <136 mmol/L.[15] Pneumonia was defined as the presence of infiltration on the chest X-ray.

Statistical analysis

The data are expressed as the mean (standard deviation) or number (%). Chi-squared test was used to analyze the categorical variables and the Mann–Whitney U-test was used to compare the two groups. Multivariate analysis was also performed. Values of $P < 0.05$ were considered statistically significant.

Results

The data of 105 patients with RSV bronchiolitis were analyzed (56 boys, 49 girls; mean age ± standard deviation: 9.1 ± 8.9 months). No patient required intensive care, including mechanical ventilation. Figure 1 shows the flow diagram of the patients according to hyponatremic status and age. A total of 35.2% (37/105) of all patients, 13.0% (7/54) of the <12-month-old patients, and 58.8% (30/51) of the 12–35-month-old patients had hyponatremia at admission.

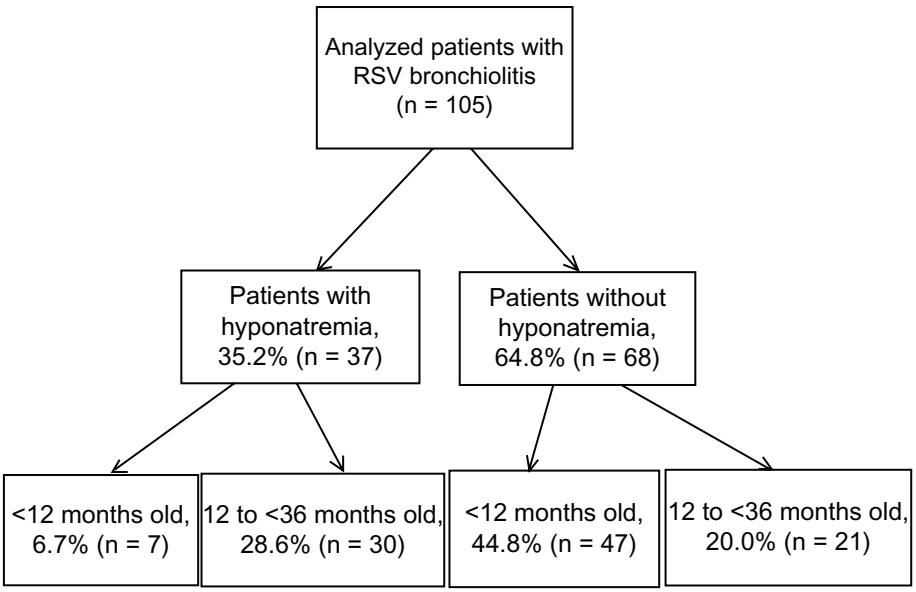

Figure 1 Patient flow diagram.
Notes: The medical records of 105 previously healthy <36-month-old children with respiratory syncytial virus bronchiolitis were reviewed and divided into two groups: those with hyponatremia (35.2%) and those without hyponatremia (64.8%). These groups were further divided into two subgroups: <12-month-old patients and 12–35-month-old patients. Among the patients with hyponatremia, 6.7% were <12 months old and 28.6% were 12–35 months old. Among the patients without hyponatremia, 44.8% were <12 months old and 20.0% were 12–35 months old. Finally, 35.2% of all patients and 58.8% of the 12–35-month-old patients had hyponatremia.
Abbreviation: RSV, respiratory syncytial virus.

At the time of admission, serum sodium concentrations were 131–141 mEq/L and there were no cases of hypernatremia. Hyponatremia was generally mild, and no patient had a serum sodium concentration of <130 mEq/L. At admission, 1.9%, 12.4%, and 20.1% of all patients had hyponatremia with a serum sodium concentration of 130 to <132 mEq/L, 132 to <134 mEq/L, and 134 to <136 mEq/L, respectively (Figure 2). The mean serum sodium concentration was 133.8 ± 1.3 mEq/L in hyponatremic patients and 137.6 ± 1.6 mEq/L in normonatremic patients.

The medical data of the patients with and without hyponatremia at admission was compared (Table 1). Patients with hyponatremia had significantly higher body temperatures at admission ($P < 0.01$) and longer duration of fever until hospitalization ($P < 0.01$). Further, a significantly greater proportion of patients with hyponatremia at admission had a high fever of ≥38.5°C ($P < 0.01$), presence of fever ($P < 0.05$), and high CRP levels ($P < 0.01$). There were no differences in gender ratio, respiratory rate, presence of tachypnea, oxygen saturation, incidence of pneumonia, creatinine level, and white blood cell count at admission between patients with and without hyponatremia. Multivariable analysis showed that the body temperature at admission and the duration of fever until hospitalization were independent risk factors.

