Hyponatremia May Reflect Severe Inflammation in Children with Kawasaki Disease

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Purpose: The aim of the present study was to investigate the risk factors for the development of coronary artery lesions (CALs) and to determine whether hyponatremia is associated with CALs in children with Kawasaki disease (KD).

Methods: We retrospectively analyzed the data of 105 children with KD who were admitted to Ilsan Hospital between January 2000 and July 2011.

Results: Erythrocyte sedimentation rate ($P = 0.013$), total bilirubin levels ($P = 0.017$) were higher and serum sodium levels ($P = 0.027$) were lower in KD children with CALs than those without. White blood cell (WBC) counts ($P = 0.006$), neutrophil counts ($P = 0.003$) were higher and albumin levels ($P = 0.009$) were lower in KD children with hyponatremia than those without. On multiple logistic regression analysis, hyponatremia ($P = 0.024$) and intravenous immunoglobulin-resistance ($P = 0.024$) were independent risk factors for CALs in KD. Furthermore, serum sodium levels were correlated negatively with WBC counts ($P = 0.004$), neutrophil counts ($P < 0.001$), total bilirubin levels ($P = 0.005$) and positively with albumin levels ($P = 0.009$).

Conclusion: Our study indicates that hyponatremia may reflect severe inflammation in children with KD.

Key words: Kawasaki disease, hyponatremia, inflammation, cardiovascular abnormalities

Introduction

Kawasaki disease (KD) is a systemic vasculitis involving multiple organs, and it can cause coronary artery lesions (CALs), carditis, hepatitis, arthritis, and central nervous system diseases¹⁾. CALs are one of the most serious complications associated with KD. Characteristic clinical symptoms of KD are prolonged fever, bilateral conjunctival injection, cervical lymphadenopathy, erythematous induration of palms and soles, mucocutaneous changes in oropharynx and lips, and polymorphous skin rashes^{1,2)}.

There have been many reports showing that patients with KD had leukocytosis and elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, which were associated with CALs^{3,4)}. However, there have been a few reports on the significance of hyponatremia in patients with KD⁵⁻⁹⁾. The previous studies were also conducted in a small number of patients, rarely analyzed the correlations between serum sodium levels and

other inflammatory parameters of KD, or were not analyzed by multivariate analysis⁵⁻⁹. The aims of the present study were to investigate the risk factors for the development of CALs and determine whether hyponatremia could be associated with CALs in Korean children with KD.

Materials and methods

We retrospectively analyzed the data of 105 children (37 girls and 68 boys; mean age, 2.35 ± 2.1 years) with KD admitted to National Health Insurance System (NHIS) Ilsan Hospital between January 2000 and July 2011. The children were divided into the following groups: KD children with and without hyponatremia, and KD children with and without CALs.

Medical charts were reviewed for clinical characteristics, including patient age, sex, duration of fever, and presence of CALs during the clinical course. Laboratory data on admission included complete blood cell count (CBC), ESR, CRP, serum sodium, potassium, chloride, total carbon dioxide (tCO₂), blood urea nitrogen (BUN), creatinine, total protein, albumin, cholesterol, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), total bilirubin, calcium, phosphorus, creatine kinase (CK), CK-MB, and urinalysis.

Serum sodium levels were measured with the Ion selective electrode (ISE) method using a Hitachi 747 chemistry analyzer (Hitachi Inc., Tokyo, Japan) and Unicel DxC 800 (Beacman Coulter Inc., Brea, CA, USA). Complete blood counts including platelet counts were immediately analyzed within 2 hour by Sysmex XE-2100 (Sysmex Corp., Kobe, Japan). CRP levels were measured with the latex-enhanced turbidimetric assay method using a Hitachi 747 chemistry analyzer and Unicel DxC 800. ESRs were measured using Sysmex VES-Matic cube. Strict quality control procedures were adopted. Echocardiography was performed in all the children with KD to detect CALs.

