Follow-Up Study of Echocardiography in 38 Children With Kawasaki Disease Complicated by Heart Lesion

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Research Article

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Abstract

Background: The most common and most serious complication of Kawasaki disease (KD) is heart lesion (HL), which is the main cause of childhood acquired HL.

Objective: Use echocardiography to study the HL recovery of children with KD complicated by HL, and provide an important theoretical basis for the prognosis of KD complicated by HL.

Methods: Using prospective research methods, 38 children with KD complicated by HL were followed up for echocardiographic examination, and the longest examination time was one year. And carry on statistical analysis to the inspection data.

Results: In 38 children with KD complicated by HL, 36 cases of coronary artery lesion (CAL), including 29 cases of coronary artery dilation (CAD), 7 cases of coronary artery stenosis (CAS), and 2 cases of simple pericardial effusion without CAL. CAL complicated with valve regurgitation in 4 cases, pericardial effusion in 3 cases, and left ventricular enlargement in 4 cases. In about 3 weeks, most of the pericardial effusion and mild CAD recovered. At 3 months, except for a few severe CAL, heart valve regurgitation and left ventricular enlargement all recovered. The recovery of moderate CAD was slow. One case still failed to return to normal after 1 year, but the coronary artery diameter gradually decreased.

Conclusion: Kawasaki disease complicated by heart lesion mainly affects the coronary arteries, and the main manifestation is expansion. The more the expansion, the slower the recovery.

Background

Kawasaki disease (KD), also called mucocutaneous lymph node syndrome, is one of the common systemic vasculitis in children. KD can involve the medium and small blood vessels of the whole body. Among them, the coronary arteries are mainly involved, leading to CAD, CAS or coronary artery aneurysm (CAA) formation, further development will lead to myocardial ischemia, myocardial infarction and sudden death in children [1]. KD can also lead to myocarditis, endocarditis and pericarditis in the acute phase and has become a leading cause of childhood acquired heart disease [2–5]. It is reported that 15%-20% of untreated children will develop CAL [6]. Early diagnosis and timely application of high-dose immunoglobulin can help reduce the incidence of CAL. In recent years, the incidence of incomplete Kawasaki disease (IKD) has gradually increased [7–9]. Because of its incomplete clinical manifestations, it is easy to cause missed diagnosis and misdiagnosis, thereby increasing the probability of HL and CAL [10–12]. Therefore, early identification and diagnosis of KD has become a hot spot in pediatric clinical research [13].

Complete Kawasaki disease (CKD) has complete symptoms and is not difficult to diagnose clinically. According to the diagnostic criteria of the 2004 American Heart Association KD diagnosis and treatment guidelines[14]: (1) Fever duration > 5 d; (2) changes in oral mucosa such as lip fissures, erythema, or strawberry tongue; (3) extremity changes including edema, redness, or desquamation; (4) polymorphous
rash; (5) nonpurulent bilateral eye injection; and (6) cervical lymphadenopathy (> 15 mm). Those who meet 5 of the above 6 diagnostic criteria are diagnosed as CKD; Those who only meet 3 or more but less than 5 items are diagnosed as IKD after CAL is found in cardiac imaging examination and other diseases are excluded [15]. Therefore, echocardiography has become an important basis for diagnosing KD.

People are not very clear about the etiology and pathogenesis of KD. Rigante D recently explored the potential role of viruses in triggering the inflammation that generates KD in genetically predisposed children [16]. Findings seem to suggest that a dysregulated immune response to various microbial agents, such as viruses, may be the main cause of the onset of KD. Although KD is a self-limiting disease, it will leave sequelae such as CAD. Severe CAD, it is difficult to recover in the short term, therefore, some children need long-term or even life-long follow-up.

This study conducts echocardiographic follow-up examinations of 38 children with KD complicated by HL, and analyzes the examination data in order to understand the recovery of HL in children with KD and provide experimental evidence for clinical research.

Materials And Methods

Research object

Selected the cases in children with KD complicated by HL who were admitted to the Pediatric Department of Weifang People's Hospital Province, China from January 2015 to January 2020 as the study objects. All cases underwent routine echocardiographic examinations when they were admitted to the hospital, and performed echocardiographic examinations continuously during the 3 weeks, 6 weeks, 3 months, 6 months, and 1 year after initial onset to observe the prognosis. If the HL had recovered, the echocardiographic examination will not be continued. Recorded medical records and all examination data in detail. The study was approved by the Ethics Committee of Weifang People's Hospital (No: 2020019) and obtained the consent of the child's family or guardian and signed an informed consent form.

