B-type natriuretic peptide and N-terminal pro-BNP in the acute phase of Kawasaki disease

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Background: **This study was undertaken to identify factors correlating with plasma levels of B-type natriuretic peptide (BNP) and its N-terminal portion (NT-pro BNP) in the acute phase of Kawasaki disease (KD).**

Methods: **This study included 91 patients with KD treated at a hospital affiliated to Hamamatsu University School of Medicine between October 2003 and June 2011. We quantified BNP and NT-pro BNP in the acute phase. The BNP level was expressed as the NT-pro BNP level using the formula NT-pro BNP=9.080×BNP$^{0.923}$. We sought relationships between NT-pro BNP values and different clinical and laboratory data in the acute phase of KD.**

Results: **Of the 91 patients, 14 failed to respond to the initial intravenous immunoglobulins therapy. NT-pro BNP levels were significantly higher in these non-responders than in the responders (1689.3±1168.8 pg/dL *vs.* 844.4±1276.3 pg/dL, *P*<0.001). Seventeen patients developed coronary artery lesions, but this was not associated with NT-proBNP levels. NT-pro BNP was positively correlated with CRP (*r*=0.421, *P*<0.001) and negatively correlated with the hematocrit (*r*=-0.206, *P*=0.050), Na value (*r*=-0.214, *P*=0.041) and albumin level (*r*=-0.345, *P*<0.001). Stepwise multiple linear regression analysis with NT-pro BNP as a dependent variable revealed significant correlations with CRP and albumin (beta=0.345, *P*=0.001; beta=-0.225, *P*=0.027).**

Conclusions: **A high level of NT-pro BNP in acute phase KD is associated with systemic inflammatory responses and increased vascular permeability. The NT-pro BNP level is a useful marker to identify potential non-responders to IVIG among KD patients.**

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Key words: **B-type natriuretic peptide; Kawasaki disease; myocarditis; NT pro BNP**

Original article

Introduction

Kawasaki disease (KD) is an acute, self-limiting vasculitis of unknown etiology that occurs predominantly in infants and young children. The myocardial injury associated with KD has been classified into two main types: inflammatory myocardial injury associated with myocarditis or valvulitis during the acute phase, and ischemic myocardial injury secondary to coronary aneurysms or microcirculation disorders due to coronary arteritis. Both B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-pro BNP) have been established as useful biomarkers for the assessment of congestive heart failure (CHF) in adults. Recently, several studies reported increased plasma BNP levels in patients with acute phase KD without coronary artery abnormalities (CALs), which decreased to normal during their convalescence.[1] This predicted the risk of CALs[2] and supported the diagnosis of incomplete KD.[3] Printz et al[4] reported that non-coronary cardiac abnormalities were associated with laboratory evidence of inflammation within the first 5 weeks of diagnosis of KD. Myocarditis occurs in almost all patients with KD in the acute phase. However, the relationship between NT-pro BNP levels and laboratory inflammatory markers in KD remains unclear. The aim of the present study is to estimate the association between levels of BNP and NT-pro BNP, and laboratory evidence of systemic inflammation in the context of myocarditis in the acute phase of KD.

Methods

This study included patients with KD who had been treated at the hospital attached to Hamamatsu University School of Medicine between October 2003 and June

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2011. Our criteria for diagnosing KD included fever exceeding 38°C accompanied by the presence of at least 4 of the following 5 findings: bilateral conjunctival injection, changes in the lips and oral cavity, non-purulent cervical lymphadenopathy, polymorphous exanthema, and changes in the extremities. These diagnostic criteria are consistent with the Diagnostic Guidelines for KD.[5] The study protocol was approved by the Ethics Committee of Hamamatsu University School of Medicine. Informed consent was obtained from parents or legal guardians before examination.