KD was diagnosed if children had a fever (temperature, $>38^{\circ}\text{C}$) for at least 5 days in addition to at least four of the following: (1) changes in the mucous membranes of the upper respiratory tract, including injected pharynx, injected or fissured lips and strawberry tongue, (2) bilateral conjunctival injections, (3) cervical lymphadenopathy, (4)

polymorphous rash, and (5) changes in the extremities, including peripheral edema or erythema, and periungual desquamation^{1,2}.

Hyponatremia was defined as a serum sodium concentration (Na^+) ≤ 135 mEq/L. CALs were defined as either an internal diameter of the coronary artery lumen >3 mm in a child <5 years of age or >4 mm in a child ≥ 5 years of age, the internal diameter of a segment being at least 1.5 times larger than that of an adjacent segment, or the presence of a clearly irregular lumen^{10,11}. Intravenous immunoglobulin (IVIG) was defined when additional rescue therapies were required owing to persistent or recrudescence fever (≥ 38.0 or 100.4°F) at least 48 hours after the end of initial IVIG infusion¹².

All data were analyzed using Statistical Package for the Social Sciences (SPSS) for Windows, version 20.0 (SPSS Inc., Chicago, IL, USA). The data were expressed as mean $\pm$ standard deviation (SD). Univariate analysis was performed using the independent t-test and chi-square test. Correlation analysis was performed to determine the relationship between two variables using Pearson correlation. A comparison between two paired groups was performed using the paired t-test. Multiple logistic regression analyses were performed to identify the independent risk factors for CALs in children with KD. Statistical significance was set at a P -value of <0.05 .

This study design and the use of patients' information stored in the hospital database were approved by the Institutional Review Board (IRB) at NHIS Ilsan Hospital. We were given exemption from getting informed consents by the IRB because the present study was a retrospective study and personal identifiers were completely removed and the data were analyzed anonymously. Our study was conducted according to the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Results

Clinical characteristics were not significantly different between KD children with CALs and those without (Table 1). However, IVIG-resistance was significantly higher (32.4% vs. 8.8%, $P = 0.003$) in KD children with CALs than those without. ESR levels were higher (50.3 ± 39.4 mm/hr vs. 24.8

Table 1. Clinical characteristics of KD patients with or without coronary artery lesions (CALs)

	CALs (n= 37)	No CALs (n=68)	P-value
Age (yrs)	2.3 ± 2.2	2.4 ± 2.1	0.844
Sex (M:F)	27 : 10	41 : 27	0.209
Fever before IVIG (days)	5.0 ± 1.9	5.0 ± 2.0	0.919
Fever after IVIG (days)	1.9 ± 2.4	1.7 ± 1.8	0.685
Strawberry tongue	29 (78.4%)	48 (70.6%)	0.490
Conjunctival injection	30 (81.1%)	56 (82.4%)	1.000
Cervical lymphadenopathy	24 (64.9%)	42 (61.8%)	0.834
Polymorphous rash	37 (81.1%)	49 (72.1%)	0.352
Periungual desquamation	24 (64.9%)	34 (50.0%)	0.157
IVIG resistance	12 (32.4%)	6 (8.8%)	0.003*

