A Review on Kawasaki Disease

Yao Jing [a], Weiyv [b] and Fu Yong Jiao [c*]

[a] Xian Medical College, Master of Clinical Medicine, China.
[b] Xian Medical College, Clinical Medicine(Pediatrics) Class 1401, China.
[c] Shaanxi Provincial People's Hospital, China.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Review Article

ABSTRACT

Kawasaki disease is an acute, self-limited vasculitis of unknown etiology, which mainly occurs in infants and children. The target organs of Kawasaki disease are coronary arteries and other cardiovascular structures. The initial manifestations of Kawasaki disease are high fever, inflammation of skin and mucosa, and enlargement of cervical lymph nodes. About 25% of children who are not treated with intravenous immunoglobulin during the acute phase of the disease will develop coronary artery aneurysms. Nowadays, Kawasaki disease has replaced rheumatic fever as the main cause of acquired heart disease in children in developed countries. However, there is still no specific diagnostic test, echocardiography is still the main diagnostic method of coronary artery involvement in children with Kawasaki disease, and risk stratification assessment is carried out according to Z value to assist in the short-term and long-term diagnosis and treatment of Kawasaki disease. In the aspect of treatment, there are reports on the application of corticosteroids, infliximab, cyclosporine, methotrexate, interleukin receptor blockers and so on.

This article makes a detailed elaboration on the epidemiology, pathology, diagnostic criteria, differential diagnosis, treatment and prognosis of Kawasaki disease, so as to improve clinicians' understanding of Kawasaki disease and reduce misdiagnosis possible.

Corresponding author: Email: 1395204056@qq.com;

1. INTRODUCTION

Kawasaki disease was first reported and named after Tomisaku Kawasaki in 1967. Kawasaki disease is more common in children, 80% of the age is less than five years old, and there are also teenagers. The young age of onset indicates that the susceptibility may be related to the maturity of the immune system [1]. Now we have some knowledge and understanding of Kawasaki disease, and its incidence varies greatly in different populations. Japan has the highest incidence rate, and the number of cases continues to rise. According to the survey, the incidence rate has reached 264.8 per 100000 children (< 5 years old) [2]. South Korea is also increasing year by year, according to a retrospective epidemiological survey, the incidence rate has reached 217.2 per 100000 children (< 5 years old) [3]. In China, the incidence rate of a 10-year survey in Beijing has reached 55.1 per 100000 children (< 5 years old); the result of a five-year survey in Shanghai is 46.3; in a recent survey in Taiwan, the incidence rate is 82.8 per 100000 children (< 5 years old), ranking third in the world [4] [5] [6]. The United States passive Monitoring and Analysis Management Database shows that the incidence rate is 19 per 100000 children (< 5 years old) and 24.7 per 100000 children (< 5 years old) in California [7]. Among American children in Hawaii and California, the high incidence of children of Asian and Pacific island descent suggests that there may be an important gene contributing to their susceptibility (incidence rates are 210,50.4 per 100000 children (< 5 years old) respectively) [8] [9]. A genome-related study in Japan also shows that susceptibility to Kawasaki disease may be related to genes [10]. In France, it is 7 per 100000 children (< 5 years old), while in Japan it is 30 times that of France. And Kawasaki disease has obvious seasonality in the northern hemisphere [11].

When people with genetic susceptibility to Kawasaki disease are exposed to an environment where Kawasaki disease triggers may be widely distributed, they cause an immune response if they enter the upper respiratory tract [12]. Some genetically susceptible children will have irreversible coronary artery wall damage. Available records can indicate the accumulation of cases in time and space, but there is still no evidence of human-to-human transmission [13]. It is assumed that potential cases can occur under the following two triggers: 1) replication of infectious pathogens in mucosal epithelial cells of the upper respiratory tract; and 2) widespread distribution of antigens in the environment. Recently, some data support the interesting hypothesis that the triggers of Kawasaki disease are carried by large-scale convective air. Moreover, the seasonal clusters and annual epidemics of Kawasaki disease cases in Japan, Hawaii and southern California are in the northeastern provinces of China [1].