Patients were treated with 2 g/kg intravenous immunoglobulin (IVIG) as a single infusion within 24 hours of diagnosis and also received aspirin at 30 mg/kg per day. Laboratory data during the acute phase included maximum high sensitivity C-reactive protein (CRP) levels, complete blood count, maximum % neutrophils, minimum sodium (Na), minimum albumin, maximum alanine aminotransferase (ALT), maximum aspartate aminotransferase (AST) and maximum total bilirubin. 2-D echocardiography was performed at the time of diagnosis and again 2 or 3 days later. It was re-performed once or twice a week during hospitalization. Children unable to cooperate were sedated according to local practice. A coronary artery was considered abnormal if the diameter of the internal lumen was more than 3 mm in a child younger than 5 years or more than 4 mm in a child older than 5 years, or if a segment was at least 1.5 times larger than that of an adjacent segment.[6] Cardiovascular complications were divided into two categories according to the duration of the condition: 1) transient dilatation, defined as a coronary artery dilatation or aneurysm observed at the acute stage but showing no cardiovascular lesions within 1 month of onset; and 2) persistent dilatation, defined in the same way, but persisting for more than 1 month after disease onset. The severity of valvular regurgitation was qualitatively assessed by color Doppler imaging, with notation made if there was at least mild mitral regurgitation (MR) or aortic regurgitation (AR). Pericardial effusion was considered present if its maximal dimension was at least 1 mm in any imaging plane. Echocardiography was performed and interpreted by pediatric cardiologists (SI and TI).

The plasma BNP concentration was measured using a commercially available immunoassay kit (Shionoria BNP assay kit; Shionogi Ltd, Osaka, Japan). The serum NT-pro BNP concentration was measured on an Elecsys 2010 analyzer with a chemiluminescent immunoassay kit (Roche Diagnostics; Mannheim, Germany). Further details are available elsewhere.[7]

First, we quantified BNP and NT-pro BNP concentrations before administration of the initial IVIG. BNP values were converted to NT-pro BNP values for comparison using the following formula: NT-pro BNP $=9.080\times BNP^{0.923}$. Cut-off points of the normal range of NT-pro BNP were: less than 3 years old: <170.5 pg/mL, older than 3 years: <124.7 pg/mL.

According to Sugimoto et al,[8] the mean NT-pro BNP level (n=32) was 1608.9±1873.9 pg/mL and the mean BNP level (n=59) was 99.3±109.9 pg/mL. NT-pro BNP levels converted from BNP levels were 613.7±614.9 pg/mL. In the present study, values for NT-pro BNP and NT-pro BNP converted from BNP together were 974.4.0±1291.1 pg/mL.

Using this approach, we first explored relationships between NT-pro BNP and several clinical and laboratory data in the acute phase. Second, we compared NT-pro BNP levels in IVIG responders and non-responders, and those with or without cardiac complications. IVIG responders were defined as those patients who were afebrile 48 hours after administration of IVIG. Non-responders remained febrile 48 hours after administration of initial IVIG, or suffered from recrudescent fever. Fever was defined as an axillary temperature of ≥37.5°C.

Data analysis

Results were expressed as mean±standard deviation. Pearson's linear regression analysis was performed to show the degree of correlation between variables. Univariate analyses of each parameter on NT-pro BNP were performed with a simple linear regression model. Only covariates that reached statistical significance in the univariate model were entered into the multivariate regression analyses. Stepwise multiple linear regression analyses were applied separately with NT-pro BNP as a dependent variable. Two-sided comparisons between groups were made using the Mann-Whitney U test, the Yates' correction for continuity, and the chi-square test. A P value <0.05 was considered statistically significant. All analyses were carried out using statistical software package, version 11.0J (SPSS, Tokyo, Japan).

Results

Totally 91 patients were included in this study. The characteristics of the patients are summarized in Table 1. Eighty-four patients (92.3%) in the acute phase had NT-pro BNP levels above the normal range. Correlations of various laboratory parameters with NT-pro BNP are shown in Table 2. The NT-pro BNP level was positively correlated with CRP (r=0.421, P<0.001), and negatively correlated with the hematocrit (r=-0.206, P=0.050), Na (r=-0.214, P=0.041), and albumin levels (r=-0.345, P<0.001). Stepwise multiple linear regression analysis was performed with NT-pro BNP as a dependent

Table 1. Characteristics of the study (n=91)

