
What Lesions Can Cause Coronary Artery Lesions in Children?

Abstract

Coronary artery lesions (CAL) are not uncommon in pediatrics, but their causes are complex, such as congenital coronary artery disease, atherosclerosis, infectious diseases, and rheumatic immune diseases, which can lead to CAL. This review systematically evaluates multiple potential causes of childhood CAL and related pathogenesis, in order to broaden clinical diagnosis and avoid misdiagnosis and underdiagnosis. The main pathogenesis of CAL is an innate immunity imbalance due to exposure of genetically susceptible people to various infections and/or environmental factors. Kawasaki disease is not the only cause of CAL, and pediatricians need to better understand the immunological mechanisms of the CAL to suspect and diagnose. In addition, attach great importance to rheumatic immune diseases and cardiovascular diseases secondary to CAL.

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

Introduction

The etiological mechanism of coronary artery lesions (CAL) 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]. 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 long-term 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 lesions (CAL). 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.

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 fungal or septic emboli, syphilis, etc. can injure 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.

The predisposing factors

1. Infection and autoimmune abnormalities: infection may directly or indirectly injure 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.

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 [2]. 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). 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 [3-4].

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 [5]. Inflammatory cells infiltrating the arterial vasculature include neutrophils, T cells (especially CD8+ T cells), eosinophils, plasma cells (especially IgA-secreting plasma cells), and macrophages [6]. Early in the course of the disease, mainly neutrophils infiltrate the arterial wall, and after 2 weeks, monocytes and CD8+ T cells predominate [7]. Thus, Kawasaki disease may be a systemic inflammatory disease with a predominantly innate immune disorder due to exposure of genetically susceptible individuals to various infections and/or environmental triggers.

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 multisystemic injury and evidence of novel coronavirus pneumonia (COVID-19). The World Health Organization defines MIS in children [8] as (1) Age < 19 years. (2) Fever ≥ 3 d. (3) Evidence of multisystem injury (≥ 2): (i) rash, bilateral non-purulent 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 procalcitonin. (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^[9]. 93% of coronary artery aneurysms are mild and 7% are moderate^[10]. 40% to 50% of children with MIS meet the diagnostic criteria for Kawasaki disease or incomplete Kawasaki disease, which is very similar to KDSS. The 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^[11]; 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^[12-14].

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^[11,15-16]. Therefore, MIS in children is an inflammatory cytokine storm disease caused by abnormal immune response induced after viral infection.

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^[17]. 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^[17-18]. The disease is similar to Kawasaki disease and may be characterized by 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^[19]. These cells cause vascular injury by releasing large amounts of the cytolytic protein perforin, which disrupts the vascular elastic membrane and mesothelial muscle layer, leading to aneurysmal dilatation^[20]. The incidence of TA CAL is 10%-30%, which manifests as focal or diffuse inflammation, dilation, stenosis or occlusion^[21], and Kawasaki disease unresponsive to IVIG treatment should be distinguished from this disease.

Systemic juvenile idiopathic arthritis (JIA)

Systemic JIA is a systemic auto-inflammatory disease^[22], 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 serositis, and is easily complicated by MAS^[23]. 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^[24]. Several papers have reported the finding of coronary artery dilation on cardiac ultrasonography in children with systemic JIA^[25-26], 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 innate 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 [27-28]. Given that systemic JIA does not respond to IVIG therapy, children with IVIG non-reactive Kawasaki disease need to be differentiated from systemic JIA, even if coronary artery dilatation is present.

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 [29-30]. Children with SLE are at significantly higher risk of CAL than the healthy population, and systemic inflammation is an independent risk factor for CAL [31]. 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, 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 [32-33].

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 [34-35]; and X-linked lymphoproliferative disease (X-linked HIE), which is caused by a variant of the XIAP gene; and partially monogenic auto-inflammatory disease (AID) [36]. AD-HIE coronary artery involvement can manifest as atherosclerosis, tortuosity, dilatation and local aneurysms. XLP-2 often presents as EBV-associated fulminant infectious mononucleosis and hemophagocytic syndrome (HSP), 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 [37]. 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 diseases, such as fever, rash, serositis, arthritis, aseptic meningitis, conjunctivitis and uveitis, among which hyper IgD syndrome caused by MVK gene variants can present with coronary artery dilation, 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.

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 [38]. Untreated T-cell CAEBV-infected patients often develop systemic organ lesions due to T-cell infiltration of tissues, phagocytic lymphocytosis, hepatic failure, and CAL [39]. The incidence of coronary artery dilation in CAEBV is approximately 8.5% [40], 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 [41]. 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.

