

Significance of Serum NT-proBNP and Endogenous H₂S for Predicting Coronary Artery Lesions in Pediatric Kawasaki Disease

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ABSTRACT

Objective: To determine the expression levels and clinical significance of serum N-terminal pro-brain natriuretic peptide (NT-proBNP), hydrogen sulfide (H₂S) and interleukin-6 (IL-6) in children with Kawasaki disease (KD).

Study Design: Descriptive comparative study.

Place and Duration of Study: Department of Pediatric Medicine, Baoding Children's Hospital, from July 2017 to July 2018.

Methodology: Ninety-five KD children were chosen as the case group, and were classified into CAL group (23 patients) and NCAL group (72 patients, according to the presence of a coronary artery lesion (CAL). Forty-six non-KD children with an upper respiratory infection in the same time period were chosen as the control group. Electrochemiluminescence method was used to detect serum NT-proBNP levels. The spectrophotometer method was used to test H₂S levels, and an enzyme-linked immunosorbent assay was used to test serum IL-6 levels and to analyse the correlation.

Results: In the acute phase and recovery phase, serum NT-proBNP and IL-6 levels were higher in the case group than the control group, while H₂S levels were lower than those in the control group ($p < 0.001$). In both the acute and recovery phases, serum NT-proBNP and IL-6 levels were higher in the CAL group than in the NCAL group, while H₂S levels were lower than those in the NCAL group ($p < 0.001$).

Conclusion: NT-proBNP and IL-6 levels rise and the H₂S level decreases in the blood of KD children, indicating that these indicators may participate in the pathogenesis of KD and that their levels are related to CAL occurrence and the vascular inflammatory response.

Key Words: Kawasaki disease (KD), Coronary artery lesion (CAL), Serum NT-proBNP, H₂S, IL-6.

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INTRODUCTION

Kawasaki disease (KD) is also called mucocutaneous lymph node syndrome and can affect children aged six months to five years. Kawasaki disease is characterised by a high activation of the immune system and vasculitis and manifests as acute fever, rash and lymphadenectasis.¹ The coronary artery is generally susceptible, and 20%-25% of KD children, who do not receive treatment, have a coronary artery lesion (CAL). This may even lead to a coronary artery aneurysm or thrombus; therefore, KD is an important pathogenic factor for secondary heart disease.²

Presently, the diagnosis of KD mainly depends on the clinical manifestations, and there is a lack of specific

indicators. In addition, CAL can be detected only 2-3 weeks after KD attack.³ Seeking detection indicators with good specificity is significant for the auxiliary diagnosis of KD, CAL reduction and prognosis improvement. NT-proBNP is a polypeptide that is secreted and synthesised by ventricle muscle cells after an external stimulus, and it is often used to diagnose acute congestive heart failure and assess prognosis.^{4,5} Endogenous H₂S, which is a gas signal transduction molecule, plays an important role in protecting the cardiovascular system and can regulate inflammatory cytokines.⁶ IL-6 is an important member of the cytokine family and is also an important indicator reflecting the severity class of heart failure.^{7,8} The aim of this study was to determine serum NT-proBNP, H₂S, and IL-6 levels in children with KD and correlate with the occurrence of CAL.

METHODOLOGY

This descriptive comparative study was conducted at the Department of Pediatric Medicine, Baoding Children's Hospital, from July 2017 to July 2018. It was approved by the Institutional Ethics Committee of the Hospital, and

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written informed consents were obtained from all participants. Ninety-five hospitalised children with KD, who conformed to the Kawasaki Disease Diagnosis Guide-9, were chosen for the case group. There were 23 patients with ultrasonic cardiogram results that conformed to the CAL diagnosis standards that were classified as the CAL group,⁹ and 72 patients without CAL were classified as the NCAL group. The inclusion criteria were the patient conforming to the above standards, patient with acute phase disease and that the patient did not receive gamma globulin (IVIG) or aspirin treatment. The exclusion criteria for the patients were cardiac, liver or kidney dysfunction, hormone or other medical treatment received within three months, autoimmune disease, and acute or chronic infectious diseases.

