N-Terminal Pro-Brain Natriuretic Peptide and Risk of Coronary Artery Lesions and Resistance to Intravenous Immunoglobulin in Kawasaki Disease

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Objective To determine whether the serum N-terminal pro-brain natriuretic peptide (NT-proBNP) can be a useful marker not only to identify the patients with Kawasaki disease (KD) who are at a higher risk of developing coronary artery lesions (CAL), and predict resistance to intravenous immunoglobulin (IVIG).

Study design We enrolled 80 patients with the acute phase of KD at a single center. The demographic, clinical, and laboratory data were prospectively collected.

Results Nineteen of the 80 patients developed CAL, despite IVIG administration. They had a significantly higher serum NT-proBNP level in comparison with the patients without CAL. The NT-proBNP cut-off value of 1300 pg/mL yielded a sensitivity of 95% and a specificity of 85% for predicting CAL. However, 17 of the 80 patients were IVIG non-responders. They also had a significantly higher serum NT-proBNP level in comparison with the IVIG responders. The NT-proBNP cut-off value of 800 pg/mL yielded a sensitivity of 71% and a specificity of 62% for predicting IVIG non-responders.

Conclusions The serum NT-proBNP level is increased in children with KD with CAL and IVIG resistance. It may be useful to predict CAL and IVIG resistance in KD. *(J Pediatr 2013;162:1205-9)*.

Kawasaki disease (KD) is an acute systemic vasculitis of unknown etiology that primarily affects small- and medium-sized arteries in infants and children, with the development of coronary artery lesions (CAL) occurring in as many as 3% to 5% of children treated with intravenous immunoglobulin (IVIG).[1] Approximately 10%-15% of patients with KD do not respond to IVIG therapy[1] and resistance to IVIG is a greater risk for developing CAL.[2] It is important to identify these patients because they might benefit from more aggressive initial treatment. Currently, several studies have reported new stratified strategies that are effective for the treatment of patients predicted to have severe KD, based on various scoring systems.[3,4] However, no useful single marker has so far been discovered. Brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) are released from ventricular cardiomyocytes in response to an increase in ventricular wall stress and to myocardial ischemia.[5,6] Both BNP and NT-proBNP have been proven to be reliable diagnostic and prognostic biomarkers in patients with heart failure and coronary artery disease in adults.[7] Several studies reported increased plasma BNP or NT-proBNP levels in patients with the acute phase of KD without cardiac involvement, thus providing useful markers for diagnosing KD.[8-11] The purpose of this study was to determine whether the serum NT-proBNP levels can be a useful marker for patients with KD who are at higher risk of developing CAL and resistance to IVIG.

Methods

The study subjects consisted of patients diagnosed with KD at the Department of Pediatrics of Kansai Medical University Hospital, Japan, between November 2008 and May 2012. All of the subjects fulfilled the Criteria for Diagnostic Guideline established by the Kawasaki Disease Research Committee in Japan.[12] The exclusion criteria included the presence of another disease known to mimic KD, previous diagnosis of KD, and incomplete KD. All patients received 30 mg/kg/d aspirin until they were afebrile and 2 g/kg of IVIG for 24 hours. The first illness day was defined as the day of fever onset.

BNP	Brain natriuretic peptide
CAL	Coronary artery lesions
CRP	C-reactive protein
IVIG	Intravenous immunoglobulin
KD	Kawasaki disease
LMT	Left main trunk
NT-proBNP	N-terminal pro-brain natriuretic peptide
pLAD	Proximal left anterior descending
pRCA	Proximal right coronary artery
WBC	White blood cell

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No response to the initial treatment with IVIG was defined as a fever lasting more than 24 hours after the end of the IVIG infusion.[13]

Echocardiograms were performed on all subjects before the initial treatment, at 36 hours after the end of the IVIG infusion, and at 2 weeks and 1 month after the day of illness. The presence of CAL was diagnosed based on the Z scores of the left main trunk (LMT) coronary artery, proximal left anterior descending (pLAD) coronary artery, and proximal right coronary artery (pRCA) using echocardiograms, and was defined as the Z scores of 2.5 or more. The value of Z scores from a standardized coronary artery dimension were calculated from the body surface area[14] based on Haycock's formula.[15]

Blood samples were obtained from the enrolled subjects. Laboratory tests, including white blood cell (WBC) counts, serum sodium levels, serum C-reactive protein (CRP) levels, serum albumin concentration, and serum NT-proBNP levels were performed on all subjects before the initial IVIG treatment. WBC were analyzed using an XE-2100 instrument (Sysmex Co, Kobe, Japan). The serum levels of sodium, CRP, and albumin were measured by an auto-analyzer (AU5400 and AU2700; Beckman-Coulter Japan, Tokyo, Japan). Serum NT-proBNP was measured using an electrochemiluminescence immunoassay on the ECLusys 2010 analyzer (Roche Diagnostics, Indianapolis, Indiana). Parental informed consent was obtained for each child enrolled in this study. The Research Ethics Committee of Kansai Medical University approved the study (no. H110401).

