



Original Contribution

N-terminal pro-brain natriuretic peptide and prediction of coronary artery dilatation in hyperacute phase of Kawasaki disease

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ARTICLE INFO

Article history:

Received 5 April 2018

Received in revised form 3 June 2018

Accepted 8 June 2018

Keywords:

Kawasaki disease

Coronary artery dilatation

N-terminal pro-brain natriuretic peptide

ABSTRACT

Background: Coronary artery dilatation (CAD) is a great concern with Kawasaki disease (KD). This study aimed to investigate the relationship between serum N-terminal pro-brain natriuretic peptide (NT-proBNP) levels and CAD in patients with the hyperacute phase (≤ 4 days of fever) of KD.

Methods: Serum NT-proBNP levels were compared between patients with and those without CAD, who underwent transthoracic echocardiography (TTE) within 24 h of the hyperacute phase of KD in the pediatric emergency department (PED). Electronic medical records of patients aged 1 month to 15 years who visited the PED were retrospectively assessed from January 2010 to December 31, 2014.

Results: One hundred nine patients were enrolled in the study. Twenty-three of those patients had CAD within 24 h of TTE. Median serum NT-proBNP levels were significantly higher in patients with CAD (824.1 pg/ml; interquartile range [IQR], 515.4–1570.0184.8–767.8 pg/ml) than in patients without CAD (396.4 pg/ml; IQR, 184.8–767.8 pg/ml) ($p \leq 0.001$). The cutoff value of serum NT-proBNP, which predicted CAD during the hyperacute phase of KD, was 515.4 pg/ml, which yielded sensitivity of 78.26% and specificity of 61.63%. The area under the curve for NT-proBNP for predicting CAD during hyperacute KD was 0.749 (95% CI, 0.642–0.856).

Conclusion: Serum NT-proBNP might be an additional laboratory marker for detecting early CAD during the hyperacute phase of KD in the PED.

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1. Introduction

Kawasaki disease (KD) is the most common acquired heart disease in children. Accurate timely diagnosis is imperative to reduce the risk of coronary artery lesion, because approximately 30% to 50% of untreated patients with KD develop transient coronary artery dilatation (CAD) during the acute stage, and approximately one-fourth progress to serious CAD [1]. CAD involves a significant risk of coronary thrombus formation, coronary artery stenosis, myocardial infarction, and sudden

death even years after acute illness [2]. Although not yet fully understood, rapid treatment will undoubtedly help prevent CAD and their complications.

Serum N-terminal pro-brain natriuretic peptide (NT-proBNP) has been recognized as a useful marker for the diagnosis of KD in recent studies [3, 4]. In addition, NT-proBNP levels of patients with the acute phase of KD and CAD were clearly higher than those of patients without CAD [5].

In our previous study, we defined KD with fever lasting 4 days or fewer as the hyperacute phase of KD [6]. NT-proBNP levels were significantly higher in patients with KD than in other febrile disease groups. Furthermore, NT-proBNP has been suggested as an adjunctive laboratory marker for the hyperacute phase of KD in the pediatric emergency department (PED). It is our hypothesis that higher NT-proBNP levels during the hyperacute phase of KD are correlated with a higher possibility of CAD.

The purpose of this study was to determine the differences in the first NT-proBNP levels at the time of PED presentation between patients who had CAD within 24 h using transthoracic echocardiography (TTE) during the hyperacute phase of KD and those who did not.

Abbreviations: AUC, area under the curve; CAD, coronary artery dilatation; CI, confidence interval; CRP, C-reactive protein; IL, interleukin; IVIG, intravenous immunoglobulin; IQR, interquartile range; KD, Kawasaki disease; NT-proBNP, N-terminal pro-brain natriuretic peptide; PED, pediatric emergency department; ROC, receiver operating characteristic; TTE, transthoracic echocardiography; WBC, white blood cells.

