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ORIGINAL RESEARCH

Expression of PCT, BNP and Inflammatory Factors in Children with Kawasaki Disease and Their Correlation with Coronary Artery Lesions

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ABSTRACT

Background • Kawasaki disease (KD), as one of the most common vascular diseases in children, will cause the risk of coronary artery lesions (CAL) without treatment. This study is to explore the expression of procalcitonin (PCT), brain natriuretic peptide (BNP), tumor necrosis factor-α (TNF-α), C-reactive protein (CRP) and interleukin-6 (IL-6) in children with KD and their correlation with CAL.

Methods • 86 KD children in Baoding Hospital of Beijing Children's Hospital were selected as the study subjects from January 2020 to June 2021. According to whether CAL occurred, they were divided into the CAL group (n=30) and NCAL group (n=56). The clinical data of the two groups were collected from the medical record system. The levels of PCT and BNP were detected by chemiluminescence microparticle assay, the CRP level was detected by immunoturbidimetry, and the levels of TNF-α and IL-6 were detected by flow immunofluorescence method. The relationship of PCT, BNP, and inflammatory factors with CAL in KD children was explored by Pearson correlation analysis.

Results • The comparative result of clinical data showed no overt difference in gender, disease types, age and blood routine indexes between the two groups, except for coronary artery diameter (P >.05). The levels of PCT, BNP, CRP, TNF-α and IL-6 in CAL group were (1.70±0.39) μg/L, (289.21±29.78) ng/L, (83.16±17.35) mg/L, (9.38±1.23) pg/mL and (59.97±0.97) ng/mL, respectively. The levels of PCT, BNP, CRP, TNF-α and IL-6 in NCAL group were (1.04±0.18) μg/L, (170.85±23.58) ng/L, (69.70±16.64) mg/L, (6.32±0.73) pg/mL and (44.16±11.97) ng/mL, respectively. The levels of each index in the CAL group were notably higher than in the NCAL group (P < .001). Pearson correlation analysis revealed that PCT, BNP, CRP, TNF-α and IL-6 were positively correlated with CAL in KD children (r=0.829, 0.865, 0.823, 0.894, 0.784, P < .001).

Conclusion • The increase of PCT, BNP, and inflammatory factors has a certain warning effect on CAL in KD children. In clinical practice, health care professionals should strengthen the detection of PCT, BNP and inflammatory factors in KD children, carry out early monitoring of CAL in children with high expression of biomarkers, and formulate personalized preventive intervention based on the disease progress, so as to reduce the risk of cardiovascular disease. However, due to the limitations of research conditions and methods, the sample size of this study is small, which may affect the reliability and representativeness of the conclusion. In order to provide a new direction for the clinical prevention and treatment of the disease, future work will improve the research design, expand the sample size, and carry out more in-depth exploration on the prediction of CAL in KD children. (*Altern Ther Health Med.* 2024;30(1):302-306).

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INTRODUCTION

Kawasaki disease (KD), an acute febrile rash in children, mainly occurs in children under 5 years old and infants and is more common in boys.[1] Its clinical features in children are mainly rash, redness of oral mucosa, hyperemia of conjunctiva and swelling of extremities, and studies have shown that it may also involve multiple system injuries.[2] Coronary artery lesions (CAL) is one of the most serious complications caused by KD, with potential long-term effects. Failure to take early treatment leads to arterial thrombosis, stenosis and even sudden death in

