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Age-adjusted plasma N-terminal pro-brain natriuretic peptide level in Kawasaki disease

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Purpose: Recent reports showed that plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) could be a useful biomarker of intravenous immunoglobulin (IVIG) unresponsiveness and coronary artery lesion (CAL) development in Kawasaki disease (KD). The levels of these peptides are critically influenced by age; hence, the normal range and upper limits for infants and children are different. We performed an age-adjusted analysis of plasma NT-proBNP level to validate its clinical use in the diagnosis of KD.
Methods: The data of 131 patients with KD were retrospectively analyzed. The patients were divided into 2 groups—group I (high NT-proBNP group) and group II (normal NT-proBNP group)—comprising patients with NT-proBNP concentrations higher and lower than the 95th percentile of the reference value, respectively. We compared the laboratory data, responsiveness to IVIG, and the risk of CAL in both groups.
Results: Group I showed significantly higher white blood cell count, absolute neutrophil count, C-reactive protein level, aspartate aminotransferase level, and troponin-I level than group II ($P<0.05$). The risk of CAL was also significantly higher in group I (odds ratio, 5.78; $P=0.012$). IVIG unresponsiveness in group I was three times that in group II (odds ratio, 3.35; $P= 0.005$).
Conclusion: Age-adjusted analysis of plasma NT-proBNP level could be helpful in predicting IVIG unresponsiveness and risk of CAL development in patients with KD.

Key words: Mucocutaneous lymph node syndrome, NT-proBNP, Child, Coronary artery lesion

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Introduction

Kawasaki disease (KD) is an acute systemic vasculitis that occurs in infants and young children, and is important cause of acquired heart disease in developed countries[1]. Recently, plasma N-terminal fragment of B-type natriuretic peptide (NT-proBNP) level has been used as a clinical biomarker in KD[2,3]. Many studies revealed that NT-proBNP was helpful in predicting intravenous immunoglobulin (IVIG) unresponsiveness or the development of CAL[4,5], and various cutoff values have been proposed. However, the serum concentration of this peptide vary according to patient age, with its normal range in infants and young children being different from that of adults[6]. So we investigated whether age-adjusted interpretation of plasma NT-proBNP level might be needed or be useful.

Materials and methods

1. Patients and materials

We performed retrospective review of the medical records of 131 patients who were

hospitalized for KD at Konyang University Hospital between May 2013 and December 2014. The diagnosis of KD was established by use of American Heart Association guidline[7]. In our center, all the KD patients were treated as follows; IVIG (2 g/kg/day) infusion was done over 10–12 hours with oral aspirin. Laboratory tests were during acute phase and 48–72 hours after IVIG treatment. The echocardiography was performed by a pediatric cardiologist to document CAL in acute phase and 8 weeks later. CAL was defined as a coronary artery internal dimeter with a *z* score of ≥2.5 in at least one of the following coronary arteries: right, left anterior descending, and left main[8].

The patients were divided into 2 groups as either higher or lower than the 95th percentile of NT-proBNP concentrations by use of reference value reported in the literature[6]. Group I was composed of patients with plasma NT-proBNP values within the 95th percentile, whereas group II was composed of those with plasma NT-proBNP values within the ≤95th percentile (Table 1). The clinical data and laboratory data including complete blood count; erythrocyte sedimentation rate; serum levels of C-reactive protein (CRP), electrolyte, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein, albumin, creatine phosphokinase-MB, troponin-I, and NT-proBNP were analyzed. We also compared the responsiveness to IVIG and the risk of CAL in both groups.

2. Statistical analysis

All of the data were analyzed using IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA). Clinical characteristics and laboratory findings were statistically analyzed via a *t* test, with a *P* value of <0.05 defined as being statistically significant. The Spearman correlation analysis was done for elucidate the relation age and plasma NT-proBNP level. We performed logistic regression analysis to yield an odds ratio (OR) that approximates the relative risk of CAL according to plasma NT-proBNP level. The Pearson chi-square analysis was used in determining whether CAL and IVIG responsiveness differed between groups I and II.