Discussion

RSV bronchiolitis is a common lower respiratory infectious disease in children that results in hospitalization. Despite being a well-known complication, hyponatremia has not been widely studied. Several reports on hyponatremia and water metabolism abnormalities including SIADH in children with bronchiolitis were published in the 1990s. Gozal et al prospectively studied 23 consecutive <12-month-old hospitalized infants with bronchiolitis. Although they did not mention RSV infection, they found that 22 (96%) of their patients showed evidence of ADH hypersecretion and ten (43%) of the 23 patients had hyponatremia at admission.[13] In another prospective study, 48 hospitalized infants (median age: 104 days) with RSV bronchiolitis were examined to determine their risk of developing SIADH.[9] The authors found elevated ADH levels and serum sodium concentrations of <135 mmol/L in 27 (56%) and ten (21%) of the 48 infants, respectively. Unlike past reports, the current study enrolled patients with a wider age range (0.5–35 months) and RSV infection; this is because many of the patients with RSV bronchiolitis in the current study were older infants (>12 months old; a total of 13 patients with RSV bronchiolitis were >24 months old [data not shown]) and detailed examinations about RSV bronchiolitis in older infants has not been reported previously. Because of these differences, the current data cannot be directly compared with data of past reports, but the authors believe that the findings have greater applicability to pediatric general practice.

In the 1980s, it was reported that the physiology of hyponatremia in pulmonary disorders was linked to inappropriate ADH secretion in childhood.[16–19] Furthermore, it was

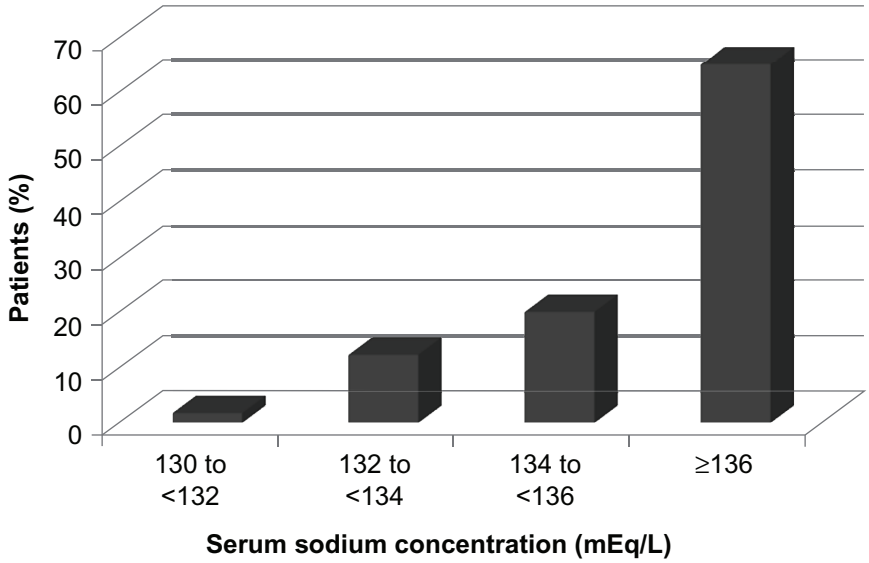

Figure 2 Percentage of patients with various degrees of hyponatremia at admission.
Notes: At admission, serum sodium concentrations were 131–141 mEq/L and there were no cases of hypernatremia. Hyponatremia was generally mild and no patient had a serum sodium concentration < 130 mEq/L. At admission, 1.9%, 12.4%, and 20.1% of all patients had hyponatremia with a serum sodium concentration of 130 to <132 mEq/L, 132 to <134 mEq/L, and 134 to <136 mEq/L, respectively.