Inspection Method

During the examination, the child was lying on the left side, and all were performed in a state of sleep or emotional stability. Used the instrument Philips i E33 ultrasonic diagnostic instrument, set the probe frequency to 3.5 ~ 8.0 MHz, followed the American Echocardiography Association Pediatric Echocardiography Guide for echocardiography examination [17]. Find out the size of the heart chamber, wall motion, heart function and blood flow, observe whether there is pericardial effusion. Focus on the coronary artery scan, measure the left main coronary artery, left anterior descending and proximal right coronary artery inner diameters, store dynamic images play back the measurement, repeat 3 times, and finally take the average value.

Observation indicators
Use echocardiography to observe HL changes and coronary artery diameter at each follow-up time point. The diagnostic criteria of CAD: mild dilation (coronary artery diameter > 3mm, ≤4mm), moderate dilation (coronary artery diameter 4 ~ 7mm) [18]. The coronary artery intima is thickened, blurred, uneven, echo enhanced, and inner diameter narrowed, which is judged as CAS. The standard value for the return of the coronary artery diameter to normal in children is: under 3 years old, coronary artery diameter < 2.5 mm; 3 to 9 years old, coronary artery diameter < 3.0 mm[19].

**Statistical analysis**

SPSS 23.0 (IBM Corp, Armonk, NY, USA) was used for statistical analysis. The measurement data was expressed as a percentage, and the counting data was expressed as a percentage. The statistical method used analysis of variance. $P<0.05$ indicates that the difference was statistically significant.

**Results**

**Basic characteristics of the study subjects**

A total of 332 cases in children with KD diagnosed were admitted to the Department of Pediatrics, Weifang People’s Hospital, Shandong Province, China from January 2013 to January 2020. Among them, 38 cases (24 males and 14 females) were complicated by HL, accounting for 11.45% of the total number of children with KD. The age of onset in children with HL was 6 months to 5 years, with an average of $(27.66 ± 12.82)$ months. The basic clinical characteristics are shown in Table 1.

| Characteristics                  | Value or percentage | Characteristics                  | Value or percentage (± s ) |
|----------------------------------|---------------------|----------------------------------|-----------------------------|
| Weight(± s)                      | 20.91 ± 5.73(Kg)    | Ages(Month)                      | 27.66 ± 12.82               |
| Feve duration (± s)              | 8.92 ± 3.75(d)      | WBC↑($\times 10^9$/L)            | 17.76 ± 6.80                |
| Boys(%)                         | 24/38               | CRP↑(mg/L)                       | 55.05 ± 50.42               |
| Rash(%)                         | 25/38               | ESR↑(mm/h)                       | 54.52 ± 23.85               |
| Cervical lymphadenopathy(%)      | 26/38               | LDH↑(U/L)                        | 310.10 ± 66.92              |
| Conjunctival hyperemia(%)        | 37/38               | CK-MB↑(U/L)                      | 32.31 ± 15.89               |
| Oralmucosa changes(%)           | 32/38               | PLT↑($\times 10^9$/L)            | 501.24 ± 192.84             |
| Changes in extremities(%)       | 27/38               |                                  |                             |

**Data of cases with heart lesion**
There were 36 cases suffered from CAL among the 38 cases with KD complicated by HL, including 29 cases of CAD (20 cases of mild, 9 cases of moderate), 7 cases of CAS. Among them, 3 cases had obvious mitral or tricuspid regurgitation, 5 cases had a small amount of pericardial effusion, and 4 cases had left ventricular enlargement; The other two cases had no obvious coronary artery abnormalities but had pericardial effusion (1 case was accompanied by obvious valve regurgitation, 1 case had left ventricular enlargement). Case information is shown in Table 2.

### Table 2
Data of HL from 38 cases

| Heart disease | No-CAD | Mild CAD | Moderate CAD | CAS | sum |
|---------------|--------|----------|-------------|-----|-----|
|               | 2      | 20       | 9           | 7   | 36  |
| LA RA LA + RA | 14 4 2 | 4 5 0    | 5 2 0       |     | 36  |
| Combined LVE  | 1      | 1 0 0    | 1 0 0       | 1 0 0 | 4   |
| Combined PE   | 2      | 0 0 1    | 1 0 0       | 1 0 0 | 5   |
| Combined VR   | 1      | 0 0 1    | 0 0 0       | 1 1 0 | 4   |

CAD: coronary artery dilation; CAS: coronary artery stenosis; LVE: left ventricular enlargement; PE: pericardial effusion; VR: valve regurgitation; LA: left coronary artery; RA: right coronary artery

