

A Short Review of coronary artery Lesions in children

Abstract

Kawasaki disease may be a systemic inflammatory disease with a predominantly intrinsic immune disorder due to exposure of genetically susceptible individuals to various infections and/or environmental triggers. The disease is prevalent in patients with autoimmune diseases or Kawasaki disease in childhood, in men with dyslipidemia, in men with hypertension, in men who are chronic smokers, and can be triggered by infections with autoimmune abnormalities and emotional agitation. Clinicians need to have a better understanding of the immunological mechanisms of the disease and to broaden their thinking about diagnosis and treatment to avoid misdiagnosis and underdiagnosis.

Keywords: Kawasaki disease, dyslipidemia, underdiagnosis, coronary artery injury

Introduction

The etiological mechanism of coronary artery lesions (CAL) and coronary artery dilatation disease is not completely clear, and its pathological manifestations are mainly the destruction of the middle layer of the coronary artery vessel wall structure and the degradation of elastic fibers. Possible causes include atherosclerosis, autoimmune or inflammatory reactions, vascular infectious diseases, and overexpression of gene susceptibility [1]. Dyslipidemia is a factor closely related to coronary atherosclerosis, and whether it is related to coronary artery disease in children with KD is still controversial. Dyslipidemia may also be one of the risk factors for coronary artery disease [2]. Multisystem inflammatory syndrome in children (MIS-C) was first reported on April 26, 2020 [3]. Its clinical manifestations are similar to Kawasaki disease (KD) and are complicated with multiple organ function impairment such as cardiovascular function. MIS-C is in a critical condition. Once it develops, it can progress rapidly and deteriorate in a short time. MIS-C has a case fatality rate of up to 2% in the United States and United Kingdom [4-5]. Previous studies have shown that viral infection in children is related to the incidence of KD, and viral infection is also related to coronary artery disease [6]. Coronary artery dilation, coronary aneurysm and coronary artery stenosis may occur, and the disease will continue to develop, leading to the formation of aneurysm thrombosis, myocardial infarction, ischemic heart disease, and even sudden death. To analyze the correlation between viral infection and KD disease, early diagnosis and treatment can avoid further damage caused by coronary artery disease, which is conducive to improving the prognosis of children. Chlamydia pneumoniae (CP) and mycoplasma pneumoniae (MP) are one of the common atypical pathogens of respiratory tract infection in children. In addition to causing respiratory tract infection, in recent years, it has been reported that CP infection in adults can damage coronary artery, cause coronary heart disease (CAD) and acute coronary artery injury syndrome (ACS) [7,8]. However, it has not been reported whether CP infection in children can lead to coronary artery damage such as ACS. However, mycoplasma pneumoniae (MP) infection can lead to Kawasaki disease, coronary

artery dilation and mural thrombosis in children ^[9]. The disease is prevalent in patients with autoimmune diseases or Kawasaki disease in childhood, in men with dyslipidemia, in men with hypertension, in men who are chronic smokers, and can be triggered by infections with autoimmune abnormalities and emotional agitation. A variety of childhood rheumatic immune diseases can lead to coronary artery damage (CAL). Among them, cardiogenic syncope/sudden death caused by coronary artery abnormalities accounts for about 36% ^[10-11]. The clinical manifestations of coronary artery abnormalities vary greatly. They can be asymptomatic for a lifetime, or they can be manifested as chest tightness and chest pain. In severe cases, the first symptom is syncope and even sudden death. In the United States, coronary artery abnormalities are the second leading cause of sudden death in adolescent athletes ^[12].

By understanding the immunological pathogenesis of the disease and broadening the diagnosis and differentiation of the disease, we can help improve the diagnosis and treatment of CAL-related rheumatologic diseases.

First. Main etiology

1, atherosclerosis: coronary artery dilatation disease is a variant of obstructive coronary artery disease.

2, autoimmune or inflammatory response: Coronary artery dilatation disease in children and adolescents is usually a complication of Kawasaki disease, and connective tissue diseases, systemic arteritis and Marfan syndrome can lead to coronary artery dilatation disease.

3, vascular infectious diseases: infections such as *Mycoplasma pneumoniae*, Chlamydia, fungal or septic emboli, syphilis, spirochete disease, etc. can damage coronary vessels and lead to coronary artery dilation.

4. The etiology of simple coronary artery dilation disease is unknown and may be related to genetic susceptibility (e.g., specific HLA class II genotype, matrix metalloproteinase gene variants), angiotensin-converting enzyme overexpression, etc.