Conclusion

The pathogenesis of CAL is based on focal or diffuse inflammation leading to destruction of the

intima and mesostructure of the coronary vessel wall, degradation of elastic fibers followed by coronary artery dilatation, stenosis or occlusion; as well as immunological mechanisms of over-activation of innate immunity and/or imbalance of adaptive immunity in the presence of infection or other causative factors in individuals with specific genetic backgrounds, followed by acute or chronic inflammatory injury are jointly involved. 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% [42]. However, CAL is not a unique manifestation of Kawasaki disease, and a variety of childhood rheumatic-immune diseases can lead to coronary artery involvement.

Therefore, clinicians should deeply understand the pathogenesis of the disease, be alert to CAL secondary to rheumatic immune diseases and cardiovascular diseases, broaden the diagnosis and differentiation of the disease in all aspects, actively manage coronary complications through multidisciplinary cooperation, and further improve the diagnosis and treatment of CAL lesions in children caused by related diseases.

Reference

- [1] Islam A-K-M-Monwarul,Majumder A-A-S. Coronary artery disease in Bangladesh: a review.[J]. Indian heart journal, 2013, (4): 424-35.
- [2] Mccrindle Brian-W,Rowley Anne-H,Newburger Jane-W, et al. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association.[J]. Circulation, 2017, (17): e927-e999.
- [3] Taichi Kato,Masaru Miura,Tohru Kobayashi, et al. Analysis of Coronary Arterial Aneurysm Regression in Patients With Kawasaki Disease by Aneurysm Severity: Factors Associated With Regression.[J]. Journal of the American Heart Association, 2023, 12(3): e022417.
- [4] Mccrindle Brian-W,Manlhiot Cedric,Newburger Jane-W, et al. Medium-Term Complications Associated With Coronary Artery Aneurysms After Kawasaki Disease: A Study From the International Kawasaki Disease Registry.[J]. Journal of the American Heart Association, 2020, (15): e016440.
- [5] Orenstein Jan-Marc,Shulman Stanford-T,Fox Linda-M, et al. Three linked vasculopathic processes characterize Kawasaki disease: a light and transmission electron microscopic study.[J]. PloS one, 2012, (6): e38998.
- [6] Kei Takahashi,Toshiaki Oharaseki,Yuki Yokouchi, et al. Kawasaki disease: basic and pathological findings.[J]. Clinical and Experimental Nephrology, 2012, 17(5): 690-693.
- [7] Sato Wakana,Yokouchi Yuki,Oharaseki Toshiaki, et al. The pathology of Kawasaki disease aortitis: a study of 37 cases.[J]. Cardiovascular pathology : the official journal of the Society for Cardiovascular Pathology, 2020: 107303.
- [8] Yue-Hin Loke,Charles I Berul,Ashraf S Harahsheh. Multisystem inflammatory syndrome in children: Is there a linkage to Kawasaki disease?[J]. Trends in Cardiovascular Medicine, 2020, 30(7): 389-396.
- [9] Kaushik Ashlesha,Gupta Sandeep,Sood Mangla, et al. A Systematic Review of Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 Infection.[J]. The Pediatric infectious disease journal, 2020, (11): e340-e346.
- [10] Lee Min-Sheng,Liu Yi-Ching,Tsai Ching-Chung, et al. Similarities and Differences Between COVID-19-Related Multisystem Inflammatory Syndrome in Children and Kawasaki Disease.[J]. Frontiers in pediatrics, 2021: 640118.

