Hyponatremia and Syndrome of Inappropriate Antidiuretic Hormone Secretion in Kawasaki Disease

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ABSTRACT

Introduction

Hyponatremia in Kawasaki disease (KD) was first reported in 1982,1 with occasional reports since then of KD associated hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH).2-4 Multiple etiologies for hyponatremia in KD have been suggested5 and cerebral vasculitis has been thought to be related to SIADH.6 However, the precise pathogenesis of hyponatremia in KD has yet to be conclusively determined. Recently, it was revealed that many inflammatory cytokines such as interleukin (IL)-6 and IL-1β are elevated during the acute phase of KD,5-8 and a relationship between these cytokines and antidiuretic hormone (ADH) secretion has been suggested.9,10 It has therefore been speculated that these cytokines may be involved in the pathogenesis of hyponatremia due to SIADH in KD.

In this study, we investigated the clinical significance of hyponatremia in the acute phase of KD, and the role of IL-6 and IL-1β in the development of hyponatremia and SIADH associated with KD.

Subjects and Methods

During the study period from November 2008 to July 2009, 54 children who met the diagnostic criteria for KD11 were prospectively enrolled and treated with intravenous immunoglobulin (IVIG), 2 g/kg and aspirin 80-100 mg/kg/day at the Department of Pediatrics, Ewha Womans University Mok-
Membrane, decreased skin turgor, sunken anterior fontanel, and/or the presence of clinical findings such as dry mucous mem-
brane criterion, dehydration was defined as weight loss >3% on-
set of disease to the start of initial IVIG infusion. As an ex-
povolemia or dehydration.

Mal renal, adrenal, and thyroid function, and 6) absence of hy-

drions of each patient.

Board of Ewha W omans University Mokdong Hospital (#216-

USA), and the relationship with cytokines was also investi-
gated. This study was approved by the Institutional Review

of IL-6 and IL-1β were measured by enzyme-linked immu-

sorption assay (ELISA) using V-MAX 220 V AC ELISA read-
er (Molecular Devices, Sunnyvale, CA, USA), and the rela-
tionship between these cytokines and serum Na concentr-
tions was investigated. Plasma ADH levels were measured in

KD patients with hyponatremia by radioimmunoassay us-

which were stored at -70°C until measurement. Serum levels

mEq/L, 2) hypotonicity (plasma osmolality <280

lumen was clearly irregular.

child ≥5 years, the internal diameter of a segment being at

or normal renal, adrenal, and thyroid function, and 6) absence of hy-

or hemocoagulation (hematocrit >50%).

IVIG-resistance was defined when additional rescue ther-

apies were required owing to persistent or recrudescent fe-

r (≥38.0°C or 100.4°F) at least 48 hours after the end of ini-
tial IVIG infusion. CALs were assessed by echocardiogra-

dy and were defined by either an internal diameter of the coro-
nary artery lumen >3 mm in a child <5 years or >4 mm in a

for correlations between each vari-

man ‘s correlation were used for correlations between each vari-

pre- and post-IVIG infusion. Pearson’s correlation and Spear-

comparison between two independent groups. Wilcoxon

d signed rank test was used for comparing variables between

of inappropriate antidiuretic hormone secretion

in Kawasaki disease

Thirteen (26%) of 50 KD patients had hyponatremia be-

before IVIG infusion. Six (46%) of the 13 KD patients with hy-

ronatremia had SIADH. One of the 6 KD patients with SI-

had aseptic meningitis. Serum Na concentrations ranged

from 125 to 134 mEq/L with a mean of 132.1

r 0.05 was considered as statistically significant.

Results

Incidences of hyponatremia and syndrome

of inappropriate antidiuretic hormone secretion

in Kawasaki disease

Thirteen (26%) of 50 KD patients had hyponatremia be-

before IVIG infusion. Six (46%) of the 13 KD patients with hy-

ronatremia had SIADH. One of the 6 KD patients with SI-

had aseptic meningitis. Serum Na concentrations ranged

from 125 to 134 mEq/L with a mean of 132.1±2.3 mEq/L be-

before IVIG infusion, and increased to within the normal range

after IVIG infusion (range, 135 to 138 mEq/L; mean, 136.4±

Fig. 1. Changes in serum sodium (Na) level in 13 Kawasaki disease

patients with hyponatremia (serum Na <135 mEq/L) before and af-

ter intravenous immunoglobulin (IVIG) infusion.
In all patients except one male patient whose serum Na was 134 mEq/L (post-IVIG infusion), he exhibited a serum Na of 125 mEq/L (pre-IVIG infusion), which was the lowest concentration in the study (Fig. 1).