2. PATHOLOGY

mong the pathological changes caused by Kawasaki disease, the most common is to affect the coronary artery, followed by other substantive muscular arteries. A comprehensive review of 32 cases of Kawasaki autopsy and 8 cases of heart transplantation described three points related to the progression of vascular lesions in the arterial wall: necrotizing arteritis, subacute / chronic vasculitis and myofibroblast hyperplasia [14].

1) Acute arteritis is characterized by neutrophil infiltration from the vascular lumen and is associated with extensive necrosis of the vascular walls of coronary arteries and other medium-sized arteries [15]. Neutrophil elastase may also cause some damage to the internal and external elastic membrane of the vascular wall, leading to the formation of aneurysms. Neutrophil elastase inhibitors have been used to block this pathway in Japan [16].

2) subacute vasculitis begins a few weeks after fever, or months and years later, and is closely related to the proliferation of myofibroblasts in the third process [13]. Inflammatory cells mainly infiltrate the lymphatic system and adventitia, and the involvement of CD8+ cytotoxic T lymphocytes has been confirmed, suggesting that anti-T cell therapy may be effective, such as calcineurin inhibitors cyclosporine and tacrolimus [17] [18] [19].

3) the proliferation of myofibroblasts may be the pathological process of myofibroblasts derived from smooth muscle cells mediated by transforming growth factor-β [20] [21]. The polymorphism of transforming growth factor pathway is associated with increased susceptibility to aneurysm inflammation in patients with Kawasaki disease [22]. Myofibroblast proliferation can lead to lumen stenosis and myocardial ischemia. A prominent histological feature of late aneurysms is that layered thrombus is commonly found

in calcification-related aneurysms, which can be detected by computed tomography ((CT)) [23]. It should be noted that because the histological description of Kawasaki disease is mainly based on autopsy of individuals with vasculitis complications, it is characterized by severe cardiovascular pathological changes. These data can be used to judge the condition of patients with potential risk of cardiovascular complications.

3. DIAGNOSIS

At present, there is no specific diagnosis of Kawasaki disease. The diagnosis is now based on clinical standards developed by the Japanese Ministry of Health and adopted by the American Heart Association, alongside non-specific laboratory tests that support the diagnosis. Timely diagnosis and treatment is very important, which largely depends on careful medical history collection and thorough physical examination.

3.1 Clinical Manifestations

The common clinical features of Kawasaki disease are as follows: fever for five days or more,generally for the retained fever or relaxation type fever, can also be irregular fever, the body temperature can be as high as 39-40℃, antibiotic treatment is ineffective. conjunctival congestion in both eyes, red lips, red bayberry tongue, diffuse hyperemia in oral and pharyngeal mucosa, pleomorphic erythema and rash, hard edema of hands and feet, erythema of metatarsus and toes, and membranous peeling at the skin migration of nail bed at fingertip (convalescent stage). Non-suppurative cervical lymph node enlargement was found in the acute stage, often unilateral and > 1.5cm in diameter [24].

3.1.1 Typical Kawasaki disease

The diagnosis of classical Kawasaki disease is based on fever for more than 5 days and the presence of 4 or more clinical features [24]. Experienced clinicians may make a diagnosis in rare cases where the hands and feet are red and swollen, and the diagnosis takes only 4 days of fever. Fever usually dissipates within 36 hours after the completion of IVIG infusion. If not, the patient is considered to be resistant to IVIG and needs further treatment. In addition, fever that dissipates spontaneously after 7 days cannot be considered evidence that the diagnosis of

Kawasaki disease has been excluded. Kawasaki disease should be considered in infants with long-term fever with unexplained aseptic meningitis or culture-negative shock and ineffective antibiotic treatment of cervical lymphadenitis.[25]

These typical clinical features do not necessarily appear at the same time, and often can not be found early in the process of diagnosis, and some clinical features may be weakened with the delay of time, so it is necessary for clinicians to carefully examine the symptoms and signs of children in order to make an early diagnosis and prevent delays in the disease.