After the children in the case group were hospitalised (5-7 days after the attack), 2ml of venous blood was gathered before IVIG and aspirin treatment as well as in the recovery phase (10 days after the attack). In the control group, 2ml of venous blood was gathered under empty-stomach conditions in the morning. The blood remained stationary for half an hour at room temperature and was then centrifuged for 10 minutes at 4°C at 3000 r/min. Then, the serum was separated and stored at -70°C. Electrochemiluminescence method was used to detect serum NT-proBNP levels. Spectrophotometer method was used to test H₂S levels, and enzyme-linked immunosorbent assay was applied to test serum IL-6 levels.

SPSS version 22.0 statistical software was applied for the analysis. Measurement data was expressed as $\bar{x} \pm s$. Comparison of gender composition was conducted by the χ^2 test. Variance analysis was used for the three-way intergroup comparisons, and paired t-test was adopted for 3-way intergroup comparisons with $p < 0.05$ indicating statistical significance.

RESULTS

Serum NT-proBNP levels of the case group in the acute phase were higher than those of the control group, the

H₂S levels were lower than those of the control group, and the IL-6 levels were higher than those of the control group ($p < 0.001$). The serum NT-proBNP levels of the case group in the recovery phase were higher than those of the control group, the H₂S levels were lower than those of the control group, and the IL-6 levels were higher than those of the control group ($p < 0.001$), as shown in Table I.

Serum NT-proBNP levels of the CAL group in the acute phase were higher than those of the NCAL group, the H₂S levels were lower than those of the NCAL group, and the IL-6 levels were higher than those of the NCAL group ($p < 0.001$). The serum NT-proBNP levels of the CAL group in the recovery phase were higher than those of the NCAL group, the H₂S levels were lower than those of the NCAL group, and the IL-6 levels were higher than those of the NCAL group ($p < 0.001$), as shown in Table II.

DISCUSSION

For acute KD, the immune system presents an over-active state. Immune cells activate and release multiple factors that influence the blood vessel endothelium to different degrees.¹⁰ Thus, CAL is the most common and severe complication of KD and can lead to myocardial infarction, coronary artery occlusion and even sudden death.¹¹ The initial symptoms of KD patients are generally fever, similar to the fever, rash and lymph node enlargement caused by the influenza virus, adenovirus or rubella virus. The early diagnosis of CAL depends only on clinical manifestations and relevant auxiliary examinations, and the diagnostic rate is low.¹²

NT-proBNP is a peptide that is mainly synthesised by ventricular muscle cells. When myocardial ischemia and necrosis occur, cardiac muscle cells speed up to secrete NT-proBNP.¹³ A change in the NT-proBNP level is of great significance in the diagnosis of cardiovascular disease in children.¹⁴ Reddy found that for KD children in northern India, serum NT-proBNP levels in the acute phase were obviously higher than those in the recovery

Table I: Comparison of NT-proBNP, H₂S and IL-6 levels in the CAL group, NCAL group, and control group in the acute and recovery phases ($\bar{x} \pm s$).

Group	No.	Acute phase			Recovery phase		
		NT-proBNP ($\mu\text{g/L}$)	H ₂ S ($\mu\text{mol/L}$)	IL-6 (ng/L)	NT-proBNP ($\mu\text{g/L}$)	H ₂ S ($\mu\text{mol/L}$)	IL-6 (ng/L)
CAL group	23	1.67 \pm 0.22	21.36 \pm 9.00	154.18 \pm 40.05	1.12 \pm 0.11	31.95 \pm 8.45	100.82 \pm 23.86
NCAL group	72	0.95 \pm 0.18	40.15 \pm 11.39	115.93 \pm 36.56	0.67 \pm 0.09	51.13 \pm 14.80	81.69 \pm 19.53
Control group	46	0.28 \pm 0.09	60.29 \pm 10.82	61.97 \pm 13.89	0.28 \pm 0.09	60.29 \pm 10.82	61.97 \pm 13.89
F		575.917	106.277	74.220	643.508	37.959	35.378
p		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Table II: Comparison of NT-proBNP, H₂S and IL-6 levels in the CAL group and NCAL group in the acute and recovery phases ($\bar{x} \pm s$).

