Research Progress of Echocardiography Combined with Blood Related Detection Indexes in the Diagnosis and Treatment of Kawasaki Disease in Children

Yongkang Li^{1*}, Jide Huang^{2*}, Guosheng Su^{2#}, Lihua Qin^{2#}

¹Baise Maternal and Child Health Hospital, Baise, China; ²People's Hospital of Guangxi-ASEAN Economic Development Zone (The 10th People's Hospital of Nanning), Nanning, China

Correspondence to: Yongkang Li, 785802225@qq.com; Jide Huang, 262618897@qq.com;

Guosheng Su, 563449581@qq.com; Lihua Qin, 787209349@qq.com

Keywords: Echocardiography, Kawasaki Disease in Children, Serum Amyloid A (SAA), Interleukin-6 (IL-6),

Procalcitonin (PCT), C-Reactive Protein (CRP)

Received: May 20, 2022 Accepted: June 21, 2022 Published: June 24, 2022

Copyright © 2022 by author(s) and Scientific Research Publishing Inc.

This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

http://creativecommons.org/licenses/by/4.0/



ABSTRACT

Aim: To explore the research progress of echocardiography combined with blood-related detection indicators in the diagnosis and treatment of Kawasaki disease in children. By collecting relevant literature reports, echocardiography and several blood-related detection indicators such as SAA, IL-6, PCT and CRP were screened out. It has good clinical application value in the clinical diagnosis and treatment of Kawasaki disease in children, but there is no report on the application of echocardiography combined with blood SAA, IL-6, PCT and CRP detection in the diagnosis and treatment of Kawasaki disease in children. The author intends to explore the role of echocardiography combined with blood SAA, IL-6, PCT and CRP detection in the diagnosis and treatment of Kawasaki disease in children, hoping to achieve better results.

1. INTRODUCTION

Kawasaki disease (KD), or mucocutaneous lymph node syndrome, is an acute self-limiting febrile disease of unknown etiology, with a high incidence in infants and young children under 5 years of age, more males than females, while adults and children under 3 months old are rare; It has become one of the main causes of children's acquired heart disease in developed countries [1]. Clinical manifestations include fever, rash, non-purulent lymphadenopathy in the neck, ocular conjunctival hyperemia, diffuse hyperemia of oral mucosa, myrica tongue, palmoplantar erythema, hard edema of hands and feet, etc. People pay at-

^{*}Co-first author.

^{*}Co-corresponding author.

tention to this disease, because it can cause serious cardiovascular complications; The incidence of untreated children is 20% - 25%. In 2017, the American Heart Association (AHA) released a new diagnosis, treatment and long-term management of Kawasaki disease—the scientific guide of the American Heart Association for medical professionals [2], which systematically expounds the evidence-based basis for the epidemiology, pathology, diagnosis, treatment and long-term management of Kawasaki disease; Echocardiography has high sensitivity and specificity in the detection of proximal coronary artery lesions in Kawasaki disease. At the same time, it puts forward relevant requirements for laboratory inspection.