5. coronary arteriovenous fistula

6. hereditary family cluster nesting hypercholesterolemia

Second, the predisposing factors

1, infection and autoimmune abnormalities: infection may directly or indirectly damage coronary arteries by stimulating autoimmune reactions.

2, emotional excitement or after strenuous activity can trigger the disease, appearing chest pain and discomfort.

3, In addition, smoking, high blood pressure, cocaine use, etc. may trigger this disease.

Third, the characteristics of coronary artery injury in common diseases and the differentiation from Kawasaki disease.

I. Kawasaki disease

Kawasaki disease is an infection-induced systemic inflammatory disease in children, in which vasculitis is the main feature, mainly involving small and medium-sized arteries ^[13]. Clinical manifestations include fever, rash, congestion of the conjunctiva of the eye and oral mucosa, palmoplantar erythema, hard edema of the finger (toe) ends and enlarged cervical lymph nodes, etc. A few children may even have Kawasaki disease shock syndrome (KDSS) or macrophage activation syndrome (MAS). A few children may even have life-threatening complications such as Kawasaki disease shock syndrome (KDSS) or macrophage activation

syndrome (MAS)^[13]. The disease usually has a good prognosis, with most temporary changes in CAL and long-term complications mainly related to the degree of coronary artery involvement. Coronary artery dilatation to an internal diameter <8 mm and a Z value <10 often results in gradual recovery, whereas giant coronary aneurysms (maximum internal diameter ≥8 mm) are highly susceptible to myocardial infarction, arrhythmia, or sudden death due to coronary occlusion [14-15].

The exact etiology of Kawasaki disease has not been elucidated. It has been found that Kawasaki disease may be associated with infection by different pathogens and genetic susceptibility. The pathology of Kawasaki disease shows inflammatory cells infiltrating the vascular tissue and destroying the luminal endothelium, elastic fiber layer and middle smooth muscle cells, which eventually leads to luminal dilation and aneurysm formation [16]. Inflammatory cells infiltrating the arterial vasculature include neutrophils, T cells (especially CD8+ T cells), eosinophils, plasma cells (especially IgA-secreting plasma cells), and macrophages [17]. Early in the course of the disease, mainly neutrophils infiltrate the arterial wall, and after 2 weeks, monocytes and CD8+ T cells predominate [18]. Thus, Kawasaki disease may be a systemic inflammatory disease with a predominantly intrinsic immune disorder due to exposure of genetically susceptible individuals to various infections and/or environmental triggers.

II. Multisystem inflammatory syndrome (MIS) in children

Since April 2020 several countries have reported the clinical features of cohorts of childhood MIS cases, which occur mostly in previously healthy children and adolescents with a clinical presentation similar to KDSS, presenting with systemic multisystem damage and evidence of novel coronavirus pneumonia (COVID-19). The World Health Organization defines MIS in children [19] as (1) age <19 years. (2) Fever ≥3 d. (3) Evidence of multisystem injury (≥2): (i) rash, bilateral nonpurulent conjunctivitis, or skin mucosal symptoms; (ii) hypotension or shock; (iii) cardiovascular dysfunction, pericarditis, valvulitis, or CAL; (iv) coagulation abnormalities; and (v) acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain). (4) Elevated inflammatory markers, such as erythrocyte sedimentation rate, C-reactive protein, or calcitoninogen. (5) Inflammation due to infection by other pathogens is excluded. (6) Evidence related to COVID-19.

Cardiac involvement is a common manifestation of MIS in children, with 32% of patients having a left ventricular ejection fraction of less than 55% and 11% of them having an ejection fraction of less than 30%. 23% of patients have myocarditis. 23.4% of patients with KD-like symptoms have coronary artery dilatation/aneurysm [20]. 93% of coronary artery aneurysms are mild and 7% are moderate [21]. 40% to 50% of children with MIS meet the diagnostic criteria for Kawasaki disease or incomplete Kawasaki disease, which is very similar to KDSS [21]. Key differences between childhood MIS and Kawasaki disease include a predominantly non-Hispanic black, Hispanic, or Latino population for childhood MIS, mostly in children aged 6-15 years [22]; more prominent gastrointestinal symptoms (especially abdominal pain), more significant elevation of inflammatory markers, lower absolute lymphocyte and platelet counts, and evidence of COVID-19 associated with childhood MIS [23-25].