After IVIG infusion, hyponatremia newly occurred in 8 KD patients including 1 KD patient with SIADH. There were no KD patients who had developed hyponatremia before IVIG infusion. Serum Na concentrations ranged from 132 to 134 mEq/L (mean, 133.4 ± 0.9 mEq/L). Four of the 8 KD patients had excessive administration of hypotonic maintenance fluid (135% to 150% of maintenance requirements proposed by Holliday and Segar[5]) during the management of accompanying rotaviral gastroenteritis (n=2), urinary tract infection (n=1), and hepatitis (n=1), leading to dilutional hyponatremia.

We clarify that we were concerned about hyponatremia at the time of presentation, not that which developed after IVIG treatment. Therefore, all the reported results relate to hyponatremia at presentation.

Comparison between Kawasaki disease patients with and without hyponatremia

Between KD patients with (n=13) and without hyponatremia (n=37), there was no difference in clinical variables including age, gender, and duration of fever at initial IVIG infusion, and the presence of diarrhea. Regarding laboratory variables, percentage of neutrophils in white blood cells (% neutrophils), CRP, and NT-proBNP were higher, and serum T3 and albumin were lower in KD patients with hyponatremia than in those without hyponatremia.

The KD patients with hyponatremia had a higher incidence of IVIG-resistance but this was not statistically significant (p=0.065). There was no difference in the incidence of CALs between the two groups (Table 1).

Comparison between hyponatremic Kawasaki disease patients with and without syndrome of inappropriate antidiuretic hormone secretion

Between hyponatremic patients with (n=6) and without SIADH (n=7), no differences existed in clinical variables (age, gender, duration of fever at initial IVIG infusion, and the presence of diarrhea), laboratory variables, and the incidence of IVIG-resistance (Table 2).

Correlation between serum Na and laboratory variables

In 50 KD patients, serum Na inversely correlated with % neutrophils (r=-0.51, p=0.000) (not shown), CRP (r=-0.41, p=0.004) (Fig. 2A) and NT-proBNP (r=-0.47, p=0.001) (Fig. 2B). In contrast, serum Na had positive correlations with T3 (r=0.34, p=0.021) (Fig. 2C) and albumin (r=0.35, p=0.014) (not shown).

Table 1. Clinical and laboratory variables in Kawasaki disease patients with and without hyponatremia

| Variables                  | Patients with hyponatremia (n=13) | Patients without hyponatremia (n=37) | p     |
|----------------------------|------------------------------------|--------------------------------------|-------|
| Age (month)                | 35.2±23.9                          | 26.8±21.2                            | 0.268 |
| Male gender, n (%)         | 9 (69.2)                           | 19 (51.4)                            | 0.339 |
| Duration of fever (day)    | 3.6±1.3                            | 4.5±1.7                              | 0.087 |
| Diarrhea, n (%)            | 2 (15.4)                           | 0 (0)                                | N/A   |
| Serum sodium (mEq/L)       | 32.1±2.3                           | 137.4±1.5                            | 0.000 |
| WBC (×10³/mm³)             | 13.4±6.5                           | 13.1±4.2                             | 0.732 |
| % neutrophils (%)          | 74.0±16.2                          | 56.7±14.0                            | 0.000 |
| Platelet (×10³/ mm³)       | 315.4±86.2                         | 337.3±90.6                           | 0.472 |
| AST (IU/L)                 | 193±502                            | 99±197                               | 0.132 |
| ALT (IU/L)                 | 117±262                            | 98±223                               | 0.195 |
| CRP (mg/dL)                | 10.9±7.1                           | 6.7±5.3                              | 0.043 |
| NT-proBNP (pg/mL)          | 1824±2603                          | 793±1321                             | 0.013 |
| T3 (ng/dL)                 | 95.6±31.8                          | 125.0±36.3                           | 0.021 |
| Albumin (g/dL)             | 3.6±1.2                            | 3.9±0.3                              | 0.026 |
| IVIG-resistance, n (%)     | 4 (30.8)                           | 3 (8.1)                              | 0.065 |
| CAL, n (%)                 | 1 (7.7)                            | 3 (8.1)                              | 1.000 |