2. APPLICATION OF ECHOCARDIOGRAPHY IN THE DIAGNOSIS OF KAWASAKI DISEASE

There is no specific biological diagnosis method for Kawasaki disease, and the diagnosis is still based on the non-specific clinical manifestations of children. Kawasaki disease can be diagnosed based on children with fever for more than 5 days and ≥4 main clinical manifestations (changes in limbs, rash, conjunctivitis, changes in lips, and cervical lymphadenitis). For more than four major clinical manifestations, especially when there is hand and foot flushing and scleredema, the heat course of 4 days can also be diagnosed; For patients with typical symptoms, experienced clinicians can make a diagnosis within 3 days of the heat process. However, because some children do not have enough clinical manifestations to diagnose, it is easy to delay the diagnosis; Kawasaki disease without timely treatment increases the risk of coronary artery disease [1, 2]. Clinically, it is called incomplete Kawasaki disease or atypical Kawasaki disease; This process emphasizes the role of echocardiography in the diagnosis of incomplete Kawasaki disease. The diagnosis of incomplete Kawasaki disease should be considered when the child has fever ≥ 5 days and has 2 or 3 main clinical manifestations, or the infant has fever ≥ 7 days and there is no other reason to explain. Once Kawasaki disease is suspected clinically, detailed echocardiography should be performed immediately. Echocardiography is an important index for the diagnosis of incomplete Kawasaki disease; The main basis includes: 1) Z value of left anterior descending (LAD) or right coronary artery (RCA) \geq 2.5. 2) Coronary artery aneurysm. 3) Features with diagnostic significance: decreased left ventricular function, mitral regurgitation, pericardial effusion, left anterior descending artery or right coronary artery Z-score 2.0 - 2.5. Compared with the 2004 American Heart Association Kawasaki disease guidelines [3], the new guidelines do not emphasize the role of enhanced coronary echo and irregular coronary lumen in the diagnosis of Kawasaki disease, which may be related to the fact that these sonographic charts are now affected by subjective judgment.

3. ECHOCARDIOGRAPHIC CRITERIA FOR KAWASAKI DISEASE

Echocardiography should be collected by experienced pediatric ultrasound doctors using high-resolution probes. Even for older children, high-frequency probes should be used for coronary artery examination as much as possible, and dynamic images should be stored for future review and follow-up comparative study. In addition to the parasternal, apical, infraxiphoid and suprasternal fossa scans, for children suspected of Kawasaki disease, echocardiography should focus on the images of left main coronary artery (LMCA), left anterior descending branch, left circumflex branch (LCX), right coronary artery (including proximal, middle and distal segments) and posterior descending coronary artery. Every effort should be made to display (visualize) all coronary segments [1, 2].

4. APPLICATION OF LABORATORY RELATED INDEXES IN THE DIAGNOSIS AND TREATMENT OF KAWASAKI DISEASE

Laboratory examination index in the diagnosis and treatment evaluation of Kawasaki disease, the guide clearly points out that if the child's fever time is $\geq 5D$ and meets 2 or 3 diagnostic criteria, or the infant fever is $\geq 7d$, and there is no other reason to explain, then the laboratory examination and evaluation can be carried out. CRP ≥ 30.0 mg/l, and/or ESR ≥ 40 mm/hr, and there are 3 or more laboratory manifestations at the same time: 1) Anemia; 2) Platelets $\geq 450 \times 10^9$ /L after 7 days of disease course; 3) Hemoglo-

bin \leq 30 g/L; 4) Elevated ALT; 5) White Blood Cell \geq 15 × 10⁹/L; 6) Urinary WBC \geq 10/HPF; Or positive echocardiography results (any one): 1) LAD or RCA Z value \geq 2.5; 2) coronary artery aneurysm; 3) \geq 3 features of specific diagnostic significance: decreased left ventricular function, mitral regurgitation, Pericardial effusion, LAD or RCA Z value is 2.0 - 2.5. If laboratory test CRP < 30.0 mg/L, and ESR < 40 mm/hr; if fever persists, perform clinical and laboratory evaluation; if typical peeling of hands and feet is present, perform echocardiography for diagnosis [1, 2].

Since both procalcitonin (PCT) and C-reactive protein (CRP) are inflammatory expression factors [4, 5], in the laboratory examination and evaluation, some researchers also used the detection of serum procalcitonin (PCT) level combined with serum C-reactive protein (CRP) level to evaluate the predictive value of coronary artery damage (CAL) in children with Kawasaki disease [6-10]. The results showed that according to the principle of maximum Youden index, combined with predictor L and serum PCT and CRP levels, the best critical values for predicting CAL in children with Kawasaki disease were 23.068, 2.32 µg/L and 22.0 mg/L, respectively. The sensitivities for predicting CAL in children with Kawasaki disease were 68.1%, 30.6%, and 68.1%, and the specificities were 83.4%, 86.9%, and 80.7%, respectively. It is considered that monitoring the levels of serum PCT, CRP and their combined predictor L value ($L = \chi_1 + 0.608\chi_2$. X_1 and X_2 refer to the levels of serum CRP and PCT respectively), which has predictive value for CAL in children with Kawasaki disease in acute stage.