Table 1. The value of the 95th percentile of plasma NT-proBNP level in normal infants, children, and adolescents from birth to 18 years of age

Age	Plasma NT-proBNP normal upper limit (pg/mL)
First 2 days	12,000
3–11 Days	6,000
1 Month To 1 year	650
1–2 Years	400
2–6 Years	300
6–18 Years	160

NT-proBNP, N-terminal pro-brain natriuretic peptide.
This table was realigned according to the data by Nir et al.[6]

Results

1. Demographic and clinical findings

One hundred thirty-one patients with KD were enrolled in our study. Male outnumbered female by 78:53. The mean duration of fever of the patients with KD before admission was 5.1±1.8 days. The total hospital days was 5.6±2.5 days. The range of age of patients was 3–92 months (mean±standard deviation, 33.1±23.6), 25 patients (19.1%) were infancy, 41 (31.3%) were 13–24 months of age, and 65 of all KD patients (49.6%) were older than 25 months. As for plasma NT-proBNP level, the younger age of patient with KD was, the higher level of this peptide was (r^2=0.457, *P*=0.001) (Fig. 1).

Among the 131 KD patients, CAL was discovered in 17 (12.9%). The CAL incidence was 8 (32%), 4 (9.7%) and 5 (7.6%) in each age groups, respectively (*P*=0.007). Plasma NT-proBNP level was notably higher in the group with CAL than in the group without CAL (1,931±1,914 pg/mL vs. 982±746 pg/mL, *P*=0.001) (Fig. 2).

Twenty-eight patients (21.4%) did not respond to the first IVIG therapy, thus additional IVIG infusion and immunosuppressive therapy such as methylprednisolone were performed. But the plasma NT-proBNP level was not statistically different in both IVIG-unresponsive and IVIG-responsive group, (1,838±2,294 pg/mL vs. 906±1,835 pg/mL, *P*=0.051).

2. Relative risk for of CAL and IVIG responsiveness

The KD patients were divided into group I (higher plasma NT-proBNP) and II (normal range of plasma NT-proBNP) as previously stated. There were 54 (41%) and 77 patients (59%) with KD

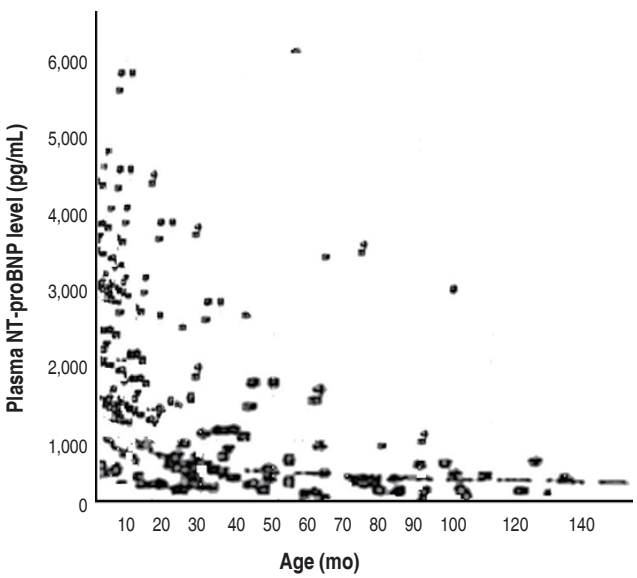

Fig. 1. Plasma NT-pro BNP level in patients with Kawasaki disease was inversely correlated with age (r^2=0.457, *P*=0.001). NT-proBNP, N-terminal pro-brain natriuretic peptide.