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children, with a high risk.[3] It can be seen that finding effective predictive factors and diagnostic markers is very important. In recent years, immunoglobulin has been widely used in clinical treatment of KD, and has achieved certain results, which can reduce coronary artery complications to a certain extent. Nevertheless, the incidence of CAL in KD children is still high, which still remains a matter of concern.[4] Recent report[5] has shows that about 30%-50% of KD children may have CAL, which can develop into acquired heart disease without treatment. Relevant research[6] has pointed out that the complication (CAL) first appears on the third day after the onset of KD in children, but the detection rate of imaging diagnosis within one week after the onset was not high, and a more accurate diagnosis could not be obtained until the second to third weeks after the onset. Therefore, it is of great significance to strengthen the study on the mechanism of CAL in KD children and explore effective disease predictors for clinical treatment and prognosis. Procalcitonin (PCT) is currently recognized as a marker of systemic infectious diseases, whose level increases during local infection caused by the invasion of bacteria and viruses, which is often used in the examination of infectious diseases such as sepsis. However, some scholars[7] have believed that it may be closely related to the inflammatory response of coronary heart disease. Brain natriuretic peptide (BNP), a cardiac endocrine hormone, has the effects of diuresis and sodium excretion, and it is mostly regarded as a sensitive index related to myocardial injury nowadays, but few studies have analyzed its application value in KD combined with CAL.[8] Clinical data show that KD is a disease of immune disorder, whose occurrence may be related to multiple immune factors.[9] In the acute and subacute stages of KD, immune activation leads to abnormal activation of T cells and monocytes, releases a large number of cytokines and inflammatory mediators, including tumor necrosis factor-α (TNF-α), C-reactive protein (CRP) and interleukin-6 (IL-6), causes the injury, apoptosis and necrosis of vascular endothelial cells, thereby leading to endothelial dysfunction, destroying vascular barrier and boosting the occurrence of CAL. Still, there is no comprehensive study to explore the correlation of the above factors with CAL in KD children. In view of this, the clinical data of 86 KD children in Baoding Hospital of Beijing Children's Hospital were collected to comprehensively explore the expression of PCT, BNP, TNF-α, CRP and IL-6 in KD children and their correlation with CAL.

MATERIALS AND METHODS

Study materials

The subjects were 86 KD children admitted to Baoding Hospital of Beijing Children's Hospital from January 2020 to June 2021, including 47 males and 39 females, with an average age of (3.44±1.15) years old. There were 49 cases with complete KD and 37 cases with incomplete KD, and patients were divided into the CAL group (n=30) and NCAL group (n=56) according to whether CAL occurred. This study conforming to the principles of Declaration of Helsinki (2013)[10] has been approved by the ethical committee of Baoding Hospital of Beijing Children's Hospital (approval No.: 202205).

Inclusion and exclusion criteria

Inclusion criteria. (1) Patients met the diagnostic criteria of KD in the Guidelines of the Italian Academy of Pediatrics,[11,] and the course of KD was less than 10 days. (2) The ultrasound cardiography was performed, and children in the CAL group were diagnosed with CAL, namely, echo enhancement of coronary tunica intima, CAL including coronary artery dilatation (coronary artery diameter>3.0 mm in children aged 0-5 years old, coronary artery diameter>4.0mm in children aged 5-14 years old), or any coronary artery diameter is 1.5 times the diameter of the adjacent segment.[12] Children in the NCAL group did not meet the above diagnostic criteria for CAL. (3) Patients had complete data.

Exclusion criteria. (1) Patients with autoimmune diseases or congenital diseases; (2) patients with malignant tumors; (3) patients with dysfunctions in vital organs such as liver and lung; and (4) patients with other hematological diseases.

Methods and Observation Indices

(1) The imaging data of echocardiography in the two groups were given to a highly qualified physician with rich clinical experience to measure the inner diameter of the coronary artery.

(2) Fasting venous blood of all children was taken for blood routine examination, and white blood cell count, neutrophils, hemoglobin, erythrocyte sedimentation rate, and other indicators were measured.

(3) In the early morning, 5 ml of fasting venous blood was taken from children, which was placed in a low-temperature environment for 30 min to centrifuge at 2500 r/min, with radius and time of centrifugation as 4cm and 10min, then storing in a refrigerator at -20°C for testing. The chemiluminescence microparticle assay was used to detect the levels of PCT and BNP, using the kit and detection instruments provided by Shenzhen Mindray Bioelectronics Co., Ltd. (Shenzhen, China), and the detection was in accordance with the instructions. The operation steps are as follows. a. The kit was opened, and the batch numbers of test card, buffer and ID chip were confirmed. b. The serum was added to the centrifuge tube containing buffer solution and thoroughly mixed for 1min. c. The above solution was added to the sample hole of test card. d. The detection mode was selected. e. After the completion of test, the test card was removed and processed in accordance with the regulations. The immunoturbidimetry was adopted to test CRP level using the kit and detection instruments produced by Shenzhen Goldsite Biotechnology Co., Ltd. (Shenzhen, China), and the detection was in accordance with the instructions. The operation steps are as follows. a. Reagent 1 was added to the sample and placed at 37°C for 2-5min. b. Reagent 2 was added to the sample and placed for 10s. c. The absorbance A1 was recorded after 10s, the absorbance A2