**Data on recovery from heart lesion**

The inflammation began to subside in the cases about 3 weeks, and pericardial effusion and most of the mild CAD returned to normal. At 6 weeks, the myocardium gradually recovered and the pericardial effusion was completely absorbed. At 3 months, except for a few severe CAL, heart valve regurgitation and left ventricular enlargement all recovered. The recovery of moderate CAD was slow. One case still failed to recover after 1 year. See Table 3 and Fig. 1.
Table 3
Data on recovery of HL from 38 cases

| heart disease | Cases | No-recovery |
|---------------|-------|-------------|
|               |       | 3W | 6W | 3M | 6M | 1Y |
| Mild CAD      | 20    | 8  | 4  | 1  | 0  | 0  |
| Moderate CAD  | 9     | 9  | 6  | 4  | 2  | 1  |
| CAS           | 7     | 5  | 3  | 2  | 0  | -  |
| LVE           | 4     | 2  | 1  | 0  | -  | -  |
| VR            | 4     | 4  | 2  | 0  | -  | -  |
| PE            | 5     | 1  | 0  | -  | -  | -  |

CAD: coronary artery dilation; CAS: coronary artery stenosis; LVE: left ventricular enlargement; VR: valve regurgitation; PE: pericardial effusion;

Coronary artery diameter values at different time points

Compared with the coronary artery diameter at the initial onset, the coronary artery diameter at each tracking point was reduced, and the coronary artery diameter in the mild dilation group recovered faster. The coronary artery diameter of children in the moderate dilation group recovered more slowly than that of mild dilation, and there was still one case at 1 year that did not recover, but the coronary artery diameter values was gradually decreasing. See Table 4.

Table 4
Coronary artery diameter at different follow-up points (x ± s) (mm)

| Group     | Initial episode | 3W     | 6W     | 3M     | 6M     | 1Y     |
|-----------|-----------------|--------|--------|--------|--------|--------|
| Mild      | 3.26 ± 0.40     | 2.70 ± 0.49* | 2.52 ± 0.37* | 2.35 ± 0.27*# | 2.28 ± 0.25*#& | 2.26 ± 0.24*#& |
| Moderately| 4.26 ± 0.21     | 3.83 ± 0.18* | 3.21 ± 0.36*# | 2.85 ± 0.26*#& | 2.61 ± 0.23*#&^ | 2.48 ± 0.21*#&^ |

(Mild group: *compared with Initial episode P < 0.01,# compared with 3 weeks P < 0.01& compared with 6 weeks P < 0.05; Moderately group: *compared with Initial episode P < 0.01#compared with 3 weeks P < 0.01##compared with 6 weeks P < 0.01##compared with 3 months P < 0.05)

Discussion

Echocardiography is an important method to assess the degree of vascular damage in KD complicated by HL. For children 5 years old and below, the chest wall is thin, echocardiography has good sound permeability, and can be repeated, non-radiation, non-invasive. The high-frequency ultrasound probe can clearly display the inner diameter, intima thickness and course of the coronary artery, and can
quantitatively measure the degree of lesions. It has high sensitivity and specificity and is the first choice for early diagnosis and follow-up of coronary artery [20]. In addition, echocardiography can clearly detect valvular regurgitation, pericardial effusion, segmental myocardial movement abnormalities, heart enlargement and other pathologies. It has become the first choice for children's cardiovascular system disease examination.

The incidence of HL in KD varies from country to country. The Pediatric Department of Weifang People's Hospital admitted 332 cases in children with KD in 5 years, of which 38 cases were complicated by HL, accounting for 11.45% of the total number of children with KD. The incidence of CAL is 10.84%, which is slightly higher than the latest Japanese report [21]. In recent years, with the increase in the incidence of IKD, the incidence of CAL has also increased [7, 8, 22]. The occurrence of HL in KD is related to its pathophysiology. Systemic vasculitis is one of the characteristic lesions of KD, which is caused by excessive activation of the immune system. Continuous fever causes the release of inflammatory transmitters, leading to dysfunction of vascular endothelial cells, thereby enhancing the adhesion of leukocytes and participating in the formation of vasculitis [20, 23]. Such as Interleukin-6 (IL-6), etc. are significantly increased, especially in patients with IKD [24, 25]. The cardiovascular system in the acute stage of KD has obvious manifestations, including the pericardium, myocardium, endocardium, various valves and coronary arteries, which can cause arrhythmia, ventricular enlargement, valve regurgitation, and myocardial ischemia. KD most often invades the coronary arteries, causing them to dilate, stenosis, or harden. Especially IKD has a higher incidence of CAL than CKD [26–28]. Severe KD can lead to macrophage activation syndrome, causing multiple organ failure [29]. Therefore, for clinically suspected KD patients, cardiac imaging examinations should be performed in time to confirm the diagnosis, so as not to miss the opportunity for diagnosis and treatment.