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2. Methods

2.1. Study design and setting

This study was a retrospective analysis of patients who were 1 month to 15 years of age and diagnosed with KD at the PED of a tertiary-care university hospital in Korea. The hospital has approximately 100,000 patient visits to the emergency department annually; of these, approximately 25,000 are children younger than age 16 years. All patients who visited the PED had been initially examined by board-certified pediatric emergency physicians and were referred to pediatricians if hospitalization was necessary. This study was approved by the hospital institutional review board [IRB no. B-1708/417-109]. Informed consent was waived owing to the retrospective nature of the study.

2.2. Extraction of data from the clinical data warehouse

Medical records of patients who were examined in the PED from January 1, 2010 to December 31, 2014 were collected retrospectively by searching the hospital clinical data warehouse based on the electronic medical records.

2.3. Definitions of patients

Among the patients who were diagnosed with KD and hospitalized after the presentation at PED, the patients of hyperacute phase of KD was enrolled if the patients' fever duration was 4 or less. They fulfilled

the classical diagnostic clinical criteria of KD according to the American Heart Association criteria [2] after 5 days of fever duration. The study group was defined as patients with CAD in TTE within 24 h of admission who presented to the PED during the hyperacute phase. The control group was defined as patients without CAD. Patients with an uncorrected structural heart abnormality, known dilated or hypertrophic cardiomyopathy, congenital heart diseases, a history of KD, and those undergoing or had undergone chemotherapy involving cardiotoxic drugs were excluded. We also excluded patients with a final diagnosis of incomplete KD because of its ambiguity. CAD was confirmed by TTE performed by a pediatric cardiologist if the intra-luminal diameter had a z-score of ≥ 2.5 mm [7].

2.4. Outcome measures

We compared the first NT-proBNP levels at the time of PED presentation between patients with and those without CAD within 24 h of TTE who were diagnosed with the hyperacute phase of KD. We determined the diagnostic performance of NT-proBNP levels for suspected coronary artery involvement during the hyperacute phase of KD.

2.5. Sample size

The calculated sample sizes were 15 and 56, respectively, for patients with and those without CAD. The sizes were based on the required sample number for each of the groups to perform the two-sided Wilcoxon test to detect any difference in NT-proBNP levels categorized as quintiles using the method developed by Zhao et al. with