Parameters	Mean (SD)	Range
Age (y)	1.6 (1.9)	0.1-8.4
Sex (male:female)	46:45	
Height (cm)	81.5 (15.6)	57.0-126.0
Weight (g)	11.2 (3.9)	5.3-25.0
Days of illness at initial therapy (d)	5.0 (1.8)	2-14
IVIG non-responders/responders	14/77	
CALs (TD:PD)	17 (14:3)	
CRP (mg/dL)	9.7 (6.8)	1.2-42.7
WBC (/μL)	15 803 (5269)	5700-34 600
Neutrophils (%)	63.7 (18.8)	10.0-93.0
Hematocrit (%)	31.4 (2.6)	24.3-37.0
Platelet ($\times10^4$/μL)	33.5 (11.4)	17.3-83.1
Na (mEq/L)	133.8 (2.9)	126.0-141.0
Albumin (g/dL)	2.9 (0.5)	1.4-4.2
AST (U/L)	108.3 (180.1)	19.0-1317.0
ALT (U/L)	103.1 (171.3)	6.0-945.0
Total bil (mg/dL)	0.85 (0.88)	0.10-4.50
LVEF (%)	73.5 (5.9)	60.5-84.3
NT-pro BNP (pg/dL)	974.4 (1291.1)	17.2-8277.0

SD: standard deviation; IVIG: intravenous immunoglobulin; CALs: coronary artery lesions; TD: transient dilatation of coronary artery; PD: persistent dilatation of coronary artery; CRP: C-reactive protein; WBC: white blood cell; AST: aspirate aminotransferase; ALT: alanine aminotransferase; Total bil: total bilirubin; LVEF: left ventricular ejection fraction; NT-pro BNP: N-terminal pro-brain natriuretic peptide.

Table 2. Univariable and multivariable linear regression analysis of NT pro BNP in the present study

Parameters	Univariable analysis		Multivariable analysis
	r	P value	P value
CRP (mg/dL)	0.421	<0.001	<0.001
WBC (/μL)	0.079	n.s.	
Neutrophils (%)	-0.083	n.s.	
Hematocrit (%)	-0.206	0.050	
Platelet ($\times10^4$/μL)	-0.133	n.s.	
Na (mEq/L)	-0.214	0.041	
Albumin (g/dL)	-0.340	<0.001	0.027
AST (U/L)	0.096	n.s.	
ALT (U/L)	0.122	n.s.	
Total bil (mg/dL)	0.119	n.s.	

CRP: C-reactive protein; WBC: white blood cell; AST: aspirate aminotransferase; ALT: alanine aminotransferase; n.s: not significant; Total bil: total bilirubin. Multivariable analysis included only covariates that reached statistical significance in univariable analysis at the level of P<0.05; results of multivariable analysis are presented only for statistically significant (P<0.05) outcome correlates.

variable, and significant correlations included CRP and albumin (R^2=0.222, beta=0.345, P=0.001; beta=-0.225, P=0.027).

Of the 91 study patients, 77 were responders and 14 non-responders. The latter received additional IVIG, and 7 afebrile. The 7 patients who were non-responders despite additional IVIG received additional rescue therapy. Six patients received steroids, and then improved. One patient needed plasma exchange after additional IVIG, and improved. The NT-pro BNP level

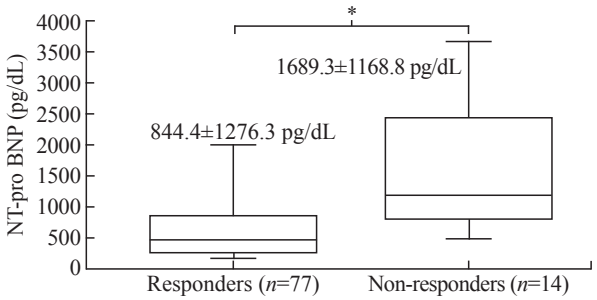

Fig. 1. Comparison of NT-pro BNP levels between IVIG non-responders and responders. The NT-pro BNP level was significantly higher in IVIG non-responders than responders (1689.3±1168.8 pg/dL *vs.* 844.4±1276.3 pg/dL, P<0.001). IVIG: intravenous immunoglobulin.