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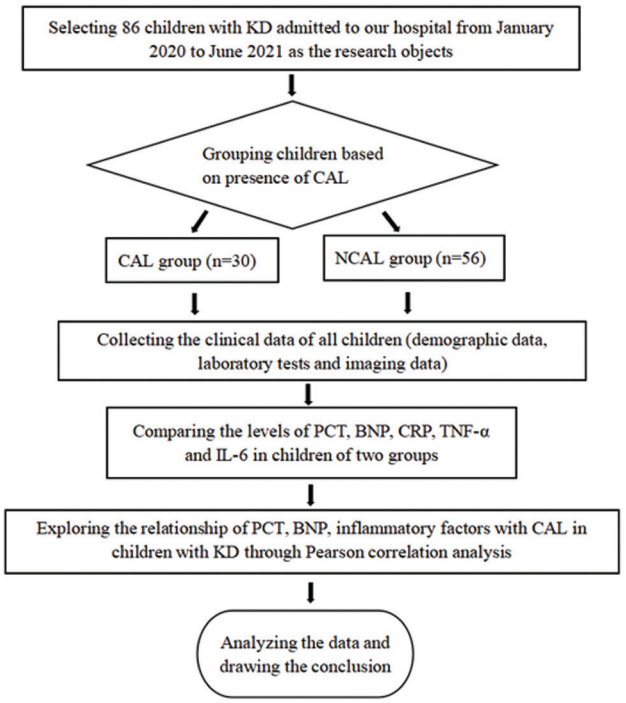
Figure 1. Technical route



was recorded after 300s, and then the results were calculated. The flow immunofluorescence method was adopted to detect the levels of TNF-α and IL-6, using the kit produced by Tianjin Kuangbo Tongsheng Biotechnology Co., Ltd. (Tianjin, China) and detection instruments produced by Shenzhen Mindray Bioelectronics Co., Ltd. (Shenzhen, China), and the detection was in accordance with the instructions. The operation steps are as follows: dilution → sample addition → incubation → fluid preparation → washing → enzyme supplementation → incubation → washing → color development → termination → detection.

The technical route of this study. 86 children with KD admitted to Baoding Hospital of Beijing Children's Hospital from January 2020 to June 2021 were selected as the research subjects. According to whether CAL occurred, they were divided into CAL group (n=30) and NCAL group (n=56). The clinical data of the two groups were collected, including demographic data, laboratory tests and imaging data. The levels of PCT, BNP, CRP, TNF-α and IL-6 in the two groups were measured and compared. Then Pearson correlation analysis was used to explore the relationship of PCT, BNP, inflammatory factors with CAL in KD children. Finally, according to the data analysis results, the discussion was carried out, as shown in Figure 1.

Statistical analysis

The data obtained in this study were processed by the professional statistical software Statistic Package for Social Science (SPSS) for Windows version 26.0 (Armonk, State of New York, USA). The enumeration data were tested by χ^2 test (importing data → weighted processing → analysis → descriptive statistics → cross table → selection statistics), and its expression format was expressed by [n(%)]. The measurement data conforming to the normal distribution were tested by *t* test, expressed by Mean±SD, and those not conforming to the normal distribution were tested by Mann-Whitney U test (importing data → non-parametric test → two-sample independent test → Mann-Whitney U test). Pearson correlation analysis was used to explore the correlation. When P<0.05, it indicated that the observed differences were statistically significant.