3.1.2 Incomplete Kawasaki disease

For incomplete (atypical) Kawasaki disease, infants or children with long-term fever of unknown causes and children with less than 4 main clinical features need to consider its possibility, if there are relevant laboratory tests and echocardiography, it can be diagnosed as incomplete Kawasaki disease [25]. Although the Z score of left anterior descending branch or right coronary artery branch is not sensitive, it has high specificity for diagnosis. A zMax cut-off of 2.0 had specificity of 95% (95%CI: 84%,99%) and sensitivity of 32% (95%CI: 25%,41%) in distinguishing non-KD febrile from KD patients; for zMax = 2.5,specificity was 98 and sensitivity was 20% [26] [27].

3.2 Laboratory Inspection

(1) the laboratory indicators in the acute and subacute stages of Kawasaki disease have been summarized in the process of continuous accumulation, including the following:

1) the acute phase of Kawasaki disease is characterized by an increase in immature and mature granulocytes, positive cell euchromic anemia, and high protein in the acute phase. 2) Thrombocytopenia may occur in the process of intravascular thrombosis and degradation, which is characterized by a significant increase in the level of D-dimer. 3) Thrombocytopenia may occur in the subacute stage of Kawasaki disease. 4) about 35% of the patients had mild to moderate increase in serum transaminase or γ-glutamyl transpeptidase activity. 5) about 10% of patients have mild hyperbilirubinemia. 6) hypoproteinemia may occur in patients, which is also a serious acute manifestation of correlation. 7) up to 80% of children's urine tests showed the

presence of sterile pyuria [28]. 8) some patients may have elevated N-terminal B-type brain natriuretic peptide (NT-BNP), but this only indicates cardiac involvement and does not fully diagnose Kawasaki disease, and its meaningful numerical increment has not been determined [24].

3.3 Echocardiography

Echocardiography is the main cardiac imaging in acute phase. In North America, echocardiographic measurements of the internal diameter of the proximal coronary artery segment corrected based on body surface area have been standardized [29]. The American Heart Association classifies as: small aneurysms $2.5 \leq Z < 5$; moderate aneurysms $5 \leq Z < 10$; giant aneurysms $Z \geq 10$ or inner diameter > 8 mm [30]. The Japanese standard is to define the size of an aneurysm according to the size of the lumen: small aneurysms ≤ 4 mm, medium aneurysms > 4 mm and ≤ 8 mm, and giant aneurysms > 8 mm. In children ≥ 5 years old, the size of aneurysms can also be classified by the ratio of their internal diameter to adjacent segments: 1.5 times for small aneurysms, 1.5 times to 4 times for moderate aneurysms, and more than 4 times for giant aneurysms [31] [32].

3.4 Differential Diagnosis

Because there are no specific diagnostic criteria, it needs to be distinguished from other diseases with similar clinical manifestations, including EB virus, adenovirus, echo virus, measles, toxic shock syndrome, scarlet fever, juvenile idiopathic arthritis, nodular polyarteritis, Los Angeles spotted fever leptospirosis, adolescent mercury poisoning and adverse drug reactions, Stephens-Johnson syndrome, etc. [33] [34] [35].

4. STAGES OF CLINICAL COURSE OF DISEASE

The clinical process of Kawasaki disease is divided into four stages:

1. **Acute phase:** this stage will last for 1-2 weeks without treatment. Children usually present with relaxation fever, which can reach as high as 40 ℃ at the peak of the disease, and show some major symptoms such as cardiac changes, including valvulitis, pericarditis and myocarditis.
2. **Subacute stage:** this stage is about 2 weeks. As the fever recedes, the child is at

high risk of sudden death from myocardial infarction.
3. In the recovery stage, the clinical symptoms basically disappeared and the level of serum reactants returned to normal in the acute stage.
4. **Chronic phase:** mainly patients with coronary artery involvement who need follow-up treatment. Therefore, we should make diagnosis and timely treatment in the acute phase as soon as possible to reduce inflammation and reduce the risk of coronary artery involvement in the later stage of the disease.