5. PROSPECTS OF OTHER LABORATORY INDICATORS IN THE ASSESSMENT OF CHILDREN WITH KAWASAKI DISEASE

The full name of SAA is serum amyloid A, which is an acute phase protein secreted into the serum after being produced by hepatocytes. When the body is infected or damaged, it can rapidly increase by about 1000 times within 4 - 6 h, and rapidly decrease to the normal level after the body antigen is cleared [11, 12]. The characteristics of SAA are as follows: 1) rapid rise and fall: SAA is an acute phase protein, which can rapidly increase about 1000 times within 4 - 6 hours after infection, and can quickly reduce to the normal level after removing pathogens; It is a sensitive index reflecting the infection and the recovery of inflammation; 2) Complementary applications: Compared with CRP, which is currently the most widely used clinically, there is one most important difference between SAA: elevated SAA is seen in viral, mycoplasma, and bacterial infections, and its sensitivity is higher than CRP; elevated CRP is seen in bacterial infections, viruses, and mycoplasma, etc. Pathogen infections are not elevated or only slightly elevated [13-17]. Clinical significance of SAA: 1) SAA is a sensitive index for diagnosing virus and bacterial infection. In bacterial infectious diseases, SAA has the advantages of early rise, large range and high sensitivity compared with CRP; Especially in the early stage of acute bacterial infection, the advantage of detecting SAA is even more significant. 2) When SAA in viral infectious diseases, SAA is significantly increased, but CRP is not increased, so SAA can be used as a sensitive indicator for the diagnosis of viral infection; 3) SAA combined with CRP detection can not only distinguish and diagnose bacterial and viral infection, but also provide new basis, which is more reliable. It can dynamically observe the curative effect and guide clinical medication; 4) SAA combined with CRP and PCT detection is conducive to the early diagnosis of infectious diseases in children (neonatal sepsis and sepsis) [11-17].

Interleukin-6 (IL-6) is a cytokine; It is a protein produced by immune cells acting on other cells; It helps to regulate and promote immune response; It can also stimulate the production of acute related reactants; The concentration in blood increases due to inflammation or tissue injury. The reason why interleukin-6 is particularly high is that inflammation occurs in some part of the body or there is a problem with immune function [18-20]. Interleukin refers to the factors of interaction between immune cells and white blood cells; it and blood cell growth factor are cytokines; they interact and coordinate with each other to complete immune regulation and hematopoietic function, it can treat coronary heart disease and lumbar disc herniation inflammatory mediators. The detection of interleukin 6 is helpful for evaluating diabetes, cardiovascular disease, inflammatory diseases and infectious diseases; The normal reference interval of serum interleukin 6 is less than 17.4 pg per milliliter; Clinical significance: detection of IL-6 is

helpful to evaluate diabetes, cardiovascular diseases, inflammatory diseases (such as lupus, rheumatoid arthritis) and infectious diseases (such as sepsis). Normally, the content of IL-6 in blood is very low and cannot be detected; If the level of IL-6 increases, it indicates inflammatory diseases, such as rheumatoid arthritis, lupus, other autoimmune diseases and infections (such as sepsis, leukemia, diabetes, cardiovascular diseases, etc.) [21-26].

6. SUMMARY AND OUTLOOK

In conclusion, serum amyloid A (SAA) and interleukin 6 (IL-6) are both very sensitive inflammatory factors, and their sensitivity and specificity are higher than PCT and CRP. Kawasaki disease in children is an acute systemic vascular inflammatory disease that easily affects medium and large arteries, especially coronary arteries; Its etiology is unknown, but it is mostly considered that infection is the cause of the disease; Rickettsia, Staphylococcus, Streptococcus, mite antigen, mycoplasma and other infections may be related to the disease, but so far, the effects of environmental pollution, drugs and poisons have not been confirmed, and the basis of etiology is not sufficient. This study intends to evaluate the diagnosis, treatment and prognosis of Kawasaki disease in children by echocardiography combined with the results of blood SAA, IL-6, PCT and CRP detection, hoping to achieve good results.