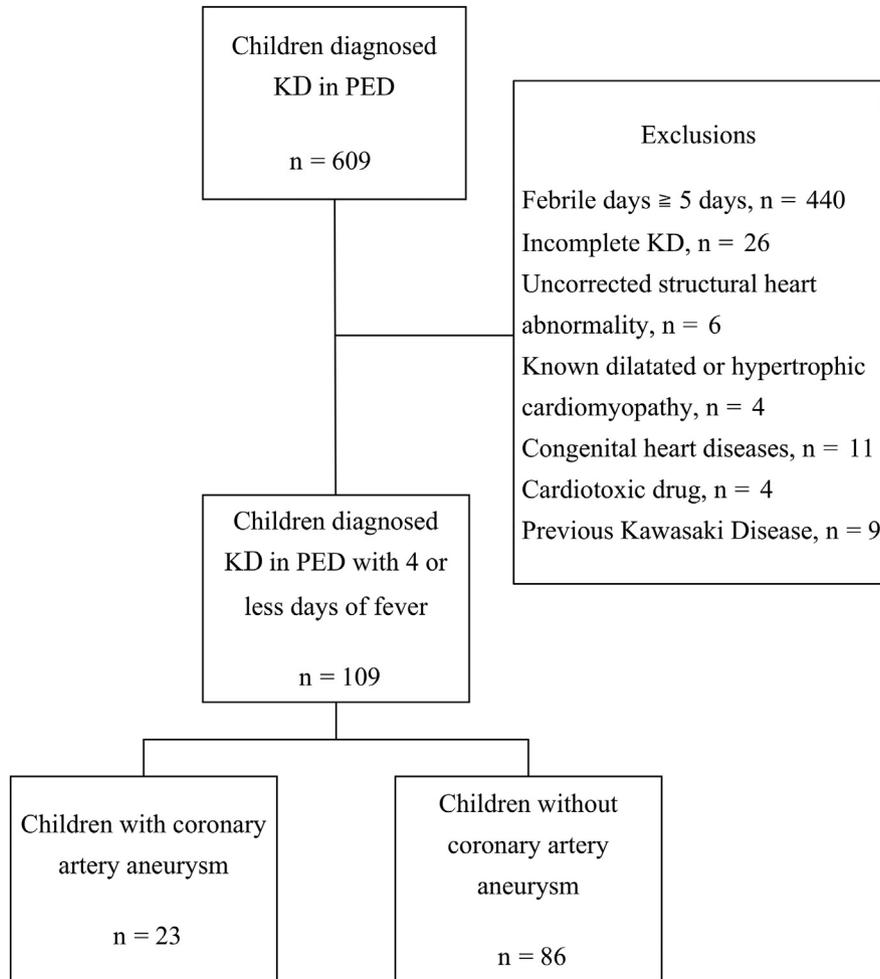


Fig. 1. Flow chart of patient enrollment. KD = Kawasaki disease, PED = pediatric emergency department.

Table 1
Patient characteristics.

	No coronary artery dilatation	Coronary artery dilatation ^a	p-value
Sex, n (%)			
Male	52 (47)	16 (15)	0.424
Female	34 (31)	7 (6)	
Age (month), median (IQR)	38.5 (17–54)	32 (18–63)	0.941
Duration of fever (day), mean (SD)	2.59 (1.12)	2.70 (1.02)	0.692
WBC ($\times 10^3/\mu\text{l}$), mean (SD)	12.44 (4.75)	12.09 (4.83)	0.767
CRP (mg/l), median (IQR)	5.57 (3.20–9.19)	5.72 (3.9–10.13)	0.447
NT-proBNP (pg/ml), median (IQR)	396.35 (184.8–767.8)	824.1 (515.4–1570)	<0.001

CRP; C-reactive protein, IQR; interquartile range, NT-proBNP; N-terminal pro-brain natriuretic peptide, SD; standard deviation, WBC; white blood cells.

^a Coronary artery dilatation was defined if the intra-luminal diameter has a z-score of ≥ 2.5 mm.

an alpha at 0.05 and power of 0.8 [8]. The proportions of NT-proBNP categories for each of the groups were retrieved from the study population of the present study because there were no prior data.

2.6. Primary data analysis

The Wilcoxon rank-sum test was used to compare the serum NT-proBNP levels (pg/ml) between patients with and those without CAD within 24 h after TTE during the hyperacute phase of KD. The Shapiro-Wilk test was used to test for normality.

Continuous variables were expressed as either the mean with the 95% confidence interval (CI) or the median with the interquartile range, depending on the presence of a normal distribution. Univariable and multivariable logistic regression analyses were used to evaluate other factors such as sex, age, duration of fever, white blood cells (WBC), and C-reactive protein (CRP), which may have relationship with CAD. Receiver operating characteristic (ROC) curves were constructed to evaluate the diagnostic performance of NT-proBNP levels for suspected coronary artery involvement during the hyperacute phase of KD. The area under the curve (AUC) of each ROC was calculated and expressed as the AUC with the 95% CI. The cutoff value was determined with the highest Youden index and calculated as (sensitivity + specificity – 1). To express the accuracy of the anticipated capacity of NT-proBNP for detecting CAD during the first 24 h, we used the terms sensitivity and specificity. We considered the results statistically significant if $p < 0.05$. All statistical analyses were performed using STATA version 14.0 (Stata Corp, College Station, TX).