There are three interrelated vascular pathological processes in KD, acute self-limiting necrotizing arteritis (NA), subacute or chronic vasculitis (SA/C) and luminal myofibroblastic proliferation (LMP)[30]. NA is the neutrophil inflammation of the vascular endothelium synchronized with KD. It is a self-limiting process that starts and ends within 2 weeks of fever. SA/C vasculitis is asynchronous with the onset of KD. It is an inflammatory process dominated by small lymphocytes. It can begin within 2 weeks of onset and last for months to years, and is closely related to LMP lesions. SA/C vasculitis damages the blood vessel wall to varying degrees from the adventitia or surrounding tissues of the blood vessel, causing the blood vessel wall to form tumor-like expansion. LMP mainly causes stenosis of the lumen. Consistent with SA/C vasculitis, LMP can start within 2 weeks of onset and last for months to years [18].

The recovery of CAL is related to the degree of injury. The pathological basis of mild dilation is mainly NA, which is relatively easy to recover. The main pathological change of moderate to severe dilatation is SA/C, the disease has a slow recovery, and the recovery rate is low, which is consistent with our research. According to literature reports, the incidence of huge CAA (severe expansion) is 0.13–0.70% [3], and the possibility of recovery is very small [31]. We have not found a huge CAA in our research. Since KD is a self-limiting disease, the coronary arteries with transient or mild dilation during the acute phase will usually return to normal within 3 months as the inflammation disappears in the late acute phase. With
the application of gamma globulin and aspirin, myocarditis, pericarditis and other pathologies returned to normal in more than 6 weeks. Consistent with our research, Numerical changes of cardiac and coronary echocardiograms are closely related to clinical pathological changes and become an important clinical reference.

The fly in the ointment was in all HL cases, the cardiac ultrasound data parameters are not available when normal, such as the size of the left ventricular diameter, the physiological regurgitation of the valve. There are individual differences in these data, so it is impossible to compare before and after the individuals themselves, which may have a certain impact on the prognostic evaluation of these disease parameters. In addition, the case of coronary artery dilation does not have the data before the onset, so when the dilated coronary artery diameter returns to the normal range, whether the data is different from the coronary artery diameter when it is normal is not known, because the inner diameter of the coronary artery itself has individual differences. On the other hand, for the HL that recovered, the follow-up could not be continued for one year, so that the later heart changes could not be observed.

Conclusion

In summary, KD can cause pericarditis, myocarditis, endocarditis, and invade various valves and coronary arteries. It has become the main cause of childhood acquired heart disease. The main manifestation is CAD. The heavier the dilation, the slower the recovery. Echocardiography plays an important role in cardiac examination and is the first choice for children's cardiovascular disease examination. The use of echocardiography to continuously track and check children with HL can accurately and conveniently grasp the prognosis of HL. In addition, KD has a certain recurrence rate [32–35], and long-term follow-up has important clinical value for studying the recurrence of KD.

Abbreviations

CAL—coronary artery lesion; CAD—coronary artery dilation; CAS—coronary artery stenosis; CAA—coronary artery aneurysm; CKD: Complete Kawasaki disease; HL—heart lesion; IKD: incomplete Kawasaki disease; KD—Kawasaki disease; LMP: luminal myofibroblastic proliferation;

NA: necrotizing arteritis; SA/C: subacute or chronic vasculitis.

Declarations

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Availability of data and materials

All important data are within the paper. The datasets generated and/or analyzed during the current study are not publicly available for privacy reasons, as well as ethical reasons.

Author's contributions

(I) Conception and design: Tingting Liu and Baihong Qiu; (II) administrative support: Tingting Liu, Weina Hou, and Liandi Xu (III) provision of study materials or patients: Tingting Liu and Tianhua Li; (IV) collection and assembly of data: Baihong Qiu, Weina Hou, and Liandi Xu; (V) data analysis and interpretation: Tingting Liu, Baihong Qiu and Tianhua Li; (VI) manuscript writing: all authors; and (VII) final approval of the manuscript: all authors.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Weifang People’s Hospital (No: 2020019)

Consent for publication

All patients and their parents provided written informed consent for their data to be used in analyses and reported.

Declaration of Conflicting Interest

The authors declare that there is no conflict of interest.

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Figures
Figure 1

HL recovery curve in childrens

CAD: coronary artery dilation; CAS: coronary artery stenosis; LVE: left ventricular enlargement; VR: valve regurgitation; PE: pericardial effusion