ACKNOWLEDGEMENTS

During the process of this topic research, we got much help from many departments and individuals, and other personnel not involved in this project research. All of them offered a great support and help in this research. Now here, all of members in this research show our deepest appreciation to them, and wish them good health and everything goes well.

FUNDING

Self-funded research project funded by the Health Commission of Guangxi Zhuang Autonomous Region (no.: z20200926).

CONFLICTS OF INTEREST

The authors declare no conflicts of interest regarding the publication of this paper.

REFERENCES

- 1. Wang, L. and Xia, B. (2019) The Application Progress of Echocardiography in the Diagnosis, Treatment and Long-Term Follow-Up of Kawasaki Disease: Interpretation of the 2017 AHA Guidelines. *Chinese Journal of Medical Ultrasound* (*Electronic Edition*), **16**, 161-165.
- 2. McCrindle, B.W., Rowley, A.H., Newburger, J.W., *et al.* (2017) Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals from the American Heart Association. *Circulation*, **135**, e927-e999.
- 3. Newburger, J.W., Takahashi, M., Gerber, M.A., *et al.* (2004) Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Statement for Health Professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation*, **110**, 2747-2771. https://doi.org/10.1161/01.CIR.0000145143.19711.78
- 4. Liu, J.H., Peng, Y.L., Wang, H.X., *et al.* (2017) The Value of CRP Combined with PCT in the Early Clinical Diagnosis of Elderly Patients with Infectious Pneumonia. *Chinese Journal of Hospital Infectious Diseases*, **17**, 2965-2967.
- 5. Huo, J.M., Huo, R., Hu, L., *et al.* (2017) Predictive Value of Combined Detection of Procalcitonin, High-Sensitivity C-Reactive Protein, and Pancreatic Stone Protein in the Prognosis of Children with Sepsis. *Sichuan University*