IVIG: intravenous immunoglobulin, CALs: coronary artery lesions

*P-value of <0.05

Table 2. Laboratory findings of KD patients with or without CALs

	CALs (n= 37)	No CALs (n=68)	P-value
WBC (/μL)	14,164 ± 5,444	13,250 ± 5,650	0.424
ESR (mm/hr)	50.3 ± 39.4	24.8 ± 18.8	0.013*
CRP (mg/dL)	8.3 ± 6.3	8.2 ± 6.3	0.964
Neutrophil (%)	70.3 ± 14.5	65.4 ± 16.9	0.142
Lymphocyte (%)	21.3 ± 11.3	26.5 ± 14.6	0.063
Monocyte (%)	6.2 ± 3.6	6.1 ± 4.3	0.835
Hb (g/dL)	11.1 ± 1.1	11.3 ± 0.9	0.200
Hct (%)	32.7 ± 3.1	33.4 ± 2.8	0.293
PLT (10×3/μL)	331 ± 123K	325 ± 100K	0.795
Sodium (mmol/L)	134 ± 2.8	135 ± 3.0	0.027*
Potassium (mmol/L)	4.2 ± 0.8	4.3 ± 0.6	0.216
Chloride (mmol/L)	101 ± 4.0	102 ± 3.8	0.221
tCO ₂ (mmol/L)	18.2 ± 3.5	19.4 ± 2.7	0.041*
BUN (mg/dL)	10.5 ± 5.8	9.1 ± 3.8	0.130
Creatinine (mg/dL)	0.6 ± 1.1	0.4 ± 0.1	0.107
AST (IU/L)	177 ± 307	94 ± 121	0.051
ALT (IU/L)	178 ± 181	120 ± 136	0.068
Total protein (g/dL)	6.8 ± 3.3	6.5 ± 0.5	0.468
Albumin (g/dL)	3.3 ± 0.7	3.6 ± 0.5	0.066
Uric acid (mg/dL)	4.3 ± 1.7	3.7 ± 1.4	0.082
Cholesterol (mg/dL)	136 ± 40.0	135 ± 28.0	0.842
Calcium (mg/dL)	12.7 ± 20.1	9.5 ± 0.6	0.192
Phosphorus (mg/dL)	3.9 ± 1.1	4.1 ± 1.0	0.391
CK (IU/L)	70 ± 79	106 ± 180	0.249
CK-MB (ng/mL)	2.6 ± 4.0	1.8 ± 1.9	0.202
LDH (IU/L)	319 ± 122	305 ± 127	0.584
Total bilirubin (mg/dL)	1.5 ± 1.4	0.9 ± 1.1	0.017*

WBC: white blood cell, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, Hb: hemoglobin, Hct: hematocrit, PLT: platelet, tCO₂: total carbon dioxide, BUN: blood urea nitrogen, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CK: creatine kinase, LDH: lactate dehydrogenase

* P-value of <0.05

Table 3. Clinical characteristics of KD patients with or without hyponatremia

	Hyponatremia (n=43)	No hyponatremia (n=62)	P-value
Age (yrs)	2.1 ± 2.2	2.5 ± 2.3	0.286
Sex (M:F)	27 : 16	44 : 18	0.392
Fever before IVIG (days)	5.0 ± 1.3	5.0 ± 2.2	0.935
Fever after IVIG (days)	1.5 ± 1.3	1.8 ± 1.3	0.576
Strawberry tongue	37 (80.4%)	48 (71.6%)	0.287
Conjunctival injection	39 (84.8%)	55 (82.1%)	0.707
Cervical lymphadenopathy	28 (60.9%)	41 (61.2%)	0.972
Polymorphous rash	36 (78.3%)	47 (70.1%)	0.337
Periungual desquamation	27 (58.7%)	35 (52.2%)	0.498
IVIG resistance	8 (17.4%)	11 (16.4%)	0.892
CALs	22 (47.8%)	19 (28.4%)	0.034*
Pyuria	25 (54.3%)	33 (49.3%)	0.595
Glucosuria	9 (19.6%)	9 (13.4%)	0.381
Hematuria	9 (19.6%)	9 (13.4%)	0.381
Proteinuria	4 (8.7%)	7 (10.4%)	0.758

IVIG: intravenous immunoglobulin, CALs: coronary artery lesions

*P-value of <0.05

± 18.8 mm/hr, $P = 0.013$), sodium levels were lower (134 ± 2.8 mmol/L vs 135 ± 3.0 mmol/L, $P = 0.027$), tCO₂ levels were lower (18.2 ± 3.5 mmol/L vs. 19.4 ± 2.7 mmol/L, $P = 0.041$) and total bilirubin levels were higher (1.5 ± 1.4 mg/dL vs. 0.9 ± 1.1 mg/dL, $P = 0.017$) in KD children with CALs than those without (Table 2).