N/A: not applicable, WBC: white blood cell, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CRP: C-reactive protein, NT-proBNP: N-terminal pro-brain natriuretic peptide, T3: triiodothyronine, IVIG: intravenous immunoglobulin, CAL: coronary artery lesion

Table 2. Clinical and laboratory variables in hyponatremic Kawasaki disease patients with and without SIADH

| Variables                  | Patients with SIADH (n=6) | Patients without SIADH (n=7) | p     |
|----------------------------|--------------------------|-----------------------------|-------|
| Age (month)                | 34.0±24.2                | 36.2±25.6                   | 0.945 |
| Male gender, n (%)         | 3 (50)                   | 6 (85.7)                    | 0.266 |
| Duration of fever (day)    | 3.7±1.2                  | 3.6±1.2                     | 0.101 |
| Diarrhea, n (%)            | 1 (16.7)                 | 1 (14.3)                    | 1.000 |
| Serum sodium (mEq/L)       | 132.8±0.9                | 131.5±3.1                   | 0.534 |
| WBC (×10³/mm³)             | 14.2±6.5                 | 12.8±6.9                    | 0.628 |
| % neutrophils (%)          | 79.3±7.9                 | 69.5±20.5                   | 0.181 |
| Platelet (×10³/ mm³)       | 344.3±94.4               | 290.7±76.7                  | 0.445 |
| AST (IU/L)                 | 150±25                   | 216±582                     | 0.366 |
| ALT (IU/L)                 | 103±57                   | 122±257                     | 0.628 |
| CRP (mg/dL)                | 13.1±7.0                 | 8.9±7.2                     | 0.181 |
| NT-proBNP (pg/mL)          | 1342±1922                | 2305±3264                   | 0.394 |
| T3 (ng/dL)                 | 93.9±25.1                | 97.1±32.8                   | 0.792 |
| Albumin (g/dL)             | 3.6±0.3                  | 3.7±0.2                     | 0.818 |
| IVIG-resistance, n (%)     | 1 (16.7)                 | 3 (42.9)                    | 0.559 |
| CAL, n (%)                 | 0 (0)                    | 1 (14.3)                    | N/A   |

SIADH: syndrome of inappropriate antidiuretic hormone secretion, WBC: white blood cell, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CRP: C-reactive protein, NT-proBNP: N-terminal pro-brain natriuretic peptide, T3: triiodothyronine, IVIG: intravenous immunoglobulin, CAL: coronary artery lesion, N/A: not applicable.
Relation of intravenous immunoglobulin-resistance and coronary artery lesions to hyponatremia

Of the 50 KD patients, there were 7 patients with IVIG-resistance: 5 patients were treated with additional IVIG (2 g/kg) and 2 patients with both IVIG and methylprednisolone pulse therapy. The KD patients with IVIG-resistance had a lower Na concentration (134.4±2.9 mEq/L vs. 136.3±2.8 mEq/L, p=0.065) and a higher incidence of hyponatremia (4/7 (57.1%) vs. 9/43 (20.9%), p=0.083) than those without IVIG-resistance, but with no statistical significance.

As for coronary complications, there were 4 patients with CALs, all of which were <5 mm in diameter. Between KD patients with and without CALs, there were no significant differences in serum Na levels (135.7±3.7 mEq/L vs. 136.1±2.9 mEq/L, p=1.000) and the incidence of hyponatremia (1/46 (26%) vs. 12/46 (26%), p=0.769).

Comparison in interleukin-6 and interleukin-1β between groups

Serum IL-6 and IL-1β levels were measured in 42 KD patients and 35 healthy controls. There were no significant differences in serum Na levels (135.7±3.7 mEq/L vs. 136.1±2.9 mEq/L, p=1.000) and the incidence of hyponatremia (1/46 (26%) vs. 12/46 (26%), p=0.769).