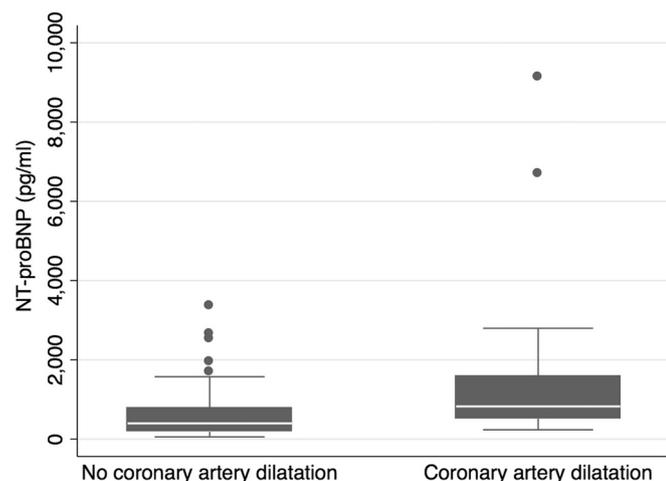


Fig. 2. NT-proBNP levels in patients with and without coronary artery dilatation. NT-proBNP = N-terminal pro-brain natriuretic peptide.

Table 2
Univariable and multivariable logistic regression of coronary artery dilatation^a, NT-proBNP, WBC, CRP, duration of fever, and patients' age.

	Univariable analysis			Multivariable analysis		
	Odds ratio	p-Value	95% CI	Odds ratio	p-Value	95% CI
NT-proBNP	1.001	0.004	1.000–1.001	1.002	0.004	1.001–1.002
WBC	0.984	0.763	0.887–1.091	0.989	0.857	0.876–1.116
CRP	1.036	0.405	0.952–1.128	0.980	0.744	0.865–1.109
Duration of fever	1.090	0.689	0.713–1.669	1.284	0.360	0.752–2.192
Age	1.006	0.466	0.990–1.022	1.013	0.238	0.991–1.035

CI; confidence interval, CRP; C-reactive protein, NT-proBNP; N-terminal pro-brain natriuretic peptide, WBC; white blood cells.

^a Coronary artery dilatation was defined if the intra-luminal diameter has a z-score of ≥ 2.5 mm.

3. Results

3.1. Patient characteristics

Six hundred nine patients were diagnosed with KD. Five hundred patients were excluded and 109 patients were enrolled in this study. Of the 109 patients, 23 had CAD and 86 did not (Fig. 1).

The proportion of male patients was higher in the groups with and those without CAD. There were no statistically significant differences in age, duration of fever, WBC, or CRP in both groups (Table 1).

3.2. CAD and NT-proBNP levels

There was a significant difference between the two groups for NT-proBNP alone (396.35 pg/ml (interquartile range (IQR), 184.8–767.8 pg/ml) for patients without CAD and 824.1 pg/ml (IQR, 515.4–1570.0 pg/ml) for patients with CAD) ($p < 0.001$) (Table 1; Fig. 2). In addition, NT-proBNP also presented significant differences during univariable and multivariable analyses confirming the correlation with CAD (Table 2).

NT-proBNP levels used to predict coronary artery involvement during the hyperacute phase of KD were assessed using ROC analysis. The cutoff value of NT-proBNP with the highest Youden index was 515.4 pg/ml and yielded sensitivity of 78.26% and specificity of 61.63% (Table 3; Fig. 3).

4. Discussion

This study examined the relationship between serum NT-proBNP and CAD during the hyperacute phase of KD. Those with elevated NT-proBNP may be at increased risk of developing coronary lesions in the child with <5 days of fever if their serum NT-proBNP levels were significantly higher. There were no differences in other values including sex, age, duration of fever, serum WBC, and CRP levels between groups with and those without CAD in TTE within 24 h of diagnosis of KD.

A few studies showed that high levels of NT-proBNP might be associated with CAD, and that the formation of CAD might be associated with intravenous immunoglobulin (IVIG) resistance [9, 10]. However, there is no report of relationship between NT-proBNP and CAD in

Table 3
Cutoff value of NT-proBNP with highest Youden index.

