J Compr Ped. 2014 November; 5(4): e19505. DOI: 10.17795/compreped-19505

Published online 2014 July 5. **Editorial**

Brain Natriuretic Peptide as a Novel Diagnostic Biomarker in Kawasaki Disease

Kazunari Kaneko [1,*]; Ken Yoshimura [1]; Shoji Tsuji [1]

[1]Department of Pediatrics, Kansai Medical University, Osaka, Japan

*Corresponding author: Kazunari Kaneko, Department of Pediatrics, Kansai Medical University, 2-5-1 Shin-machi, Hirakata-shi, P.O. Box: 573-1010, Osaka, Japan. Tel: +81-728040101-ext. 2560, Fax: +81-728042758, E-mail: kanekok@hirakata.kmu.ac.jp

Received: May 28, 2014; **Revised:** May 28, 2014; **Accepted:** June 3, 2014

Keywords: Kawasaki Disease; Brain Natriuretic Peptide (BNP); N-terminal pro-BNP (NT-proBNP)

Kawasaki disease (KD) was first described by Japanese pediatrician Tomisaku Kawasaki in 1967. Since then, KD has been reported in all racial and ethnic groups almost in children; in most series, 85% of patients were younger than 5 years. Annual incidence per 100000 children aged under 5 ranges from 3 in South America to 134 in Japan (1). KD is an acute systemic vasculitis primarily affecting small and medium-sized arteries, although its pathogenesis remains unknown. While self-limited, signs and symptoms evolve over the first 10 days of illness then gradually resolve spontaneously in most children, even in the absence of specific high-dose intravenous immunoglobulin (IVIG) therapy. Coronary arterial lesions (CAL) occur in 25% of untreated children and 3-5% of children treated with IVIG (1).

In the recent issues of this journal, two articles were published regarding the clinical characteristics of Iranian patients with KD (2, 3). Soleimani et al. concluded that KD should be considered in any infants or children with abnormal results in liver or renal function tests considering the high prevalence of abnormal value in such tests (46.8% in liver function test and 38.3% in renal function test including urinalysis) among Iranian KD children (2); meanwhile, Sedighi et al. found that common supplementary laboratory findings were leukocytosis, thrombocytosis and anemia. Furthermore, they concluded that the risk of developing CAL (22.4%) was high, probably due to the high prevalence of incomplete KD (40.4%) (3).

KD presents a challenge for clinicians as it can be difficult to recognize and no diagnostic laboratory tests are available. It is currently diagnosed by means of a case definition created for epidemiological surveys in Japan. Namely, the presence of fever for at least 5 days, lack of another known disease process to explain the illness, and the presence of four of the following five criteria (1): 1) bilateral conjunctival injection; 2) changes in the mucous membranes of the upper respiratory tract (injected pharynx, injected fissured lips, and strawberry tongue); 3) polymorphous rash; 4) changes in the extremities (peripheral edema, peripheral erythema, and periungual desquamation); and 5) cervical adenopathy. However, there is some concern over the appropriateness of this case definition as a clinical tool for identifying children requiring treatment for CAL, because in many cases not all of the clinical criteria are present. Incomplete KD has been considered for patients with fever lasting at least 5 days, at least two of the clinical criteria for KD, no other reasonable explanation for the illness, and laboratory findings consistent with severe systemic inflammation (1). This broader diagnostic definition of the disease was introduced to increase the awareness of diagnosing incomplete KD, because those patients are at considerable risk of CAL (4). Again, lack of a specific and sensitive diagnostic test remains a major obstacle in correctly identifying all patients with KD including those with incomplete KD.

Brain natriuretic peptide, or B-type natriuretic peptide (BNP), and its N-terminal moiety (N-terminal proBNP: NT-proBNP) comprise a cardiac hormone secreted mainly by the left ventricle. Cardiomyocytes synthesize a prepropeptide (preproBNP; 134 amino acids), which is split into a signal peptide and a propeptide (proBNP; 108 amino acids). During secretion from cardiomyocytes, proBNP is split at a ratio of 1:1 into physiologically active BNP (32 amino acids), which corresponds to the C-terminal fragment, and the biologically inactive NT-proBNP (76 amino acids) (5). Therefore, BNP secretion increases in proportion to the severity of ventricular dysfunction, and it has been suggested that this secretion is regulated mainly by the wall tension of the left ventricle (5).