Table 1. Comparison of clinical data in both groups

Items	CAL group (n = 30)	NCAL group (n = 56)	χ^2/t	*P* value
Gender [n(%)]			0.032	.857
Male	16 (53.33)	31 (55.36)		
Female	14 (46.47)	25 (44.64)		
Disease types			0.076	.783
Completeness	17 (56.67)	32 (57.14)		
Incompleteness	13 (43.33)	24 (42.86)		
Age (Mean±SD, years)	3.37±1.10	3.48±1.19	-0.442	.673
Coronary artery diameter (Mean±SD, mm)	3.86±0.35	2.04±0.47	20.877	<.001
White blood cell count (Mean±SD, $\times10^9$/L)	15.97±3.96	16.10±3.53	-0.177	.860
Neutrophils (Mean±SD, %)	68.85±9.07	68.06±8.97	-0.331	.743
Erythrocyte sedimentation rate (Mean±SD, mm/h)	41.43±3.67	40.71±3.85	0.142	.888
Place of residence			0.249	.617
Urban area	14 (46.47)	23 (41.07)		
Rural area	16 (53.33)	33 (58.92)		

Table 2. Comparison of PCT, BNP and inflammatory factors in both group [Mean±SD]

Groups	n	PCT (μg/L)	BNP (ng/L)	CRP (mg/L)	TNF-α (pg/mL)	IL-6 (ng/mL)
CAL group	30	1.70±0.39	289.21±29.78	83.16±17.35	9.38±1.23	59.97±0.97
NCAL group	56	1.04±0.18	170.85±23.58	69.70±16.64	6.32±0.73	44.16±11.97
t		-6.851	-7.122	3.001	12.313	5.192
P value		<.001	<.001	.005	<.001	<.001

Table 3. Correlation of PCT, BNP and inflammatory factors in KD children with CAL

Factors	R value	*P* value
PCT	0.829	<.001
BNP	0.865	<.001
CRP	0.823	<.001
TNF-α	0.894	<.001
IL-6	0.784	<.001

RESULTS

Comparison of clinical data in both groups

The comparative result of clinical data showed no overt difference in gender, disease types, age, and blood routine indexes between the two groups, except for coronary artery diameter ($P > .05$), as detailed in Table 1.

Comparison of PCT, BNP, and inflammatory factors in both groups

Table 2 showed that PCT, BNP, CRP, TNF-α and IL-6 levels in the CAL group were notably higher than in the NCAL group, with a statistical significance ($P < .001$).

Correlation of PCT, BNP, and inflammatory factors in Kawasaki disease (KD) children with coronary artery lesions (CAL)

Pearson correlation analysis revealed that PCT, BNP, CRP, TNF-α and IL-6 were positively correlated with CAL in

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KD children, with a statistical significance (r=0.829, r=0.865, r=0.823, r=0.894, r=0.784, $P < .001$), indicating that the higher the level of the above factors, the higher the risk of CAL in KD children. See details in Table 3.

DISCUSSION

KD is also known as mucocutaneous lymph node syndrome, whose incidence has been increasing in recent years and has gradually replaced acute rheumatic fever as the main cause of acquired heart disease in children.[13,14] The pathogenesis of KD is very complex, and at present, most scholars believe that it is related to the immune activation of mononuclear macrophage and vascular injury of matrix metalloproteinase.[15,16] Children with KD are prone to CAL, in which coronary artery dilatation is usually the main manifestation. This study showed that the CAL group had significantly wider coronary artery diameter than the NCAL group (P<0.001). Coronary artery dilatation is usually the formation of aneurysms after the destruction of the muscular layer caused by arteritis. CAL causes coronary artery stenosis or thrombosis in children with AD to aggravate the disease and overtly increases the risk of myocardial infarction or death in adulthood without effective treatment,[17,18] so prevention and early detection are still the focus of current treatment. PCT, a common sensitive indicator of clinical bacterial infection and a calcitonin precursor without hormone activity is also highly expressed in non-infectious diseases such as systemic lupus erythematosus and rheumatoid arthritis.[19]