Group	No.	Acute phase			Recovery phase		
		NT-proBNP ($\mu\text{g/L}$)	H ₂ S ($\mu\text{mol/L}$)	IL-6 (ng/L)	NT-proBNP ($\mu\text{g/L}$)	H ₂ S ($\mu\text{mol/L}$)	IL-6 (ng/L)
CAL group	23	1.67 \pm 0.22	21.36 \pm 9.00	154.18 \pm 40.05	1.12 \pm 0.11	31.95 \pm 8.45	100.82 \pm 23.86
NCAL group	72	0.95 \pm 0.18	40.15 \pm 11.39	115.93 \pm 36.56	0.67 \pm 0.09	51.13 \pm 14.80	81.69 \pm 19.53
t		21.958	-11.034	6.378	28.138	-9.684	5.898
p		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

phase, and the rise in serum NT-proBNP levels in the coronary artery change group was more significant than that in the nonchange group.¹⁵ However, there is still no single biochemical criterion to effectively predict CAL in KD children.¹⁶ Yoshimura *et al.* believed that the serum NT-proBNP level could serve as an indicator to predict CAL in KD children.¹⁷ The current study showed that the NT-proBNP level change was not only related to the pathogenesis of KD, but also could serve as a potential marker to reflect CAL in KD children.¹⁸

IL-6 can induce the growth and differentiation of T and B lymphocytes, and it is an important indicator to predict criticality and morbidity in cardiovascular disease.¹⁹ IL-6 participates in KD attack and CAL occurrence by causing a vascular inflammatory response due to its strong pro-inflammatory effect. This study showed that the IL-6 levels in KD children were higher than those in children with a fever caused by an upper respiratory infection, indicating that a rise in IL-6 levels might be related to KD attack. Additionally, the IL-6 levels in the CAL group were higher than those in the NCAL group, indicating that CAL occurs more easily with higher IL-6 levels.

H₂S possesses multiple physiological effects, such as dilating blood vessels and inhibiting vascular smooth muscle cell proliferation and myocardial strength, and it extensively participates in cardiovascular disease attack and prognosis.²⁰ H₂S can neutralise oxidized low-density lipoprotein and reduce endangium and myocardial damage by inhibiting the release of inflammatory mediators and eliminating and lightening calcium overload.²¹ This study showed that the H₂S levels in KD children were lower than those in children with a common fever and that the H₂S levels in the CAL group were lower than those in the NCAL group, proving that a change in the H₂S level is related to KD attack and CAL occurrence.

IL-6 can facilitate cardiomyocyte brain natriuretic peptide (BNP) and heart natriuretic peptide gene expression, thus leading to cardiac insufficiency.²² H₂S can inhibit the inflammatory response through the inhibition of IL-6 inflammatory cytokines. This study found that the serum NT-proBNP and IL-6 levels in KD children were positively correlated and that the H₂S and IL-6 levels were negatively correlated. Therefore, it is inferred that in the initial phase of KD, inflammatory cytokine inhibition increases or decreases, and cytokines are released in quantity, thus resulting in immune dysfunction, vasculitis and even CAL.

CONCLUSION

Serum NT-proBNP, H₂S and IL-6 levels can be used as important indicators to diagnose KD in the early phase and to assess CAL.

ETHICAL APPROVAL:

The study was approved by the Institutional Ethics Committee of Baoding Children's Hospital, and ethical approvals were obtained prior to initiation of the research work.

PATIENTS' CONSENT:

The informed consents were obtained from all patients to publish the data concerning this case.

CONFLICT OF INTEREST:

Authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

HBS, YDZ: Designed this study and prepared this manuscript.

QWD, LPH, RFQ: Collected and analysed clinical data.

BBB, LM, HZ: Significantly revised this manuscript.

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