RESEARCH PAPER

N-Terminal Pro–Brain Natriuretic Peptide Levels in Kawasaki Disease, Sepsis and Other Febrile Illnesses

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Received: Jun 2, 2022; *Initial review*: Aug 17, 2022; Accepted: May 27, 2023.

PII: S097475591600558

ABSTRACT

Objectives: To compare the values of N-Terminal Pro–Brain Natriuretic Peptide (NT-proBNP) in acute phase of Kawasaki disease (KD), sepsis and other acute febrile illnesses. ***Methods***: We conducted a cross-sectional study on 40 KD patients and 40 age- and sex-matched controls with sepsis and other febrile illnesses between January, 2019 and June, 2020. Complete blood count, C-reactive protein (CRP), liver and renal function tests, serum electrolytes, chest *X*-ray, NT-proBNP level, Bactec blood culture, urine microscopy and culture along with detailed physical examination was done for all cases and control. **Results**: Mean (SD) values of NT-proBNP levels in acute KD was higher than sepsis/other febrile illnesses (914.9 (pg/mL) vs 219 (pg/mL); *P*=0.001). Also, the number of KD patients whose NT-proBNP was elevated were significantly higher compared to controls [(70%) vs (32.5%); *P*<0.001]. **Conclusions**: NT-proBNP may be useful as a bio-marker in the diagnosis of acute phase KD.

Keywords: *Biomarker, Diagnosis, Infection, Myocardial stress*.

Kawasaki disease is an acute self-limiting vasculitis predominantly affecting medium sized arteries. In the absence of specific diagnostic tests, diagnosis is based mainly on clinical criteria [1,2]. Because of overlapping clinical features, differentiation from sepsis and other inflammatory fevers of childhood becomes difficult. Thus we need to investigate for new markers which might help us to diagnose Kawasaki disease with certainty.

Brain-type natriuretic peptide (BNP) was first described in 1988 after isolation from porcine brain. Later it was found to originate mainly from the heart representing a cardiac hormone [3]. NT-proBNP level rises in children with acute Kawasaki disease, but the mechanism is not clear [4,5]. Sepsis is a dreaded complication of severe trauma, extensive burns, shock, and other severe infections that result in multi-organ dysfunction. Affection of the cardiovascular system in sepsis leads to increased plasma NT-proBNP levels [6,7].

This study was undertaken to compare NT-proBNP levels in Kawasaki disease, sepsis and other febrile conditions to evaluate its utility, if any, as a biomarker in acute Kawasaki disease [8].

METHODS

This was a hospital based cross-sectional observational study conducted at a tertiary referral hospital in eastern India. Children admitted between January, 2019 to April, 2020 with Kawasaki disease, sepsis and other febrile illnesses were included. Since the average number of KD admissions at the institute ranged between 35 to 40 in a year since 2015, and the study was over 16 months, we decided to enroll 40 KD patients presenting during the study period as the ‘case’ group. KD was diagnosed based on 2017 AHA (American Heart Association) criteria. The ‘control’ group comprised of another 40 children with sepsis or

other febrile illnesses. Patients with structural heart disease, cardiomyopathy, renal failure, and those receiving chemotherapy/immunosuppressive therapy were excluded.

All patients had a complete blood count, C-reactive protein (CRP), liver and renal function tests, serum electrolytes, chest x-ray, NT-proBNP level, Bactec blood culture, urine microscopy and culture along with detailed physical examination. KD patients as well as those with suspected cardiac dysfunction had ECG and echocardiography. Blood samples were collected at admission before administering specific therapy. NTproBNP levels were measured by ROCHE e411 using electrochemiluminiscence immunoassay.

Institutional Ethics Committee clearance (IEC/174/2018) was taken prior to conducting the study. Since this was a pre-COVID study, patients with multi system inflammatory syndrome (MIS-C) were not included.

Statistical analysis: Data was entered into a Microsoft excel spread sheet and then analyzed by SPSS (version 27.0; SPSS Inc.) and Graph Pad Prism version 5. We used two-sample *t*-test for difference in mean and a chi square test for difference in categorical variables chi-squared distribution when the null hypothesis is true. Correlation was calculated by Pearson correlation analysis. P value ≤ 0.05 was considered as statistically significant.

RESULTS

The median (range) age of 40 children with Kawasaki disease (21 boys) was 19 (3-108) months, and for the control group (24 boys), it was 44 (3-204) months. The mean (SD) duration of fever in Kawasaki disease was 7.8 (2.47) days, and 9.7 (2.36) days for the control group.

The control group comprised of 13 children with culture proven sepsis, 4 with pneumonia, 5 with enteric fever, 3 with systemic juvenile idiopathic arthritis, 2 with systemic lupus erythematosus, 3 with malaria, 4 with dengue, and the rest of the children had viral respiratory tract infections. Of the KD patients, 13 (32.5%) had coronary artery aneurysms at diagnosis, and 8 (20%) were intravenous immunoglobulin resistant.