5. EVALUATION OF ACUTE KAWASAKI DISEASE

Clinical laboratory examination can support clinicians' suspicion of Kawasaki disease, but it needs to be combined with symptoms and auxiliary examinations to assist in differential diagnosis and assess the intensity of inflammation. There are no systematic and accurate diagnostic methods for both clinical standards and laboratory characteristics, and clinical standards depend on non-specific symptoms that may not occur, but can be present in many other vasculitis toxin-mediated diseases [33], as mentioned above. It is not possible to rely solely on clinical criteria, because the characteristics of Kawasaki disease do not necessarily occur at the same time. The main clinical manifestations may be accompanied by a variety of symptoms of febrile vasculitis, including arthritis, gastrointestinal discomfort, fatigue and other systematic clinical manifestations, all of which may lead to misdiagnosis and delay treatment [24] [36]. Especially in infants under 6 months of age, clinical symptoms may only find high fever of unknown causes, and most of them are irritable or sleepy [1]. Easily misdiagnosed as upper respiratory tract infection, acute conjunctivitis, skin allergy, lymphadenitis. Other occasional features such as abnormally increased cells in pyuria and cerebrospinal fluid may indicate the presence of other infections that may delay diagnosis [37]. The diversity of symptoms makes it difficult for clinicians to make a diagnosis. It is necessary to consider the delay of Kawasaki disease in any case and other fever of unknown causes. This also hinders the diagnosis of incomplete Kawasaki disease, which is an important part of patients with Kawasaki disease.

Children less than 1 year old and children over 5 years old are more likely to develop incomplete

Kawasaki disease [38] [39]. These patients account for about 25% [40] of Kawasaki disease, and may delay treatment due to a high misdiagnosis rate, resulting in an increased risk of coronary artery complications. A case-control study in Australia has shown that for children with potentially high cardiovascular risk, changes in aortic intima-media thickness are likely to be a sensitive indicator of cardiovascular risk after Kawasaki disease. however, it is not clear whether this change in mid-childhood indicates atherosclerotic burden or cardiovascular risk in adulthood [41].

5.1 Changes in Laboratory Tests During the Acute Phase

Including neutropenia, euchromic anemia, and acute high protein, there are also changes in platelets, slightly higher activity of serum transaminase or γ-glutamyl transpeptidase, hypoproteinemia, aseptic pyuria, and so on.

5.2 Echocardiography is the Main Manifestation of Cardiac Imaging in Acute Phase

1) The Japanese standard defines the size of the aneurysm according to the size of the lumen, and it can also be classified by the ratio of the internal diameter to the adjacent segments. The American Heart Association's assessment of coronary artery abnormalities has been described earlier.
2) Echocardiography is an important auxiliary method in abnormal diagnosis. But normal echocardiography does not rule out Kawasaki disease. In addition, normal baseline echocardiography does not rule out the possibility of later development of coronary artery aneurysms in the first week of onset; therefore, echocardiography should be reexamined at 1-2 weeks and 4-6 weeks after treatment. Coronary artery z values > 2 at baseline or with high-risk clinical features (e.g. persistent fever, intravenous gamma globulin resistance) should be examined more frequently [1].
3) Two-dimensional and M-mode echocardiography only showed temporary left ventricular dilatation, systolic dysfunction, pericardial effusion and valvular regurgitation (especially mitral regurgitation). Systolic dysfunction on the echocardiographic baseline is a risk factor for coronary artery aneurysms [42].

Kawasaki disease shock syndrome is rare in patients, and warm shock usually occurs with decreased peripheral vascular resistance [43], which can be confused with toxic shock syndrome or sepsis.

6. ACUTE PHASE MANAGEMENT

6.1 Initial Treatment

The purpose of acute treatment is to minimize systemic and cardiovascular inflammation in order to prevent cardiovascular sequelae. The main method is high-dose IVIG combined with aspirin, fever within 10 days (early) IVIG should reduce the incidence of coronary artery disease from 25% to 5% [44] [45].