The climb in the number of cases of childhood MIS occurred several weeks after the peak of COVID-19 community onset, and studies have shown persistent monocyte activation, elevated levels of anti-severe acute respiratory syndrome coronavirus IgG antibodies,

enhanced CD8+ T cell activation, and elevated levels of inflammatory cytokines, interleukin (IL), gamma interferon, and tumor necrosis factor TNF and ferritin levels are significantly elevated, among others [22,26-27]. Therefore, MIS in children is an inflammatory cytokine storm disease caused by abnormal immune response induced after viral infection.

III. multiple aortitis (takayasu arteritis, TA)

TA is a chronic nonspecific inflammatory disease of large and medium-sized vessels, mainly involving the aorta and its major branches, but also the pulmonary and coronary arteries [28]. TA often has nonspecific systemic symptoms in its early stages, such as fever, rash, and malaise; while symptoms such as ischemic limb pain and/or cyanosis, dizziness, and hypertension due to arterial stenosis, occlusion, or dilation are not evident in infants and children [28-29]. The disease is similar to Kawasaki disease and may be associated with abnormal inflammatory indicators, such as elevated levels of acute phase reactants, anemia, leukocytosis and/or thrombocytosis; histopathology shows a predominantly cytotoxic lymphocyte infiltration in the arterial tissue, especially $\gamma\delta$ T cells; other inflammatory cells include histiocytes, macrophages and plasma cells [30]. These cells cause vascular damage by releasing large amounts of the cytolytic protein perforin, which disrupts the vascular elastic membrane and mesothelial muscle layer, leading to aneurysmal dilatation [30-31]. The incidence of TA CAL is 10%-30%, which manifests as focal or diffuse inflammation, dilation, stenosis or occlusion [32], and IVIG treatment unresponsive to Kawasaki disease should be distinguished from this disease.

IV. Systemic juvenile idiopathic arthritis (JIA)

Systemic JIA is a systemic auto-inflammatory disease [33], which may have no early manifestations of arthritis, but more prominent extra-articular manifestations, including daily intermittent fever (fever peak ≥ 38.5 °C), pale red maculopapular rash, enlarged liver and spleen lymph nodes, and plasmacytosis, and is easily complicated by MAS [34]. Laboratory features of systemic JIA include increased white blood cell count, elevated granulocyte count and ratio, thrombocytosis, anemia, increased erythrocyte sedimentation rate, and elevated C-reactive protein and serum ferritin, while being negative for autoantibodies [35]. Several papers have reported the finding of coronary artery dilation on cardiac ultrasonography in children with systemic JIA [36-37], which is easily misdiagnosed as Kawasaki disease or incomplete Kawasaki disease similar to Kawasaki disease, and the immunopathogenesis of systemic JIA in individuals with a certain genetic background, in which the intrinsic immune system is dysregulated and overactivated by various promotive factors, producing large amounts of inflammatory cytokines (IL-1, IL-6 and IL-10, IL-17, IL-21, etc.) and pro-inflammatory proteins (S100-A8, S100-A9 and S100A-12), which in turn lead to systemic multisystemic inflammation and even complications of MAS [38-39]. Given that systemic JIA does not respond to IVIG therapy, children with IVIG-naïve Kawasaki disease need to be differentiated from systemic JIA, even if coronary artery dilatation is present.

V. Systemic lupus erythematosus (SLE)

SLE in children is a chronic recurrent autoimmune disease that presents with multisystemic multi-organ involvement, positive signature autoantibodies, and decreased complement [40-41]. The main manifestations are pericarditis, myocarditis, endocarditis, valvular disease and coronary artery disease. Early detection of coronary artery disease in SLE patients,

especially in children, and early intervention and treatment are of great significance to reduce the incidence of coronary heart disease and mortality rate. children with SLE are at significantly higher risk of CAL than the healthy population, and systemic inflammation is an independent risk factor for CAL [42]. children with SLE have larger coronary artery diameters than healthy children, and a small number of children with SLE can be complicated by coronary arteritis and/or coronary artery dilation [42], which may be diagnosed early as Kawasaki disease or incomplete Kawasaki disease. It has been suggested that coronary arteritis may be a more common clinical feature of childhood SLE than currently recognized, and early recognition and management would be beneficial in improving long-term cardiovascular outcomes in children with SLE [43-44]. Therefore, in cases of unexplained fever, rash, anemia, coronary artery dilatation and multi-system damage in children, Kawasaki disease should not be limited to SLE, and attention should be given to the exclusion of SLE, the establishment of thinking procedures for the diagnosis of systemic lupus erythematosus in children [45], further examination of complement and anti-autoantibody, and early diagnosis of SLE. At the same time, children with SLE must undergo routine electrocardiogram, heart B-ultrasound, and coronary angiography if necessary, so as to achieve early diagnosis and early reasonable treatment, so as to delay or prevent the progression to coronary heart disease, reduce the rate of SLE death, improve the prognosis, and achieve continuous clinical remission