Twenty eight (70.0%) patients in KD group had high NT-proBNP levels. In control group, 13 (32.5%) had high NT-proBNP and 27 (67.5%) had normal levels. Association of frequencies of patients having NT-proBNP level above and below cut-off value between KD and control group was statistically significant ($P<0.001$).

In KD, the mean (SD) NT-proBNP level was 914.91 pg/mL, whereas amongst controls the level was 219.03 pg/mL ($P=0.001$). Correlating NT-proBNP levels with other laboratory parameters, it was found it to be significantly positively correlated with platelet count and negatively correlated with leukocyte count, serum potassium and albumin levels (**Table I**). However, NT-proBNP levels with respect to echocardiographic findings/ IVIG resistance in the KD patients was not analyzed.

DISCUSSION

Diagnosis of KD depends on the recognition of a sequence of characteristic clinical findings. All clinical features may not be present at same time, and in the absence of a sensitive and specific pathognomonic laboratory test, diagnosis maybe difficult. Hence differentiation from sepsis and other autoimmune/

inflammatory fevers of childhood becomes difficult [1]. The difficulty is more with incomplete and atypical presentations, consequently leading to a delayed diagnosis and increased risk of coronary artery involvement.

Several studies have explored the use of potential bio markers to aid in the diagnosis of KD, NT-proBNP being one of the markers. Studies have shown the utility of this biomarker in diagnosis of infantile and incomplete forms of KD [10,11] and also in predicting Intravenous Immunoglobulin (IVIg) resistance and coronary artery lesions [12,13].

BNP is synthesized as a pro-hormone (proBNP) by the myocardium. Myocardial ischaemia, cytokines and endocrine (paracrine) modulation by other neurohormones are important stimulus for release of these molecules. Natriuresis or diuresis, peripheral vasodilatation, inhibition of the renin–angiotensin–aldosterone system and the sympathetic nervous system are the main physiological effects of BNP. NT-proBNP is mainly cleared from body by renal excretion, half-life is 120 mins.

Sepsis being a severe complication of many critical situations, early evaluation of its severity and initiation of proper treatment is important to reduce mortality. Procalcitonin, C-reactive protein, activated protein C, are the known predictors. Recently NT-proBNP has been included in the list, increased levels being used as a marker of cardiac insufficiency secondary to sepsis and a poor prognostic indicator.

Based on the IAP (Indian Academy of Pediatrics) Position Paper on KD, we considered values of NT-proBNP above 225 pg/ml as significant.[8] As already mentioned, the number of patients with KD who had NT-proBNP levels above cut-off value was significantly more than the number in control group. This was consistent with the results of previous studies [14,15]. It was also shown that even patients with incomplete KD had higher NT-proBNP levels than febrile control group (84% vs 4%; $P<0.001$).

There are some limitations to our study. It was a cross-sectional, single centre study. Sample size was small and study subjects were enrolled from the inpatient department of a tertiary hospital, thereby raising the possibility of a referral bias. We did not analyse NT-proBNP values with respect to coronary artery dimensions. Future studies with

a larger sample size and longitudinal design should be able to contribute more in the diagnostic importance of NT-proBNP in KD and generate cutoff values to distinguish KD and other fevers.

To ease diagnosis of KD and for timely initiation of immunoglobulin therapy, there is need for an early diagnostic test. Like previous studies from Northern India that explored the role of NT-proBNP in KD [14], we too state that NT-proBNP measurement may play a significant role in the diagnostic algorithm of suspected KD, even in patients with incomplete presentations.

Ethics clearance: Institutional Ethics Committee, Institute of Child Health, Kolkata; No. ICH/IEC/91/2018 dated Dec 29, 2018.

Contributors: PP: formulated and designed the study and provided statistical support; PB: conducted the study including preparation of proforma, data collection, blood sample collection and manuscript writing; SC: guided PB and assisted in writing the manuscript; SB: conducted the laboratory tests and interpreted them; NA helped PB in data collection and manuscript writing. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.

Funding: None; *Competing interests*: None stated.

WHAT THIS STUDY ADDS

NT-proBNP measurement plays a significant role in the diagnostic algorithm of suspected KD, even in patients with incomplete presentations.

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Table I Correlation Between NT-proBNP Level and Other Laboratory Parameters in Children with Kawasaki Disease (*N*=40)

Parameters	*Correlation Coefficient*	*P value*
Hemoglobin (g%)	0.066	0.688
Total leukocyte count	0.315	0.048
Platelet count	0.469	0.002
Erytherocyte sedimentation rate	0.075	0.646
C-reactive protein	0.233	0.148
Serum sodium	0.110	0.500
Serum potasium	0.370	0.019
Blood urea	0.087	0.595
Serum creatinine	0.077	0.637
Serum albumin	0.660	<0.001