Although the mechanism of Kawasaki disease is not fully understood, the efficacy of intravenous immunoglobulin (IVIG) as first-line treatment for acute Kawasaki disease has been verified in many prospective multicenter trials. Administration of IVIG within ten days after fever helps to reduce inflammation, but has little effect on preventing coronary artery damage. Aspirin is widely recognized as a therapeutic drug, but there is little evidence of its therapeutic benefits. A retrospective study in Canada showed that low-dose aspirin was no less effective in reducing the risk of coronary artery abnormalities than high-dose aspirin in the case of combined immunoglobulin injection [36]. However, the risk of high-dose aspirin administration, including aspirin toxicity, Reye syndrome and conductive hearing loss, has led to adjustments in administration practices in some countries, including Japan, where the recommended acute dose has been reduced to 30-50mg/kg/d [46]. Timely treatment is the key to prevent the adverse outcome of coronary artery.

6.2 Treatment of Patients with IVIG Resistance

(AHA) of the American Heart Association defines drug-resistant Kawasaki disease as "relapse or persistent fever at least 36 hours after the first injection of IVIG." [25] it is reported that if patients are treated in the first five days of fever, the rate of IVIG resistance is higher, although it is not clear whether early treatment will lead to a worse prognosis, or whether patients with Kawasaki disease have more severe symptoms on the fifth day [47]. Two kinds of IVIG action mechanisms have been established in patients' peripheral blood mononuclear cell related studies

in vitro: the first is to stimulate myeloid dendritic cells to secrete IL-10, and make T cells differentiate into regulatory phenotypes through the constant region of immunoglobulin molecule Fc. The second mechanism is to present the treated Fc peptide to a subset of regulatory T cells to amplify and produce IL-10 [49]. Peptide mapping studies have identified the specific Fc region that mediates this amplification [50]. As the effect of gamma globulin on fever and the improvement of skin and mucosal symptoms is very rapid, other mechanisms such as anti-cytokines and anti-idiotypic antibodies, although lack of specific data, may also be important. Most patients with rapid improvement in clinical experience and infusion of gamma globulin will stop fever, but about 10% to 20% of patients will develop recurrent fever and require additional anti-inflammatory treatment [51]. The prognosis of IVIG resistance is poor because intractable fever indicates progressive arteritis, and these patients tend to have a higher risk of developing coronary artery aneurysms.

6.2.1 Second dose of immunoglobulin

Many authorities recommend the use of a second dose of IVIG2g/kg for treatment. Repetitive IVIG has been shown to be safe and effective, but it has not been proved by sufficient randomized trials. There may be a theoretical advantage when using different IVIG products for initial treatment, as preparations from different donor pools may have different antibody sequences or different quantities and components, as well as other anti-inflammatory factors [52].

6.2.2 Corticosteroids

The use of steroids in the treatment of Kawasaki disease has gone through a tortuous process, which is more reasonable and acceptable because of its wide availability and relatively low price. There is evidence that the use of steroids can improve inflammatory markers, disappear rapidly, and may reduce the incidence of CALS [52]. AHA suggests that a short course of high-dose steroids can be used as a reasonable change in the second intravenous gamma globulin, or as a reasonable treatment after two doses of IVIG are ineffective. AHA's alternative recommendation for drug-resistant KD is to start taking steroids in addition to a second dose of IVIG and aspirin [25]. However, there is no clear evidence of the optimal dose, formulation, duration and duration of corticosteroids. A recent

randomized controlled trial in Japan found that prednisolone added to the standard IVIG regimen significantly reduced the incidence of undesirable coronary arteries, but these have not been found outside the Japanese population [53].

6.2.3 Infliximab

Infliximab in patients with IVIG resistance can solve fever and inflammatory markers more quickly, reduce hospitalization days, reduce medical costs, and have better tolerance. In the largest randomized trial of infliximab as an adjuvant primary therapy for IVIG, there was no evidence that infliximab reduced resistance to Kawasaki disease [54]. On the basis of retrospective data, AHA believes that infliximab can replace the second dose IVIG [25].