Relation of antidiuretic hormone to syndrome of inappropriate antidiuretic hormone secretion and cytokines

Plasma ADH levels (normal, <6.7 pg/mL) were measured in 50 patients with acute Kawasaki disease. In the 11 KD patients with hyponatremia, serum IL-6 and IL-1β levels were higher in 5 KD patients with SIADH than in 6 patients without hyponatremia (IL-6, 184.3±77.8 pg/mL vs. 70.7±58.4 pg/mL, p=0.002; IL-1β, 104.6±143.7 pg/mL vs. 31.4±35.6 pg/mL, p=0.129) (Fig. 3B).

In the 11 KD patients with hyponatremia, serum IL-6 and IL-1β levels were higher in 5 KD patients with SIADH than in 6 patients without hyponatremia (IL-6, 210.0±288.6 pg/mL vs. 145.7±59.8 pg/mL, p=0.400; IL-1β, 150.6±182.2 pg/mL vs. 35.7±19.6 pg/mL, p=0.800), but with no statistical significance (Fig. 3C).
patients without SIADH (17.0±8.2 pg/mL vs. 6.8±1.1 pg/mL, \(p=0.095\)). Plasma ADH concentrations positively correlated with serum levels of IL-6 (\(r=0.57, p=0.180\)) (Fig. 4A) and IL-1\(\beta\) (\(r=0.64, p=0.119\)) (Fig. 4B). However, this correlations were not statistically significant.

**Contributing factors to hyponatremia in Kawasaki disease**

To detect the contributing factors to hyponatremia, five laboratory variables (% neutrophils, CRP, NT-proBNP, T3, and albumin) selected by the Mann-Whitney test plus two cytokines (IL-6 and IL-1\(\beta\)) were subjected to multivariate logistic regression analysis. No factors, however, were identified as independent contributors to hyponatremia in KD.

**Discussion**

In the acute phase of the illness before IVIG infusion, hyponatremia occurred in 13 of 50 KD patients (26%) and SIADH was detected in 6 patients who comprised 46% of hyponatremic patients. The incidence of hyponatremia in this study was lower than those (43.3% to 54.5%) reported by others. As serum Na levels were ≥125 mEq/L, no symptomatic hyponatremia occurred. Without specific management, hyponatremia normalized in almost all cases. Hyponatremia and SIADH also developed in the subacute phase after IVIG infusion. However, such occurrences are usually due to extrinsic factors such as fluid therapy.

The clinical significance of hyponatremia in KD was investigated. The patients with hyponatremia had higher % neutrophils, CRP, and NT-proBNP levels, and lower T3 and albumin levels, indicating that hyponatremia occurs in patients exhibiting severe inflammation. Regarding T3 in KD, we have previously demonstrated that low T3 occurs in KD patients with higher CRP and NT-proBNP during the acute phase, suggesting that T3 also may be useful in monitoring the degree of inflammation together with CRP and NT-proBNP. Low albumin level has been recognized as a predictor of more severe KD with a higher risk of sequelae. The finding of hyponatremia being associated with severe inflammation is in close agreement with other studies. With regard to fever duration, there was no difference between patients with and without hyponatremia. This finding is inconsistent with other studies reporting a longer duration of fever in patients with hyponatremia.

This difference could be attributed to hyponatremic patients with severe manifestations presenting to hospitals earlier than patients without mild hyponatremia. In fact, the time elapsed from the disease onset to initial treatment was approximately one day shorter in patients with hyponatremia than in those without. Considering the relationship between hyponatremia and IVIG-resistance, IVIG-resistance might occur more frequently in patients with hyponatremia, and hyponatremia might occur more commonly in patients with IVIG-resistance. Thus, hyponatremia and IVIG-resistance may have a mutual relationship and hyponatremia may serve as a predictor of IVIG-resistance as described previously. In contrast, there was no correlation between hyponatremia and CALs in this study, which was in contrast to the results of other reports. This difference was probably due to the small number of patients who had CALs in our study. Contrary to hyponatremia, the presence of SIADH was not associated with severe inflammation or IVIG-resistance.