Table 1 Comparison of the clinical and laboratory data according to hyponatremia status

Characteristics	Hyponatremia (n = 37)	No hyponatremia (n = 68)	Univariate analysis *P*-value	Multivariate analysis *P*-value
Male patients	24 (64.9)	36 (52.9)	NS	NS
Patients aged 12–35 months	30 (81.1)	21 (30.9)	<0.01	NS
Body temperature at admission (°C)	38.8 ± 1.0	38.0 ± 0.9	<0.01	<0.01
Limits of temperature (°C)	36.2–40.3	36.6–40.6		
Presence of fever at admission (≥37.5°C)	34 (91.9)	49 (72.1)	<0.05	
High fever (≥38.0°C)	29 (78.4)	31 (45.6)	<0.01	
Duration of fever until hospitalization (days)[a]	4.1 ± 1.9	3.7 ± 2.0	<0.01	<0.05
Respiratory rate (breaths/minute)	43 ± 10	47 ± 11	NS	NS
Presence of tachypnea	15 (40.5)	28 (25.0)	NS	
Oxygen saturation (%)	93.8 ± 4.1	94.4 ± 3.7	NS	NS
Incidence of pneumonia	9 (24.3)	8 (11.8)	NS	
Serum sodium concentration (mEq/L)	133.8 ± 1.3	137.6 ± 1.6	<0.01	
Creatinine level (mg/dL)	0.24 ± 0.05	0.22 ± 0.04	NS	NS
WBC count (cells/μL)	10,640 ± 4249	10,885 ± 3386	NS	NS
≥15,000 cells/μL	2 (5.4)	8 (11.8)	NS	
CRP level (mg/dL)	1.90 ± 2.63	1.09 ± 1.55	<0.01	NS
≥2 mg/dL	12 (32.4)	9 (13.2)	<0.01	

Notes: [a]Of the patients who had a fever at admission (n = 75). Values represent mean ± standard deviation or number of patients (%).
Abbreviations: CRP, C-reactive protein; NS, not significant; WBC, white blood cell.

also reported that levels of ADH are markedly elevated among infants with RSV bronchiolitis during the acute phase, and the levels decrease as the disease process resolves.[7,9] ADH is generally secreted by the pituitary gland in response to high plasma osmolality (high serum sodium concentration); however, in various clinical conditions, including fever, hypoxia, hypercarbia, pain, nausea, and vomiting, nonosmotic stimulation of ADH secretion can lead to hyponatremia. Also, the stimulus of ADH release in pulmonary disease is likely to be nonosmotic; in particular, lung hyperinflation and pulmonary infiltrates may stimulate ADH secretion by causing a false perception of hypovolemia by intrathoracic receptors.[13] The development of hyponatremia in RSV bronchiolitis requires the presence of both an increased ADH level and a source of electrolyte-free water. Infants with RSV bronchiolitis frequently meet both requirements.[7]

Hasegawa et al[20] reported that acute febrile diseases including acute pharyngitis, febrile convulsions, acute bronchitis, pneumonia, and Kawasaki disease in children commonly cause hyponatremia (18%) due to ADH excess and electrolyte-free water retention; such hyponatremia and ADH oversecretion are temporally observed in the febrile period and normalize within a week.[20] Therefore, they suggested that fever is a contributing factor to hyponatremia and that fever and other nonosmotic stimuli directly lead to excess ADH levels and hyponatremia. The current results, indicating that the presence of fever and high fever at admission are risk factors for hyponatremia in RSV bronchiolitis, are similar to those of a past report stating that hyponatremia is significantly more common in febrile patients than in afebrile patients.[20] Moreover, the patients with hyponatremia in the current study exhibited more severe inflammatory findings (eg, high fever, longer duration of fever until hospitalization, and higher CRP level) than the patients without hyponatremia. These results suggest that fever severity and CRP level at admission are early markers of hyponatremia.

This study has some limitations. ADH levels at admission could not be determined since this measurement is not covered by insurance in Japan; therefore, it is unclear whether SIADH contributed to the development of hyponatremia. However, results of earlier reports suggest that ADH was oversecreted in many patients with hyponatremia in the current study. Since the serum sodium concentration was not measured in most of the patients after parenteral therapy, the degree of change could not be determined. Fortunately, there were no side effects of hyponatremia observed in the current study. However, it is possible that some patients developed asymptomatic hyponatremia.

Conclusion

The results indicate that mild hyponatremia is common in children with RSV bronchiolitis and its development is associated with age (12–35 months), body temperature, high fever (≥38.5°C), presence of fever at admission, duration of fever until hospitalization, and CRP level. Serum electrolyte

levels should be measured in all children hospitalized for RSV bronchiolitis, fluid management should be carefully regulated in such patients who develop hyponatremia, and serum sodium concentration should be monitored regularly. Furthermore, the use of isotonic fluids is recommended for parenteral therapy of patients with RSV bronchiolitis who have the risk factors for developing hyponatremia.

Disclosure

The authors report no conflicts of interest in this work.

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