Clinical characteristics were not significantly different between KD children with hyponatremia and those without (Table 3). However, CALs were significantly higher (47.8% vs 28.4%, $P = 0.034$) in KD children with hyponatremia than those without. In KD children with hyponatremia, white blood cell (WBC) counts were higher ($15,355 \pm 6,159/\mu\text{L}$ vs. $12,335 \pm 4,794/\mu\text{L}$, $P = 0.006$), neutrophil counts were higher ($72.6 \pm 13.8\%$ vs. $63.2 \pm 16.8\%$, $P = 0.003$), lymphocyte counts were lower ($20.2 \pm 10.5\%$ vs. $27.7 \pm 14.8\%$, $P = 0.005$), neutrophil-lymphocyte ratio were higher (5.1 ± 4.1 vs. 3.6 ± 3.2 , $P = 0.048$), chloride levels were lower (100 ± 3.8 mmol/L vs. 103 ± 3.6 mmol/L, $P = 0.001$), tCO₂ levels were lower (18.1 ± 3.1 mmol/L vs. 19.6 ± 2.9 mmol/L, $P = 0.013$), albumin levels were lower (3.3 ± 0.5 g/dL vs. 3.6 ± 0.6 g/dL, $P = 0.009$), uric acid levels were higher (4.3 ± 1.8 mg/dL vs. 3.7 ± 1.3 mg/dL, $P = 0.037$), and phosphorus levels were lower (3.6 ± 0.9 mg/dL vs. 4.3 ± 1.0 mg/dL, $P = 0.001$) than those without hyponatremia (Table 4).

On multiple logistic regression analysis, hyponatremia (Odd ration (OR) = 3.148, 95% confidence interval (CI)

1.161-8.536, $P = 0.024$) and IVIG-resistance (Odd ratio = 4.816, 95% CI 1.234-18.797, $P = 0.024$) were independent risk factors for CALs in children with KD. Also, low serum chloride levels (Odd ratio = 1.246, 95% CI 1.049-1.479, $P = 0.012$), low serum tCO₂ levels (Odd ratio = 1.311, 95% CI 1.040-1.653, $P = 0.022$) and low serum phosphorus levels (Odd ratio = 2.670, 95% CI 1.241-5.747, $P = 0.012$) were independent risk factors for the development of hyponatremia in children with KD (Table 5).

Furthermore, serum sodium levels were correlated negatively with WBC counts ($r = -0.276$, $P = 0.004$), neutrophil counts ($r = -0.414$, $P < 0.001$), lymphocyte counts ($r = 0.398$, $P < 0.001$), neutrophil-lymphocyte ratio ($r = -0.348$, $P < 0.001$), total bilirubin levels ($r = -0.280$, $P = 0.005$) and positively with albumin levels ($r = 0.255$, $P = 0.009$) (Table 6). However, IVIG-resistance was not correlated with WBC counts ($P = 0.287$), ESR levels ($P = 0.160$), CRP levels ($P = 0.268$), total bilirubin levels ($P = 0.999$) and albumin levels ($P = 0.230$).

Changes in serum sodium levels (Na levels at the convalescent phase – Na levels at the acute phase, ΔNa) correlated positively with changes in lymphocyte counts ($\Delta\text{lymphocyte}$) ($r = 0.236$, $P = 0.019$), chloride ($\Delta\text{chloride}$) ($r = 0.517$, $P < 0.001$), tCO₂ levels (ΔtCO_2) ($r = 0.227$, $P = 0.020$) and negatively with neutrophil counts ($\Delta\text{neutrophil}$) ($r = -0.230$, $P = 0.022$), neutrophil-lymphocyte ratio ($\Delta\text{neutrophil-lymphocyte}$)