VI. primary immunodeficiency diseases (PID)

Some primary immunodeficiency diseases may also involve coronary arteries, including autosomal dominant hyperimmunoglobulin E syndrome (AD-HIE), which is caused by a subtractive variant of the STAT3 gene^[46-47], and X-linked lymphoproliferative disease (X-linked HIE), which is caused by a variant of the XIAP gene. X-linked lymphoproliferative disease 2 (XLP-2) and partially monogenic auto-inflammatory disease (AID)^[48]. AD-HIE coronary artery involvement can manifest as atherosclerosis, tortuosity, dilatation and local aneurysms^[47]. XLP-2 often presents as EBV-associated fulminant infectious mononucleosis and phagocytic syndrome, which can lead to Kawasaki disease-like CAL, and the underlying mechanism may be related to excessive activation of CD8+ T cells and inflammatory cytokine storm in EBV infection [48]. AID often presents as recurrent or persistent inflammation of unknown origin, and the clinical features of the exacerbation phase are similar to those of Kawasaki disease has many overlapping clinical features, such as fever, rash, plasma membrane inflammation, arthritis, aseptic meningitis, conjunctivitis and uveitis, among which hyper IgD syndrome caused by MVK gene variants can present with coronary artery dilation^[49], which is easily misdiagnosed as Kawasaki disease or incomplete Kawasaki disease in early stages, and recurrent Kawasaki disease should be distinguished from AID in particular.

VII. Chronic active Epstein-Barr virus (CAEBV) infection

CAEBV infection is a rare, life-threatening lymphoproliferative disorder that manifests as persistent infectious mononucleosis-like syndrome, EBV viremia, or EBV-associated phagocytic syndrome [50]. Untreated T-cell CAEBV-infected patients often develop systemic organ lesions due to T-cell infiltration of tissues, phagocytic lymphocytosis, hepatic failure, and CAL [51]. The incidence of coronary artery dilation in CAEBV is approximately 8.5% [52], with some early misdiagnosis as incomplete Kawasaki disease. The mechanism by which CAL occurs in CAEBV may be related to abnormal secretion of inflammatory factors (e.g. tumor necrosis factor α , IL-16 and IL-10), and T-cell immune imbalance [53]. In children with

persistent fever, hepatosplenomegaly, and abnormal liver enzymes with coronary artery dilatation, especially those without the typical clinical manifestations of Kawasaki disease, care needs to be taken to differentiate from CAEBV.

A variety of rheumatic immune and cardiovascular diseases in children can lead to CAL, and in individuals with a specific genetic background, over-activation of intrinsic immunity and/or imbalance of adaptive immunity in the presence of infection or other triggers, leading to acute or chronic inflammatory injury, are the key immunologic mechanisms leading to CAL. Based on a deep understanding of the pathogenesis of the disease, clinicians should broaden the diagnosis and differentiation of the disease in all aspects to avoid falling into the trap of diagnosing Kawasaki disease or incomplete Kawasaki disease; at the same time, they should pay high attention to CAL secondary to rheumatic immune diseases and cardiovascular diseases, and actively manage coronary complications based on multidisciplinary cooperation to further improve the diagnosis and treatment of CAL lesions in children with related diseases.

Conclusion

CAL is not uncommon in pediatrics but has a complex etiology. congenital coronary artery disease, atherosclerosis, infectious diseases and rheumatic immune diseases can all cause CAL. the core pathogenesis is focal or diffuse inflammation leading to destruction of the intima and mesostructure of the coronary artery wall, degradation of the elastic fibers and subsequent dilatation, stenosis or occlusion of the coronary arteries. The incidence of CAL due to Kawasaki disease is most common in pediatrics, and timely treatment with intravenous immunoglobulin (IVIG) has reduced the incidence of CAL from 25% to approximately 4%^[54]. CAL is not unique to Kawasaki disease, and many rheumatic immune diseases in children can lead to coronary artery involvement. Clinicians need to have a better understanding of the immunological mechanisms of the disease and to broaden their thinking about diagnosis and treatment to avoid misdiagnosis and underdiagnosis.

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