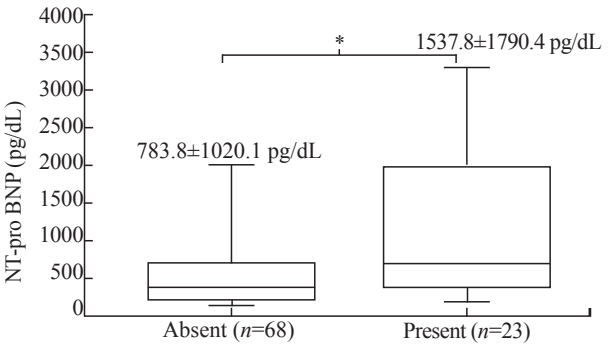

Fig. 2. Comparison of NT-pro BNP levels between patients with or without mitral regurgitation. The NT-pro BNP level was significantly higher in patients with mitral regurgitation (MR) than in those without MR (1537.8±1790.4 pg/dL *vs.* 783.8±1020.1 pg/dL, P=0.009).

was significantly higher in the non-responders than in the responders (1689.3±1168.8 pg/dL *vs.* 844.4±1276.3 pg/dL, P<0.001, Fig. 1). CALs developed in 17 patients, of whom 14 developed transient lesions and 3 persistent lesions. Twelve patients with CALs were responders and 5 non-responders.

One 10-month-old girl was referred to our institution to investigate bilateral conjunctival congestion and low-grade fever of unknown origin two weeks after onset. She already manifested CALs by echocardiography at this time and was diagnosed as having incomplete KD. Her NT-pro BNP level was 167 pg/dL at admission. She improved after administration of IVIG therapy at admission, and her CALs were transient.

Another patient was a boy of one year and 9 months of age who was referred to our institution to investigate fever of unknown origin two weeks after onset. He also had CALs by echocardiography. He was also diagnosed as having incomplete KD. His NT-pro BNP level was 172 pg/dL at admission. He improved after administration of IVIG therapy at admission but his CALs persisted. A three-month-old boy with CALs was referred to our institution to investigate a 12-day fever

of unknown origin, and he also received a diagnosis of incomplete KD. His NT-pro BNP was 79.6 pg/dL at admission; he improved on administration of IVIG therapy at admission, but his CALs were persistent.

No significant difference in the NT-pro BNP level was found between patients with or without CALs (n=17, 1247.8±1185.4 pg/dL *vs.* n=47, 911.5±1313.6 pg/dL, respectively). Mild MR was noted in 23 (25.3%) of the patients in the present study, and none had severe MR and AR. The NT-pro BNP level was significantly higher in patients with MR than in those without (1537.8±1790.4 pg/dL *vs.* 783.8±1020.1 pg/dL, P=0.009, Fig. 2). Effusion was noted in 8 patients (8.8%), but there was no apparent difference in NT-pro BNP level between patients with or without effusions.

Discussion

In the present study, we found that 92.3% of acute KD patients had elevated NT-pro BNP levels which was associated with laboratory evidence of inflammation, including elevated CRP and decreased serum albumin. Printz et al[4] reported that myocarditis associated with KD in the acute phase was accompanied by laboratory evidence of acute inflammation, and that acute left ventricular (LV) dysfunction in KD was typically transient and rapidly improved. Myocarditis of KD was unique comparing with other etiologies of myocarditis in which function improves more slowly and less consistently. However, some cases of myocarditis could be severe.[9,10] This rapid LV function improvement has led some investigators to postulate that acute LV dysfunction in KD is modulated by immune-mediated processes related to neutralization of circulating toxins or activated cytokines.[11,12] Other instances of increased BNP levels in inflammatory disease may not necessarily reflect cardiac dysfunction, but the effects of inflammation itself. Maeder et al[13] reported that patients with sepsis showed high BNP levels despite echocardiographically-preserved left ventricular function. Similarly, Nikolaou et al[14] reported that BNP levels were high in septic patients without clinical shock; Rudiger et al[15] found that BNP levels correlated with CRP as well as leukocyte counts but not with pulmonary capillary wedge pressure in critically ill patients. Ma et al[16] reported that interleukin-1 beta (IL-1 beta) and tumor necrosis factor-alpha (TNF-α), cytokines produced in many inflammatory diseases including KD, elicited a significant dose- and time- dependent increase in BNP mRNA, and secretion from rat neonatal ventricular cardiocyte cultures. Additionally, increased vascular permeability due to vasculitis and resultant vascular leakage are key features of the pathophysiology of KD. Increased vascular leakage may cause hypoalbuminemia and tissue edema.[17] A previous report showed that serum albumin concentration was significantly associated with myocardial swelling during the acute phase of KD, which was caused by increased vascular permeability.[18] Kishimoto et al[19] reported that an increased plasma BNP concentration in the acute phase of KD was a common phenomenon and might be associated with systemic inflammation itself. Thus, increasing NT-pro BNP in the acute phase of KD is associated with systemic inflammatory responses and increased vascular permeability.