Cutoff value (pg/ml)	Sensitivity (%)	Specificity (%)	AUC	95% CI	LR (+)	LR (–)
515.4	78.26	61.63	0.749	0.642–0.856	2.040	0.353

AUC; area under the curve, CI; confidence interval, LR; likelihood ratio, NT-proBNP; N-terminal pro-brain natriuretic peptide.

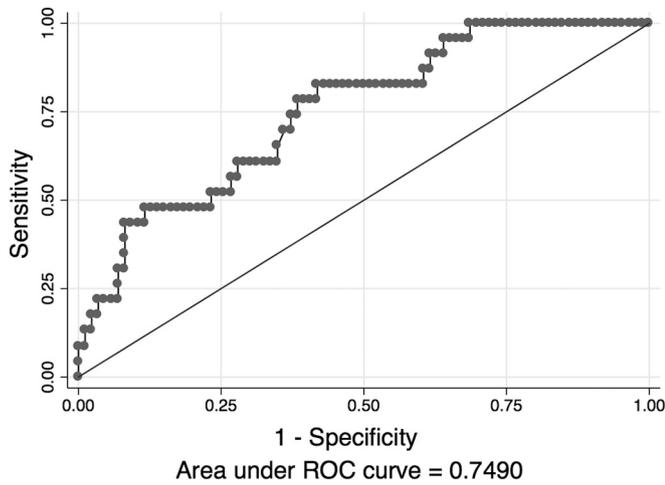


Fig. 3. Receiver operating characteristic curves comparing the sensitivity and specificity of NT-proBNP level in patients with and without coronary artery dilatation. ROC = receiver operating characteristic.

hyperacute phase of KD, and this is the first study showing their relationship.

The mechanisms by which serum NT-proBNP levels are elevated in patients with KD have not yet been clarified, but two possibilities have been suggested. One possibility is local myocardial inflammation or local areas of ischemia. During the acute phase of KD, the pericardium, myocardium, endocardium, and coronary arteries may be affected [11]. Another possibility is the involvement of cytokines that stimulate BNP secretion. It is known that tumor necrosis factor- α , interleukin (IL)-1 α , IL-1 β , and interferon- γ are present during the acute phase of KD [12]. However, the associated mechanism for CAD and NT-proBNP has not yet been clearly identified.

Yoshimura et al. reported that the NT-proBNP cutoff value of 1300 pg/ml yielded sensitivity of 95% and specificity of 85% for predicting CAD [9]. Kaneko et al. indicated that a cutoff value of 1000 pg/ml to predict CAD produced specificity of 0.68 and sensitivity of 0.83 [5]. In the present study, the cutoff value was 515.4 pg/ml, which yielded sensitivity of 78.26% and specificity of 61.63%. The relatively lower value of NT-proBNP in our study may have occurred because we performed the test during the hyperacute phase of KD.

This study had several limitations of note. First, this was a single-center study, and patient characteristics and presence of illness may differ from those of other institutions. Second, serum NT-proBNP levels are age-dependent [13]. This study did not include patients within 1 month of birth, and the median age of the enrolled patients was 32 months (range, 1 to 5 years). However, except for within 1 month of age,

there was little difference in age. Third, we could not include the patients' history of aspirin, steroids or other anti-inflammatory medications prior to the NT-proBNP measurement. Fourth, factors such as cytokines known to affect the secretion of NT-proBNP and IVIG resistance were not evaluated because of the retrospective nature of study. We have planned future studies dealing with the associations between cytokines, NT-proBNP, and IVIG resistance.

In conclusion, serum NT-proBNP levels might be higher in CAD patients during the hyperacute phase of KD. Additional therapy and careful follow-up such as more frequent TTE should be considered for patients with high levels of NT-proBNP.

Funding

No external funding for this manuscript.

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