6.2.4 Cyclosporine

The efficacy of cyclosporine has been shown in some cases, and studies have shown that targeting the calcium signaling pathway may prevent T cells from destroying the coronary artery wall [18] [19]. Small sample studies have shown that cyclosporine has few serious adverse events and is a good choice for patients with drug-resistant Kawasaki disease, but further research is needed [52].

6.2.5 Methotrexate

A retrospective study and evaluation of 10 years' data in South Korea showed that low-dose methotrexate was effective in the treatment of patients with IVIG resistance. The results showed that the clinical symptoms of the patients were improved, the fever disappeared rapidly, the reactants decreased in the acute phase, and no adverse reactions of methotrexate were observed [37]. Therefore, methotrexate may be a candidate treatment for patients with anti-IVIG resistance.

6.2.6 Interleukin receptor blockers

There are data for patients with progressive aneurysms in an interleukin receptor blocker-Anakinra (Anakinra in Infants and Children with Abnormal Coronary Artery Diseases), Phase I/IIa Trial To investigate whether it can effectively (atorvastatin pharmacokinetics/safety studies in children with Kawasaki disease and coronary artery abnormalities) inhibit endothelial to mesenchymal transition and promote T cell regulation [55]. Further clinical trials are still

needed to improve its therapeutic effects and methods.

6.2.7 Cyclophosphamide

Cyclophosphamide, a cytotoxic drug, is often used in combination with corticosteroids to treat other rare cases of refractory severe progressive aneurysms [56].

There are many reports on the use of other drugs, including other biological agents, cytotoxic agents, ulinastatin and plasma exchangers in drug-resistant Kawasaki disease [57]. In the case of severe inflammation, patients with giant aneurysms have a higher risk of coronary artery thrombosis. These drugs are used in refractory patients who fail to treat. However, further research and clinical practice are needed for the treatment of Kawasaki disease.

6.2.8 Percutaneous coronary intervention in the treatment of Aneurysm

The treatment of aneurysms in the acute phase of Kawasaki disease is an uncertain area. If echocardiography shows coronary artery dilatation or aneurysm diagnosis, pediatric cardiologists should participate in patient care and develop individualized treatment plans. The existence of coronary artery dilatation requires the early participation of pediatric cardiologists, multiple echocardiographic monitoring of the coronary artery, and long-term routine stress and perfusion tests on the heart [58] [59].

In patients with high risk of ischemia, percutaneous coronary intervention is feasible. This includes intracoronary thrombolysis, balloon angioplasty, stent implantation and rotational grinding, and should be performed in patients with symptomatic ischemia, laboratory examinations showing ischemia, or patients with severe stenosis, and in patients with progressive coronary artery ischemia. If angiography detects severe occlusion or endangers collateral blood supply, coronary artery bypass surgery should be performed [57] [59].

7. LONG-TERM ASSESSMENT

AHA stratifies the risk of coronary artery disease according to the risk of coronary artery thrombosis or stenosis / occlusion associated with myocardial ischemia [25], which facilitates long-term prediction and individualized management of patients, including follow-up,

diagnostic trials, assessment and management of cardiovascular risk factors, drug therapy, thrombosis prevention, physical activity and reproductive counseling. (1) Coronary artery lumen diameter measured by echocardiography, risk stratification was performed using Z value converted to body surface area correction (class Ⅱa, class B); (2) based on the most severe degree of coronary artery involvement and current coronary artery involvement (type Ⅱa, grade C). (3) in addition to coronary artery diameter, other clinical features that may increase the risk of long-term myocardial infarction (such as distal terminal aneurysm, number of aneurysms, number of affected coronary artery branches, irregular coronary artery lumen, irregular inner layer of coronary artery wall (calcification, wall fibrosis), coronary artery dysfunction (vasodilation damage, hemodynamic changes), lack of collateral circulation, insufficient blood supply. Premature angiogenesis, premature thrombus regeneration, premature myocardial infarction, ventricular dysfunction) were considered for risk stratification (class Ⅱa, class C). In general, the coronary artery lumen Z score is stable, the lumen is no longer enlarged. If the Z value of the patient is still increasing after the end of the recovery period, coronary artery changes should be evaluated and followed up.