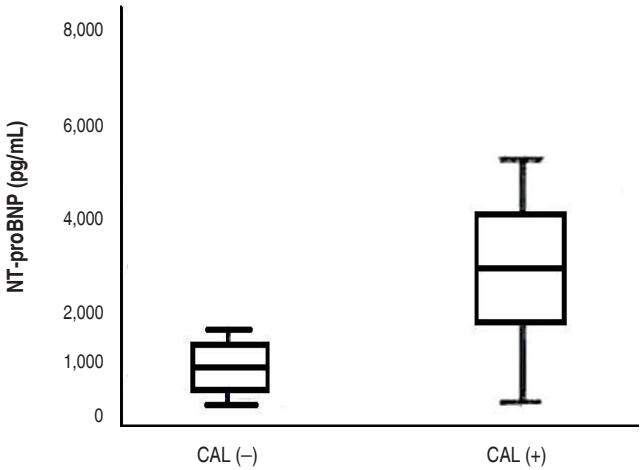

Fig. 2. Serum NT-proBNP levels in Kawasaki disease (KD) patients with and without coronary artery lesions (CALs). Serum NT-proBNP levels in KD patients with CAL (+) were 1,931±1,914 pg/mL and in KD patients without CAL (–) was 982±746 pg/mL (P<0.05). NT-proBNP, N-terminal pro-brain natriuretic peptide.

Table 2. The clinical characteristics of KD patients with high level of NT-proBNP (group I) and normal level of NT-proBNP (group II)

Characteristic	Group I (n=54)	Group II (n=77)	*P* value
Sex			
Male:female	35:19	43:34	0.58
Age group (mo)			0.49*
<12	15	10	
13–24	14	27	
≥25	25	40	
Body weight (kg)	14.1±5.4	13.4±4.6	0.94
Hospital days	5.4±1.7	6.5±3.5	0.26
Fever duration (day)	6.2±2.0	4.9±1.5	0.04

Values are presented as number or mean±standard deviation.
KD, Kawasaki disease; NT-proBNP, N-terminal pro-brain natriuretic peptide.
*Comparison between the age groups.

in groups I and II, respectively. The gender, body weight, and total hospital days were not different in both group. Fever duration was longer in group I than group II (6.2+2.0 and 4.9+1.5 days, P=0.041) (Table 2). Group I showed significantly higher measurements of WBC, ANC, CRP, AST, and troponin I level (Tables 3, 4). The CAL was developed in 13 (24.0%) in group I and 4 patients (4.5%) in group II. The patient showing IVIG unresponsiveness were 18 (29.4%) and 10 (11.4%) in group I and II, respectively.

Group I had a significantly higher probability of CAL occurrence (OR, 5.78; 95% CI, 1.771–18.910; P=0.001). IVIG unresponsiveness was three times higher in group I than group II (OR, 3.35; 95% CI, 1.400–9.018; P=0.005) (Table 5).

Table 3. Laboratory findings at the time of admission of patients with high level of NT-proBNP (group I) and normal level of NT-proBNP (group II)

Variable	Group I	Group II	*P* value
NT-proBNP (pg/mL)	1,759.3±2,801	355.4±913	<0.001*
WBC (10^3/μL)	1,6461±5,678	13,368±3,616	0.001*
ANC (/μL)	11,817±4,957	8,355±3,324	0.001*
PLT (10^3/μL)	340±95	371±105	0.083
ESR (mm/hr)	60±20	57±24	0.473
CRP (mg/dL)	11.1±7.5	6.9±3.9	0.001*
Hb (g/dL)	11.1±1.5	11.1±1.1	0.293
AST (IU/L)	107±185	41±45	0.003
ALT (IU/L)	68±87	52±103	0.287
Protein (g/dL)	6.8±0.59	6.6±0.6	0.692
Albumin (g/dL)	3.9±0.4	4.0±0.2	0.293
CK-MB (ng/mL)	3.1±4.1	2.9±3.1	0.384
Troponin-I (ng/mL)	0.0179±0.014	0.0105±0.005	0.041*

Values are presented as mean±standard deviation.
NT-proBNP, N-terminal pro-brain natriuretic peptide; WBC, white blood cell; ANC, absolute neutrophil count; PLT, platelet; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; Hb, hemoglobin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CK-MB, creatine kinase-MB.
*P<0.05, significantly different.