Table 4. Laboratory findings of KD patients with or without hyponatremia

	Hyponatremia (n=43)	No hyponatremia (n=62)	P-value
WBC (/μL)	15,355 ± 6,159	12,335 ± 4,794	0.006*
ESR (mm/hr)	47.4 ± 23.6	40.4 ± 20.0	0.106
CRP (mg/dL)	9.2 ± 7.0	7.5 ± 5.7	0.245
Neutrophil (%)	72.6 ± 13.8	63.2 ± 16.8	0.003*
Lymphocyte (%)	20.2 ± 10.5	27.7 ± 14.8	0.005*
Neutrophil-Lymphocyte ratio	5.1 ± 4.1	3.6 ± 3.2	0.048*
Hb (g/dL)	11.0 ± 1.0	11.4 ± 1.0	0.092
Hct (%)	32.4 ± 2.7	33.6 ± 2.9	0.03*
PLT (10×3/μL)	331 ± 129K	324 ± 92K	0.765
Potassium (mmol/L)	4.2 ± 0.7	4.3 ± 0.7	0.297
Chloride (mmol/L)	100 ± 3.8	103 ± 3.6	0.001*
tCO ₂ (mmol/L)	18.1 ± 3.1	19.6 ± 2.9	0.013*
BUN (mg/dL)	9.5 ± 3.6	9.7 ± 5.2	0.852
Creatinine (mg/dL)	0.4 ± 0.1	0.5 ± 0.9	0.574
AST (IU/L)	144 ± 254	109 ± 173	0.411
ALT (IU/L)	154 ± 178	130 ± 138	0.446
Total protein (g/dL)	6.2 ± 0.6	6.8 ± 2.6	0.117
Albumin (g/dL)	3.3 ± 0.5	3.6 ± 0.6	0.009*
Uric acid (mg/dL)	4.3 ± 1.8	3.7 ± 1.3	0.037*
Cholesterol (mg/dL)	132 ± 34	138 ± 31	0.360
Calcium (mg/dL)	9.3 ± 0.6	11.5 ± 15.6	0.344
Phosphorus (mg/dL)	3.6 ± 0.9	4.3 ± 1.0	0.001*
CK (IU/L)	67 ± 77	112 ± 187	0.140
CK-MB (ng/mL)	2.0 ± 2.9	2.1 ± 2.8	0.848
LDH (IU/L)	298 ± 87	318 ± 145	0.434
Total bilirubin (mg/dL)	1.4 ± 1.3	1.0 ± 1.1	0.132

WBC: white blood cell, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, Hb: hemoglobin, Hct: hematocrit, PLT: platelet, tCO₂: total carbon dioxide, BUN: blood urea nitrogen, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CK: creatine kinase, LDH: lactate dehydrogenase

*P-value of <0.05

Table 5. Multiple logistic regression analysis of laboratory parameters associated with the development of CALs and hyponatremia

	Odds ratio	95% CI	P-value
Risk for CALs			
Hyponatremia	3.148	1.161-8.536	0.024*
IVIg resistance	4.816	1.234-18.797	0.024*
Risk for hyponatremia			
Chloride (mmol/L)	1.246	1.049-1.479	0.012*
tCO ₂ (mmol/L)	1.311	1.040-1.653	0.022*
Phosphorus (mg/dL)	2.670	1.241-5.747	0.012*

CALs: coronary artery lesions, IVIG: intravenous immunoglobulin, tCO₂: total carbon dioxide

*P-value of <0.05

lymphocyte ratio) ($r = -0.263$, $P = 0.019$), AST levels (Δ AST) ($r = -0.271$, $P = 0.018$) (Table 7). Changes in serum sodium levels were negatively correlated with changes in inflammatory markers.

Discussion

Table 6. Correlation between serum sodium levels and laboratory parameters

	Correlation coefficient	P-value
WBC (/μL)	-0.276	0.004*
ESR (mm/hr)	-0.125	0.203
CRP (mg/dL)	-0.193	0.082
Neutrophil (%)	-0.414	<0.001*
Lymphocyte (%)	0.398	<0.001*
Neutrophil-Lymphocyte ratio	-0.348	<0.001*
Albumin (g/dL)	0.255	0.009*
Total bilirubin (mg/dL)	-0.280	0.005*

WBC: white blood cell, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein

*P-value of <0.05

Our study is the first study which showed that hyponatremia was an independent risk factor for the development of CALs in KD using multivariate analyses and it was also closely associated with other well known inflammatory markers of KD such as WBC count, ESR, and serum albumin level. Although WBC count, CRP, low serum albumin levels, or elevated serum ALT were reported to be associated with the development of CALs in KD^{13,14}, these biomarkers were not statistically significant between children with KD and those without KD in our study. Although previous studies exhibited that increased CRP and total bilirubin on admission were indicated as significant predictors for IVIG resistance and serum albumin levels before IVIG treatment were also suggested to be a useful predictor of IVIG resistance in patients with KD^{15,16}, we did not find any significant difference between the two groups. These contrasting results may be due to different ethnic groups and disease severities among studies. We also intended to investigate the independent risk factors for the development of hyponatremia in KD and found that low serum chloride, tCO₂ levels, and hypophosphatemia were independent risk factors for hyponatremia, which has not been analyzed and reported previously.