Several theories have been put forward as etiologies of hyponatremia: hyponatremic dehydration, ingestion of hypotonic fluid relative to excessive fluid loss, SIADH, and renal salt wasting. Recently, as it has been recognized that ADH secretion may be activated by IL-6 and IL-1\(\beta\), involvement of these cytokines was focused on as a pathogenesis of hyponatremia due to SIADH. Mastorakos et al. have demonstrated increased ADH levels after IL-6 injection to cancer patients, indicative of stimulation of ADH secretion from magnocellular neurons by IL-6. Ohta and Ito have reported 4 cases of hyponatremia due to SIADH associated with inflammation. Hyponatremia occurred when the patients had fever and high CRP levels. Simultaneously, IL-6 and ADH levels were elevated with a significant correlation.
between them. They also demonstrated in animal studies that intravenous administration of IL-1β increases ADH, atrial natriuretic peptide, adrenocorticotropic hormone, and urinary Na excretion. As one of the main endocrine inflammatory cytokines IL-6 is involved in the de novo production of acute phase proteins by hepatocytes, causes fever in response to tissue injury, and plays a central role in endothelial damage in KD.\(^5\) Also, IL-1β acts as a mediator of endothelial damage in KD.\(^5\) Therefore, it is conceivable that these cytokines may be involved in the pathogenic mechanisms of hyponatremia and SIADH associated with KD.

We confirmed increased IL-6 and IL-1β levels during the acute phase of KD as reported in previous studies\(^5-8\) and that KD patients with hyponatremia have higher levels of these cytokines compared with those without hyponatremia. In patients with SIADH, these cytokines and ADH levels might be higher than in those without. In addition, there was a tendency of positive correlation between cytokines and ADH. These findings indicate that increased levels of serum IL-6 and IL-1β in acute KD may activate ADH secretion, leading to SIADH and hyponatremia.

With regard to the pathogenesis of hyponatremia in KD, several mechanisms may be suggested. KD is a systemic vasculitis and increased microvascular permeability is an initial step of the disease, causing hypoalbuminemia and noncardiogenic edema.\(^21\) Vascular leakage induces decreased intravascular volume and then activation of baroreceptors, leading to increased ADH secretion and hyponatremia.\(^21\) This is an appropriate pathophysiological response to restore extracellular fluid volume at the expense of hypoosmolality. Hyponatremia also occurs as a result of ADH secretion that is inappropriate to both osmotic and fluid stimuli. Hyponatremia may result from increased natriuresis by IL-1β\(^28\) and natriuretic peptide activity,\(^25\) or from renal salt wasting due to either renal involvement\(^14\) or a reduction in renal Na absorption.\(^21\) It may also be caused by dilution of extracellular fluid due to impaired free water excretion, frequently occurring during fever and severe infections.\(^20\) The precise mechanisms for hyponatremia and SIADH in KD are not fully understood, but several factors could be active in the same patient.

The study has several limitations. First, as a prospective study, it was difficult to enroll a large patient population during a short study period. Because of the small number of subjects in each group, no statistical differences between groups existed with respect to incidence of CALs, cytokines and ADH levels, nor did ADH statistically correlate with cytokine levels. Secondly, because there were no KD patients who had CALs > 5 mm in diameter, we were not able to investigate serum Na levels in patients with more severe coronary complications. Finally, although the results suggest that serum IL-6 and IL-1β play a key role in the pathogenesis of hyponatremia due to SIADH, these cytokines actually did not prove to be independent determinants of hyponatremia. This may have been partly due to the fact that hyponatremia secondary to cytokine-mediated ADH secretion occurred in only 46% of all cases.

Despite these limitations, this study indicates that hyponatremia in KD occurs in patients exhibiting severe inflammation. Hyponatremia may serve as a predictor of IVIG-resistance. As a possible pathogenesis model, we suggest that increased IL-6 and IL-1β levels during the acute phase of KD may activate ADH secretion, leading to SIADH and hyponatremia. Larger studies are needed to clarify the pathogenic role of IL-6 and IL-1β on hyponatremia and SIADH in KD patients.

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