Table 4. Laboratory findings 48–72 hours after completion of intravenous immunoglobulin infusion in patients with high level of NT-proBNP (group I) and normal level of NT-proBNP (group II)

Variable	Group I	Group II	*P* value
NT-proBNP (pg/mL)	794.3±1,201	210.4±313	0.001*
WBC (10^3/μL)	12,219±5,012	8,691±2,341	0.001
ANC (/μL)	4,385±4,542	2,691±1,399	0.005*
PLT (10^3/μL)	432±114	426±159	0.811
ESR (mm/hr)	66±20	63±26	0.511
CRP (mg/dL)	2.4±2.0	1.4±0.9	0.002*
Hb (g/dL)	9.9±10.8	10.3±0.9	0.487
AST (IU/L)	98±85	34±45	0.003*
ALT (IU/L)	48±76	37±63	0.472
Protein (g/dL)	7.8±0.9	7.2±0.6	0.782
Albumin (g/dL)	2.9±0.3	3.4±0.2	0.383
CK-MB (ng/mL)	2.7±4.1	2.8±3.7	0.425
Troponin-I (ng/mL)	0.0134±0.012	0.0105±0.005	0.061

Values are presented as mean±standard deviation.
NT-proBNP, N-terminal pro-brain natriuretic peptide; ANC, absolute neutrophil count; PLT, platelet; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; Hb, hemoglobin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CK-MB, creatine kinase-MB.
*P<0.05, significantly different.

Discussion

We divided the KD patients into 2 groups according to reference value reported in the literature[6] for age adjusted analysis. In

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Table 5. Coronary artery lesions and responsiveness to intravenous immunoglobulin treatment in patients with high (group I) or normal (group II) plasma NT-proBNP level

Variable	Group I	Group II	Odds ratio	95% CI	*P* value
CAL			5.78	1.771–18.910	0.001*
(+)	13	4			
(–)	41	73			
Responsiveness to IVIG			3.35	1.400–9.018	0.005*
(+)	36	67			
(–)	18	10			

NT-proBNP, N-terminal pro-brain natriuretic peptide; CI, confidence interval; CAL, coronary artery lesion; IVIG, intravenous immunoglobulin.
*$P<0.05$, significantly different.

group I, fever lasted for a longer time and the serum level of acute phase reactants such as WBC, CRP, ANC were higher than group II. Moreover, AST and troponin-I level were also elevated. In other words, KD patients with serum NT-proBNP level higher than the 95th percentile in the corresponding age group tend to be with severe clinical feature.

Traditionally, plasma NT-proBNP level has been used as an indicator of ventricular dysfunction related to congestive heart failure. Recently, it has emerged as an important biomarker in KD as a tool for diagnosis of incomplete KD[2,3] and to predict the IVIG unresponsiveness or CAL development. There have been several reports that higher plasma NT-proBNP level might also be associated with CAL and myocarditis in KD. Bang et al.[4] reported that plasma NT-proBNP level>150 pg/mL in pediatric KD patients is strongly associated with a decrease in myocardial velocity and contractility. Moreover, Kaneko et al.[5] stated that plasma NT-proBNP level>1,000 pg/mL is a strong predictor of the presence of CAL in KD patients.

However, the normal range of plasma NT-proBNP levels can vary significantly according to age[9,10]. Many studies have reported highly elevated levels of the plasma NT-proBNP level immediately after birth. This is probably related to the physiologic water excretion in the first week following birth and possibly also to the important placental metabolism no longer occurring in this period[11]. Therefore, single cutoff values without consideration for the age are difficult to apply to individual patients in clinical settings. In particular, dramatic changes in plasma NT-proBNP level occur in infants and young children, which is the KD-prevalent age group. Actually plasma NT-proBNP level of KD patients was inversely correlated with their age in our study (r^2=–0.457, P=0.001). Thus, we must consider the age factor in interpreting the concentrations of this peptide.