The patients were categorized into 2 groups according to whether they were complicated with CAL: those who developed a significant CAL (CAL^+), and those who did not develop CAL (CAL^-), and also whether they responded to the initial IVIG treatment: those who respond to the initial IVIG treatment ($IVIG^+$), and those who resisted the initial IVIG treatment ($IVIG^-$). Demographic data, such as the age or sex, and clinical data, such as the day of illness and response to treatment, were compared between the CAL^+ and CAL^- groups, and between the $IVIG^+$ and $IVIG^-$ groups. In addition to the serum levels of NT-proBNP, routine laboratory data, such as the WBC, the serum levels of sodium, CRP, and albumin were compared between the CAL^+ and CAL^- groups, and also the $IVIG^+$ and $IVIG^-$ groups. A receiver operating characteristic curves analysis was performed on NT-proBNP, WBC, sodium, albumin, and CRP to predict CAL and IVIG resistance.

Statistical Analyses

The data are presented as the medians with the 25th and 75th percentiles in square brackets. The statistical analysis for comparisons of the CAL^+ versus the CAL^- group and the $IVIG^+$ and $IVIG^-$ groups were performed by the Mann–Whitney U test for numerical data and 2-sided χ^2 test for categorical data. All P values were 2-tailed. A value of $P < .05$ was considered to be statistically significant for all tests. All of the statistical analyses were performed using the statistical package for social sciences (add-in software for Microsoft Excel: Excel Statistics 2010; SSRI, Tokyo, Japan) for the Windows software package.

Results

Eighty children (54 males and 26 females) with the acute phase of KD, age range 0.2-6.4 years (median age: 1.7 years), were enrolled in this study. Nineteen of the 80 eligible patients developed CAL despite receiving IVIG. The distribution of CAL was LMT in 6 patients, pLAD artery in 13 patients, and pRCA in 10 patients. Although a maximum Z score ≥2.5 was noted in 24% (19/80) of patients during the first month of illness, all patients demonstrated a Z score <2.5 thereafter.

There were no significant differences in the age or the ratio of males to females between the CAL^- and CAL^+ groups (age: 2.0 [0.8-3.3] and 1.1 [0.6-2.4] years; male/female: 43/18 and 11/8, respectively) (**Table I**). No significant difference was found for the day of the illness before IVIG (4.0 [4.0-6.0] and 5.0 [3.5-5.0] day) and the sampling day of illness (4.0 [3.0-6.0] and 4.0 [3.0-5.0] day). The number of initial IVIG-resistant patients was significantly higher in the CAL^+ group (42% in CAL^+ vs 15% in CAL^-, $P = .0213$). In the laboratory data that have been previously reported as possible predictors for risk of CAL,[16-20] the patients in the CAL^+ group had higher WBC counts (CAL^+ vs CAL^- group, 16.9 [14.4-19.9] vs 12.8 [10.8-14.7] $\times 10^3/\mu L$; $P = .0041$), a lower serum albumin level (3.4 [3.4-3.7] vs 3.7 [3.5-4.0] g/dL; $P = .0231$), and a higher serum NT-proBNP level (2592 [1685-3644] vs 453 [252-886] pg/mL; $P < .0001$) in comparison with the patients in the CAL^- group. There were no significant differences in any other examined variables, such as the serum sodium and CRP levels, between the 2 groups.

The serum NT-proBNP levels to predict CAL in patients with KD was assessed by a receiver operating characteristic curves analysis (**Figure**). The area under the curve for predicting CAL with various variables were as follows: serum NT-proBNP 0.932, WBC 0.719, CRP 0.646, serum sodium 0.539, serum albumin 0.673. Thus, the serum level of NT-proBNP was considered to be the best single predictor for CAL among these biochemical markers in patients with KD. A NT-proBNP cut-off value of 1300 pg/mL yielded a sensitivity of 95%, a specificity of 85%, a positive predictive value of 67%, and a negative predictive value of 98% for predicting CAL in the acute phase of KD (**Table II**). McCrindle et al reported that the normal anatomic variations in the size of LMT render the interpretation of CAL less reliable.[14] Therefore, we reanalyzed our data, excluding the two patients with enlargement of the LMT without accompanying dilation of pLAD artery or pRCA. Re-analysis confirmed the serum level of NT-proBNP to be the best single predictor for CALs. Its cut-off value of 1300 pg/mL yielded a sensitivity of 94%, a specificity of 83%, a positive predictive value of 59%, and a negative predictive value of 98%.

Seventeen of the 80 eligible patients were IVIG non-responders ($IVIG^-$) (**Table III**). There was no significant