- Journal (Medical Edition), 48, 422-426.
- 6. Liu, Y. and Yang, X.L. (2016) Study on the Relationship between Serum Procalcitonin and Coronary Artery Damage in Kawasaki Disease. *Journal of Shanxi Medical University*, **47**, 645-647.
- 7. Deng, Y.C., Wang, X., Tang, X.C., *et al.* (2015) Analysis of Risk Factors for Coronary Artery Damage in Children with Kawasaki Disease. *Chinese Journal of Contemporary Pediatrics*, **17**, 927-931.
- 8. Li, P. and Zhou, Z.S. (2015) Changes and Significance of Serum Procalcitonin in Children with Kawasaki Disease. *Journal of Shanxi Medical University*, **46**, 179-180.
- 9. He, Y.W., Tian, J., Yi, Q.J., *et al.* (2018) Predictive Value of Serum Procalcitonin Combined with C-Reactive Protein in Children with Kawasaki Disease Complicated with Coronary Artery Damage. *Chinese Journal of Maternal and Child Clinical Medicine* (*Electronic Edition*), **14**, 31-37.
- 10. Dominguez, S.R., Martin, B., Heizer, H., *et al.* (2016) Procalcitonin (PCT) and Kawasaki Disease: Does PCT Correlate with IV IG-Resistant Disease, Admission to the Intensive Care, Unit, or Development of Coronary Artery Lesions. *Journal of the Pediatric Infectious Diseases Society*, **5**, 297-302. https://doi.org/10.1093/jpids/piv019
- 11. Gao, Y., Liu, Y.L. and Jiang, J.J. (2019) The Diagnostic Value of SAA, PCT, CRP and SAA/PCT Ratio for Infectious Diseases in Infants and Young Children. *China Medical Frontiers* (*Electronic Edition*), **11**, 115-118.
- 12. Deng, W.C., Wang, W.D., Zhang, J.L., *et al.* (2019) Application Value of CRP Combined with SAA in the Differential Diagnosis of Bacterial Pneumonia and Mycoplasma Pneumonia in Children. *Hebei Medicine*, **25**, 1737-1741.
- 13. He, G.Q. and Li, B. (2019) Expression and Clinical Value of SAA, WBC and Immune Factors in Children with Bronchial Pneumonia. *International Journal of Laboratory Medicine*, **40**, 2116-2119.
- 14. Zheng, Z.F., Chen, G.L. and Sun, P. (2019) The Diagnostic Value of IL-6 and SAA in Comorbid Infection in Children with Recurrent Primary Nephrotic Syndrome. *Journal of Chengde Medical College*, **36**, 112-114.
- 15. Xia, X.G. (2019) Expression Levels and Clinical Significance of SAA and CRP in Children with Mycoplasma Infection. *Friends of Health*, No. 22, 47.
- 16. Huang, H.L., Chen, R.F., Ou, L.R., *et al.* (2019) Analysis of the Application Value of SAA/CRP in the Differential Diagnosis of Viral and Bacterial Infections in Children. *Modern Diagnosis and Treatment*, **30**, 2075-2077.
- 17. Ke, X.L., Li, P., Ye, F., *et al.* (2019) Application of Serum SAA, CRP and PCT in Differential Diagnosis of Central Nervous System Infection in Children. *China Maternal and Child Health*, **34**, 5419-5422.
- 18. Li, F., Li, S.T., Peng, H.B., *et al.* (2019) The Predictive Value of SAA and NGAL in Preterm Infants with Sepsis. *Laboratory Medicine and Clinical*, **16**, 1401-1405.
- 19. Zhao, D.X., Liu, Y.Q., Chi, G.X., *et al.* (2019) Changes in Serum Levels of IL-6, IL-4, IL-10, TNF-α and T Cells in Children with RMPP. *International Medical and Health Herald*, **25**, 1261-1264.
- 20. Yang, Y.E., He, W., Li, Y.H., *et al.* (2020) Relationship between Serum IL-6 and IL-10 Levels and Respiratory Virus Infection in Children with Febrile Seizures. *Journal of Clinical Pulmonology*, **25**, 19-24.
- 21. Pan, J., Hu, J., Xu, L.Q., *et al.* (2019) Analysis of the Early Diagnostic Value of Serum PCT, IL-6 Detection Combined with CT Examination for Neonatal Pneumonia. *China Journal of CT and MRI*, **17**, 49-51.
- 22. Tang, M.S., Liu, W.D., Yue, Q.J., *et al.* (2019) The Significance of Angiopoietin-Like Protein 2 Combined with IL-1β and IL-6 in Children with Kawasaki Disease. *China Medical Innovation*, **16**, 138-141.
- 23. Li, Z.Q., Sun, C.M., Zhu, L.N., *et al.* (2019) Significance of MP-IgM, YKL-40, APOC1 and IL-6 in the Treatment and Prognosis of Mycoplasma Pneumonia in Children. *Marker Immunoassay and Clinic*, **26**, 576-579, 619.
- 24. Yang, L.F., Cai, J.J., Zhou, X.L., et al. (2019) Study on Serum Levels of High-Sensitivity C-Reactive Protein,

- TNF-α, IL-6 and Immunoglobulin in Children with Severe *Streptococcus pneumoniae* Pneumonia. *Infectious Disease Information*, **32**, 346-347, 351.
- 25. Chen, Q., Liu, H. and Jiang, J.L. (2019) The Efficacy of Azithromycin on Children with MPP and Its Effects on Serum sIL-2R, IL-6, IL-17 and IL-23. *Infectious Disease Information*, **32**, 142-144, 147.
- 26. Zhuang, M.L. and Zhang, X.M. (2019) Early Changes and Significance of CRP, sTREM-1, SPA and IL-6 in Premature Infants with Acute Respiratory Distress Syndrome. *Chinese Journal of Emergency Resuscitation and Disaster Medicine*, **14**, 961-964.