8. CHRONIC PHASE MANAGEMENT

The purpose of chronic phase management is to prevent coronary artery occlusion and myocardial infarction by reducing platelet aggregation and inhibiting thrombosis.

Long-term treatment included antiplatelet aspirin dose of 3-5 mg/kg/day until normal echocardiography was displayed at 6-8 weeks [25]. If the abnormality of the coronary artery cannot be reversed during this period, long-term drug treatment and diagnostic follow-up are involved. Patients with coronary artery involvement need to take aspirin for a long time to fight platelets. In addition, systemic anticoagulation therapy with warfarin or low molecular weight heparin is used in patients with large or multiple large aneurysms. Low molecular weight heparin may be statistically beneficial to reduce coronary artery score and is unlikely to cause severe bleeding, which makes it a feasible choice for children with severe coronary artery involvement [60]. Children with Kawasaki disease and children with acute coronary artery

disease should reduce exposure to atherosclerotic risk factors, including obesity, hyperlipidemia and smoking [61]. There is a delay in immunization in children treated with IVIG, as this treatment blocks the acquisition of active immunization by preventing the replication of live viral vaccines [62], so immunization should be postponed appropriately.

9. CLINICAL RESULTS

Possible results of Kawasaki disease include [62]:

1) No cardiac sequelae;
2) Coronary artery abnormalities, of which about 60% are reversed within one year;
3) Cardiac involvement, including myocarditis, aneurysm thrombosis, cardiac rhythm disorders or myocardial infarction.
4) Recurrence of Kawasaki disease:

Before IVIG was found as a safe and effective treatment in 3% of patients, 20 to 30% of patients progressed to coronary artery dilatation, with a mortality rate of 2% [63] [64]. If IVIG was treated within 10 days of fever, only 3% of children had transient coronary artery relaxation and 1% developed giant aneurysms [65]. The risk factors of cardiovascular sequelae in patients with Kawasaki disease include longer duration of fever before treatment, low serum albumin at admission (< 3g/L), age less than 1 year or more than 5 years old, and IVIG resistance or incomplete Kawasaki disease [62]. During the 5-year period, Shaanxi Provincial people's Hospital classified and analyzed 170 children with Kawasaki disease, and regularly followed up and found that nearly 1/4 were incomplete Kawasaki disease, and about 1/5 had abnormal coronary arteries. Most of the children with giant aneurysms recovered after treatment but often showed persistent abnormalities [66]. For healthy survivors of Kawasaki disease, the long-term effect is to accelerate the development of atherosclerosis. Only a few cadavers have been studied in patients with coronary artery involvement, and there appears to be endothelial dysfunction and coronary artery scarring. Although the contractile force of patients with transient myocarditis is normal during Kawasaki disease, there are histopathological abnormalities during myocardial biopsies [24]. However, the increase in secondary atherosclerosis with intramural fibrotic degeneration indicates an increased risk of atherosclerosis development, which may become

apparent as asymptomatic Kawasaki disease patients approach middle age [67] [68].

10. CONCLUSION

Kawasaki disease is a disease with high risk and there is no specific diagnosis. The main features of Kawasaki disease and the rational use of echocardiography are helpful to timely treatment and improve the prognosis of patients, but the diagnosis of incomplete Kawasaki disease is more complicated and accompanied by severe coronary artery disease. If patients with Kawasaki disease have not been diagnosed and treated, coronary artery disease may become an important factor in the morbidity and mortality of heart disease. More and more people in developing countries such as China and India realize that Kawasaki disease may replace rheumatic fever as the most common cause of childhood acquired heart disease, which is of great significance to doctors and cardiologists. it may also affect the health care system in developing countries, so Kawasaki disease is by no means a childhood disease, it has significant public health importance. Especially for developing countries like China and India [69] [70]. In view of the serious consequences of late diagnosis and the rising global incidence of Kawasaki disease, newborns and pediatric clinicians should be prepared to diagnose Kawasaki disease for children with long-term fever.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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