In our study, group I showed a higher probability of CAL occurrence (OR, 5.78; 95% CI, 1.771–18.910; P=0.001). IVIG unresponsiveness was three times higher in group I than group II (OR, 3.35; 95% CI, 1.400–9.018; P=0.005).

Kim et al.[12] reported that higher plasma NT-proBNP levels was identified in the first and second blood tests for IVIG-unresponsive patients, as compared with IVIG-responsive patients. The plasma NT-proBNP level was not statistically different in both IVIG-unresponsive and IVIG-responsive group in our study. We supposed that it was due to small sample size, because P value was quite low (0.051). The risk of IVIG unresponsiveness was three times higher in group I than group II (OR, 3.35, 95% CI, 1.400–9.018, P=0.005). We found that the analysis applying individual upper normal limit of plasma NT-proBNP level on each age categories provided good predictive power for CAL and IVIG unresponsiveness.

In conclusion, age-considering analysis of plasma NT-proBNP level would provide an insight into the disease severity and could be used as a predictive indicator for the the risk of CAL and IVIG unresponsiveness development in KD.

The limitations of the present study are that it was retrospective, and the patient sample size was relatively small.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

References

1. Lee CA. Kawasaki disease. J Insur Med 2003;35:125-7.
2. Lee DW, Kim YH, Hyun MC, Kwon TC, Lee SB. NT-proBNP as a useful tool in diagnosing incomplete Kawasaki disease. Korean J Pediatr 2010;53:519-24.
3. Lee H, Kim H, Kim HS, Sohn S. NT-pro BNP: a new diagnostic screening tool for Kawasaki disease. Korean J Pediatr 2006;49:539-44.
4. Bang S, Yu JJ, Han MK, Ko HK, Chun S, Choi HS, et al. Log-transformed plasma level of brain natriuretic peptide during the acute phase of Kawasaki disease is quantitatively associated with myocardial dysfunction. Korean J Pediatr 2011;54:340-4.
5. Kaneko K, Yoshimura K, Ohashi A, Kimata T, Shimo T, Tsuji S. Prediction of the risk of coronary arterial lesions in Kawasaki disease by brain natriuretic peptide. Pediatr Cardiol 2011;32:1106-9.
6. Nir A, Nasser N. Clinical value of NT-ProBNP and BNP in pediatric cardiology. J Card Fail 2005;11(5 Suppl):S76-80.
7. Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Pediatrics 2004;114:1708-33.
8. McCrindle BW, Li JS, Minich LL, Colan SD, Atz AM, Takahashi M, et al. Coronary artery involvement in children with Kawasaki disease: risk factors from analysis of serial normalized measurements. Circulation 2007;116:174-9.
9. Mir TS, Laux R, Hellwege HH, Liedke B, Heinze C, von Buelow H,

et al. Plasma concentrations of aminoterminal pro atrial natriuretic peptide and aminoterminal pro brain natriuretic peptide in healthy neonates: marked and rapid increase after birth. Pediatrics 2003; 112:896-9.
10. Rauh M, Koch A. Plasma N-terminal pro-B-type natriuretic peptide concentrations in a control population of infants and children. Clin Chem 2003;49:1563-4.
11. Hammerer-Lercher A, Mair J, Tews G, Puschendorf B, Sommer R. N-terminal pro-B-type natriuretic peptide concentrations are markedly higher in the umbilical cord blood of newborns than in their mothers. Clin Chem 2005;51:913-5.
12. Kim HK, Oh J, Hong YM, Sohn S. Parameters to guide retreatment after initial intravenous immunoglobulin therapy in kawasaki disease. Korean Circ J 2011;41:379-84.

 http://dx.doi.org/10.3345/kjp.2016.59.7.298