A foreign study[20] has measured the serum PCT level of 85 KD children, finding that the PCT level of children with resistance of gamma globulin significantly increases, and the treatment effect of children with high PCT levels is very small, which is more likely to occur CAL. The results of this study were similar to above results, showing that the level of PCT in the CAL group was significantly higher than that in the NCAL group ($P < .001$), illustrating that it is necessary to conduct the early monitoring of PCT in KD children. BNP is a peptide hormone produced by myocardial cells, whose level expression is related to ventricular pressure and myocardial function, as a sensitive index to judge heart failure. The data of this study showed that the BNP level in the CAL group was significantly higher than that in the NCAL group ($P < .001$), which was similar to the research viewpoint of Zheng Xiaolan et al[21]. They believed that N-terminal pro-brain natriuretic peptide can be used as a biomarker for predicting CAL. In the future, more comprehensive studies can be carried out to explore the correlation between different types of BNP and CAL in KD children, so as to find more accurate prediction indexes.

The nuclear factor kappa-B (NF-kB) system mainly involves the body's defense reaction, tissue damage and stress, cell differentiation and apoptosis, and information transmission during tumor growth inhibition, playing an important role in vascular inflammation caused by KD in children by regulating the expression of inflammatory factors. A variety of cytokines can activate NF-kB, and current studies have confirmed that TNF-α can activate NF-kB by activating corresponding signaling pathways. Meanwhile, coronary arterial endothelial injury is an important pathological phenomenon of CAL in KD. It can be seen that the expression of TNF-α may be related to the occurrence of vascular inflammation.[22] IL-6 is a member of the chemokine family, which is involved in activating and regulating immune cells. The study[23] has suggested that IL-6 and TNF-α work together in the microcirculation system and participate in the progression of vascular inflammation. Based on the above theory, this study compared the differences of CRP, TNF-α, and IL-6 between KD children with CAL and those without CAL, aiming to more intuitively understand the relationship of immune activation and inflammatory response with CAL.

The results showed that the levels of PCT, BNP, CRP, TNF-α and IL-6 in the CAL group were overtly higher than in the NCAL group (P<0.001), speculating that KD Children have immune disorders in the acute phase of the disease, and the abnormal activation of the immune system produces a large amount of TNF-α and IL-6, increases the level of inflammatory factors in the body, and aggravates the inflammatory response in KD children. In particular, TNF-α directly damages vascular endothelial cells in children, resulting in the recruitment of coronary artery lymphocytes, the degradation of elastic fibers and the damage to the vascular wall. In addition, the immune injury mediated by these inflammatory factors can cause vasculitis and induce vascular lesions, which is consistent with some conclusions of previous studies[24,25]. Therefore, it is believed that there is a certain correlation between the changes of PCT, BNP, CRP, TNF-α, and IL-6 in KD children with CAL. Subsequently, Pearson correlation analysis fully confirmed that PCT, BNP and inflammatory factors were positively correlated with CAL in KD children.

In summary, the monitoring of PCT, BNP and inflammatory factors in children with KD has a certain warning effect on the occurrence of early CAL, that is, once the above indicators of children are found to be abnormally high expression, health care professionals should immediately associate with the possible risk of CAL. The monitoring results have a guiding significance for clinical medication, diet and complication prevention, which is helpful for the formulation of personalized treatment plan. At the same time, as early warning indicators, the above factors can be used to reduce the risk of cardiovascular disease and improve the clinical efficacy and prognosis of KD children through closer monitoring and earlier intervention. Moreover, the results of this study have a broader impact on the understanding of immune inflammatory responses in pediatric diseases, which is contribute to better understanding the occurrence and prevention of cardiovascular risks in children in clinical work. However, due to the limitation of study conditions, the sample size selected in this study is small. To obtain more objective research conclusions, future

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work will improve the experimental design, select the representative children, and conduct more in-depth researches on the risk factors of KD complicated with CAL, so as to select a reliable CAL prediction index method, provide more reliable data support for the clinical treatment and disease progression prediction of KD, and promote the healthy growth of children.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

AUTHOR CONTRIBUTIONS

HF and YL designed the study and performed the experiments, HC and DL collected the data, CS and YX analyzed the data, HF and YL prepared the manuscript. All authors read and approved the final manuscript.

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