In the last decade, BNP and NT-proBNP serum levels have been suggested as promising biomarkers for diagnosing KD (6-11). All found significant diagnostic values for KD as shown in Table 1. Dahdah et al. reported a clear advantage of NT-proBNP over BNP indicating superiority as a diagnostic biomarker in KD (7). This might be due to different half-lives of BNP and NT-proBNP

Table 1. BNP and NT-proBNP as Diagnostic Biomarkers in Kawasaki Disease [a]

BNP or NT-proBNP	Value of KD, Mean ± SD (No.)	Value of Febrile Control, Mean ± SD (No.)	Cut-Off Value	Specificity, %	Sensitivity, %	PPV, %	NPV, %	LR	Ref
NT-proBNP, pg/mL	749.66 ± 997.11 (59)	174.11 ± 144.30 (59)	219.7	71.2	71.2	78.0	64.9	2.47	(6)
NT-proBNP, ng/L	923.6 ± 1361.7 (43)	186.2 ± 198.0 (19)	170	63	78	n.a.	n.a.	2.14	(7)
BNP, pg/mL	55.0 ± 39.5 (32)	6.8 ± 7.3 pg/mL (26)	16.8	86.2	96.6	n.a.	n.a.	7.0	(8)
BNP, pg/ml	169.6 ± 529.6 (54)	12.2 ± 4.1 pg/ml (18: non-febrile)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	(9)
NT-proBNP, ng/L	1287.7 ± 2090.3 (81)	199.5 ± 274.3 ng/L (49)	Z-score > 2.0	91.8	70.4	93.4	65.2	8.59	(10)
NT-proBNP	n.a. (149)	n.a. (506)	Age dependent cut-offs (see text)	98.0	43.6	n.a.	n.a.	21.8	(11)

[a] Abbreviations: Ref: Reference Number; BNP: Brain Natriuretic Peptide; NT-proBNP: N-Terminal proBNP; KD: Kawasaki Disease; S.D.: Standard Deviation; PPV: Positive Predictive Value; NPV: Negative Predictive Value; LR: Likelihood Ratio; n.a.: Not Available; Z-Score: Absolute Value of Standard Deviation From the Mean.

(20-30 minutes versus 60-120 minutes, respectively). A rapid rise and fall of circulating BNP may not be readily captured in a disease where myocardial dysfunction is not an overt feature as in KD, while increased NT-proBNP appears to be sustained in the circulation, providing a more practical tool for tracing myocardial stress. Serum levels of BNP and NT-proBNP vary with age during childhood (12). Therefore, use of a single cut-off value would be inappropriate. For convenient use at the bedside, Shiraishi et al. reported age-related reference values of NT-proBNP. They established the following simple cut-off values every 100 pg/mL according to age based on a Z-score (standard deviation from the mean) > 2.0: 1000 pg/mL for age of 1-11 months, 900 pg/mL for 1 year, 800 pg/mL for 2 years, 700 pg/mL for 3 years, 600 pg/mL for 4 and 5 years, 500 pg/mL for 6 and 7 years, 400 pg/mL for 8 and 9 years, and 300 pg/mL for 10-15 years (11). In addition to the usefulness of NT-proBNP in diagnosis, we are the first to report it as a useful single biomarker to predict patients with KD at greater risk of CAL before initial IVIG. A NT-proBNP cut-off value of 1300 pg/mL yielded a sensitivity of 95% and a specificity of 85% for predicting CAL, while a cut-off value of 800 pg/mL yielded a sensitivity of 71% and a specificity of 62% for predicting IVIG nonresponders (13). Taken together, although not specific to the disease, NT-proBNP serum level should be measured as it is clearly superior to other laboratory tests not only for diagnosing KD, but also for predicting IVIG resistance and risk of CAL in KD.

Authors' Contributions

Study concept and design: Kazunari Kaneko and Ken Yoshimura; analysis and interpretation of data: Kazunari Kaneko, Ken Yoshimura and Shoji Tsuji; drafting of the manuscript: Kazunari Kazunari Kaneko; critical revision of the manuscript for important intellectual content: Kazunari Kaneko, Ken Yoshimura and Shoji Tsuji; statistical analysis: Kazunari Kaneko and Ken Yoshimura.

Funding/Support

This study was funded in part by grants (H26) from the Mami Mizutani Foundation, Japan.

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