Although the pathogenesis of hyponatremia in KD still remains elusive, some plausible explanations have been proposed. Firstly, as we previously hypothesized, hyponatremia can be a result of ADH excess caused by inflammatory cytokines such as interleukin (IL)-1 β , IL-6, and tumor necrosis factor (TNF)- α ¹⁷. IL-1 β and IL-6 have been known to activate the magnocellular ADH-secreting neurons, leading to SIADH¹⁸. Activation of CD8+ T-cells and

Table 7. Correlation between changes in serum sodium levels and changes in laboratory parameters (Δ changes in parameters)

	Correlation coefficient	P-value
Δ WBC (/μL)	-0.108	0.288
Δ Neutrophil (%)	-0.230	0.022*
Δ Lymphocyte (%)	0.236	0.019*
Δ Neutrophil-Lymphocyte ratio	-0.263	0.009*
Δ Chloride (mmol/L)	0.517	<0.001*
Δ tCO ₂ (mmol/L)	0.227	0.020*
Δ AST (IU/L)	-0.271	0.018*

WBC: white blood cell, tCO₂: total carbon dioxide, AST: aspartate aminotransferase

*P-value of <0.05

macrophages are thought to play a central role in the development of hyponatremia, which results from elevated concentrations of IL-1, IL-6, IL-8, and TNF- α secreted by the CD8+ T-cells¹⁹. Secondly, these inflammatory mediators can cause hyponatremia by inhibiting the function of the apical epithelial sodium channel and/or sodium potassium adenosine triphosphatase at the basolateral membrane of renal epithelial cells¹⁹. Not only renal epithelial cells but also tubular dysfunction occurs in impaired proximal, distal, and collecting tubules due to severe renal interstitial inflammation, which causes hyponatremia. Thirdly, this is also related to renal tubular unresponsiveness to aldosterone in late distal and cortical collecting tubules, leading to secondary pseudohypoaldosteronism²⁰, because KD can also involve renal tubules²¹. Finally, increased concentrations of atrial and brain natriuretic peptide (ANP; BNP) can cause hyponatremia and natriuresis by inhibiting tubular reabsorption of sodium^{22,23}.

We speculate that hypophosphatemia which was found to be an independent risk factor for the development of hyponatremia in our study might be caused by renal loss of phosphorus, because urinary phosphorus is mainly reabsorbed by proximal tubules and tubular injury by KD could lead to urinary phosphate wasting. To confirm its pathogenesis, however, assessment of urine output, urinary electrolytes, phosphorous, creatinine, osmolality, serum ADH levels, and plasma rennin and aldosterone concentration should be investigated in the future randomized, prospective, and controlled study.

In our study, low tCO₂ levels were more common in KD children with hyponatremia than in those without, presumably indicating hypovolemic hyponatremia, which was

consistent with the previous result⁶⁾. This suggests that hypovolemic hyponatremia can frequently occur in KD patients, and it should be treated with isotonic fluids or an acetated Ringer's solution containing 130 mEq/L Na⁺ for parenteral fluid therapy instead of 0.25% NaCl saline to prevent aggravation of hyponatremia.

In conclusion, our findings suggest that hyponatremia was a substantial inflammatory marker for the development of CALs in KD, because it was an independent risk factor for the development of CALs in KD and it was also closely associated with other well known inflammatory markers of KD. Because there is no single biomarker for CALs in KD, measurement of serum sodium levels as well as conventional inflammatory markers could improve the prediction for the development of CALs in KD.

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Author contributions

IR Lee, SJ Park performed the statistical analysis, took part in data interpretation and drafted the manuscript. GC Jang, Uria Kim, JI Shin, and KH Kim designed study, coordinated data acquisition, analyzed and interpreted the data, drafted and revised the manuscript. All authors read and approved the final manuscript.

Additional information

Competing Financial Interests: The authors declare no competing financial interests.

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