We found that approximately one quarter of patients with KD presented with MR with increasing levels of NT-pro BNP. In KD, LV systolic dysfunction could be one of the mechanisms increasing NT-pro BNP. Even without overt myocarditis, increased plasma BNP in the acute phase of KD has been reported.[1,20,21] Printz et al[4] reported that mild or moderate MR in KD occurred in approximately one quarter of subjects and was associated with laboratory evidence of acute inflammation. We speculate that MR complicated with increasing NT-pro BNP in KD is induced by inflammation and complicated MR commonly transient when inflammation subsites.

The NT-pro BNP level in IVIG non-responders was significantly higher than that in IVIG responders. However, it could not be established that an elevated NT-pro BNP level in the acute phase was a risk factor for the development of CALs. Kaneko et al[2] reported that the NT-pro BNP level was elevated in KD patients who developed CALs, and that patients with an elevated serum NT-pro BNP had an increased risk for CALs. The primary therapeutic endpoint in patients with acute KD is reduction of systemic vasculitis and prevention of coronary artery injury and secondary ischemic heart disease. If the initial treatment with IVIG fails, systemic inflammation is maintained and remains the most consistent risk factor for cardiac abnormality.[22] In several recent publications, investigators have constructed risk scores for the Japanese population in order to predict resistance to IVIG from baseline data.[23-26] As noted by Ravekes et al,[27] microvascular vasculitis occurs within 10 days of KD onset, whereas vasculitis involving larger arteries occurs on days 12 to 25. It was reported that it is difficult to predict the development CALs in KD patients by investigating serial changes in plasma BNP levels because increasing BNP might be occurring in acute phase KD.[11] In the present study, three cases with incomplete KD with CALs received a delayed diagnosis two weeks after onset. Their NT-pro BNP levels were only slightly elevated. We speculate that their NT-pro BNP levels were only slightly elevated because too much time had elapsed since the onset of KD. We believe that a high NT-pro BNP level within 10 days after the onset of

KD is a risk factor for non-responsiveness to initial IVIG and for the development of CALs. Thus, high NT-pro BNP predicts failure of initial IVIG therapy in patients with KD. The NT-pro BNP concentration may be a key marker for systemic vasculitis in KD.

Several limitations in the present study should be addressed. The number of patients was rather small, and we could not evaluate cytokine production. There might be some bias in measuring NT-pro BNP because we converted BNP to NT-pro BNP. The difference between BNP and NT-pro BNP concentrations might be attributable to their different clearances: BNP has a short half-life of 20-30 minutes, whereas NT-pro BNP circulates unchanged in the serum for 60-120 minutes before being cleared primarily by the kidneys.[28] Dahdah et al[3] concluded that NT-pro BNP was a better marker of myocardial involvement in patients with acute KD than BNP. Sugimoto et al[8] reported a strong correlation between BNP and NT-pro BNP levels. In the clinical context, we believed that expressing BNP levels as NT-pro BNP was appropriate. We did not estimate cardiac function in the present study, because it was reported that LV diastolic dysfunction by Doppler echocardiography is a cause of increased BNP in the acute phase of KD.[23] It was also reported that LV wall motion abnormality assessed by tissue Doppler echocardiography is a cause of increased BNP in acute phase KD.[24] The statistical methods used were appropriate. However, it was true that the R^2 was small. We speculate that there are several reasons for the small R^2 in the present study. First, the number of patients was rather small. Second, the NT-pro BNP value varied widely (mean±SD: 974.4±1291.1 pg, range: 17.2-8277.0 pg/dL). Further investigation is required including a large number of patients with KD to establish relationships between markers of inflammation including cytokine production and myocarditis with increasing NT-pro BNP in acute phase KD. Moreover, whether stratifying patients by serum level of NT-pro BNP can be used to select optimal treatment strategies to reduce the risk of CALs should be studied.

In conclusion, increased NT-pro BNP in acute phase KD is associated with systemic inflammatory responses and increased vascular permeability. The NT-pro BNP level is a useful marker to identify potential non-responders to IVIG among KD patients.

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