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- [11] Cheung Eva-W,Zachariah Philip,Gorelik Mark, et al. Multisystem Inflammatory Syndrome Related to COVID-19 in Previously Healthy Children and Adolescents in New York City.[J]. JAMA, 2020, (3): 294-296.
- [12] Jerin Jose,Elif Seda Selamet Tierney,Ashraf S Harahsheh, et al. COVID-19 Positive Versus Negative Complete Kawasaki Disease: A Study from the International Kawasaki Disease Registry.[J]. Pediatric Cardiology, 2023: 1-9.
- [13] Alberto García-Salido,Juan Carlos de Carlos Vicente,Sylvia Belda Hofheinz, et al. Severe manifestations of SARS-CoV-2 in children and adolescents: from COVID-19 pneumonia to multisystem inflammatory syndrome: a multicentre study in pediatric intensive care units in Spain.[J]. Critical Care (london, England), 2020, 24(1): 666.
- [14] Elizabeth Whittaker,Alasdair Bamford,Julia Kenny, et al. Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2.[J]. Jama, 2020, 324(3): 259-269.
- [15] Consiglio Camila-Rosat,Cotugno Nicola,Sardh Fabian, et al. The Immunology of Multisystem Inflammatory Syndrome in Children with COVID-19.[J]. Cell, 2020, (4): 968-981.e7.
- [16] Conor N Gruber,Roosheel S Patel,Rebecca Trachtman, et al. Mapping Systemic Inflammation and Antibody Responses in Multisystem Inflammatory Syndrome in Children (MIS-C).[J]. Cell, 2020, 183(4): 982-995.e14.
- [17] Souza Alexandre-Wagner-Silva-de,Carvalho Jozélio-Freire-de. Diagnostic and classification criteria of Takayasu arteritis.[J]. Journal of autoimmunity, 2014: 79-83.
- [18] Seza Ozen,Angela Pistorio,Silvia M Iusan, et al. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria.[J]. Annals of the Rheumatic Diseases, 2010, 69(5): 798-806.
- [19] Aeschlimann Florence-A,Yeung Rae-S-M,Laxer Ronald-M. An Update on Childhood-Onset Takayasu Arteritis.[J]. Frontiers in pediatrics, 2022: 872313.
- [20] Podgorska Dominika,Podgorski Rafal,Aebisher David, et al. Takayasu arteritis - epidemiology, pathogenesis, diagnosis and treatment.[J]. Journal of applied biomedicine, 2019, (1): 20.
- [21] Aeschlimann Florence-A,Twilt Marinka,Yeung Rae-S-M. Childhood-onset Takayasu Arteritis.[J]. European journal of rheumatology, 2020, (Suppl1): S58-S66.
- [22] Ravelli Angelo,Martini Alberto. Juvenile idiopathic arthritis.[J]. Lancet (London, England), 2007, (9563): 767-778.
- [23] Erdal Sağ,Berna Uzunoğlu,Fatma Bal, et al. Systemic onset juvenile idiopathic arthritis: a single center experience.[J]. The Turkish Journal of Pediatrics, 2019, 61(6): 852-858.
- [24] Kumar Sathish. Systemic Juvenile Idiopathic Arthritis: Diagnosis and Management.[J]. Indian journal of pediatrics, 2016, (4): 322-7.
- [25] A Felix,F Delion,B Suzon, et al. Systemic juvenile idiopathic arthritis in French Afro-Caribbean children, a retrospective cohort study.[J]. Pediatric Rheumatology Online Journal, 2022, 20(1): 98.
- [26] Arsenaki Elisavet,Georgakopoulos Panagiotis,Mitropoulou Panagiota, et al. Cardiovascular Disease in Juvenile Idiopathic Arthritis.[J]. Current vascular pharmacology, 2020, (6): 580-591.
- [27] Saverio La Bella,Marta Rinaldi,Armando Di Ludovico, et al. Genetic Background and

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- Molecular Mechanisms of Juvenile Idiopathic Arthritis.[J]. *International Journal of Molecular Sciences*, 2023, 24(3).
- [28] Yu-Tsan Lin,Chen-Ti Wang,M Eric Gershwin, et al. The pathogenesis of oligoarticular/polyarticular vs systemic juvenile idiopathic arthritis.[J]. *Autoimmunity Reviews*, 2011, 10(8): 482-9.
- [29] Silva Clovis-A,Avcin Tadej,Brunner Hermine-I. Taxonomy for systemic lupus erythematosus with onset before adulthood.[J]. *Arthritis care & research*, 2012, (12): 1787-93.
- [30] Ohara Asami,Iwata Naomi,Sugiura Shiro, et al. Evaluation of the European League Against Rheumatism/American College of Rheumatology-2019 classification criteria in patients with childhood-onset systemic lupus erythematosus: a single-center retrospective study.[J]. *Clinical rheumatology*, 2022, (8): 2483-2489.
- [31] Shen C-C,Chung H-T,Huang Y-L, et al. Coronary artery dilation among patients with paediatric-onset systemic lupus erythematosus.[J]. *Scandinavian journal of rheumatology*, 2012, (6): 458-65.
- [32] Sherif M Gamal,Sally S Mohamed,Marwa Tantawy, et al. Lupus-related vasculitis in a cohort of systemic lupus erythematosus patients.[J]. *Archives of Rheumatology*, 2021, 36(4): 595-692.
- [33] Agarwal Arunima,Student Stephanie-Biglarian-Medical,Lim-stavros Sophia, et al. Pediatric systemic lupus erythematosus presenting with coronary arteritis: A case series and review of the literature.[Z], 2015: 42-7.
- [34] Khaled Z Abd-Elmoniem,Nadine Ramos,Saami K Yazdani, et al. Coronary atherosclerosis and dilation in hyper IgE syndrome patients: Depiction by magnetic resonance vessel wall imaging and pathological correlation.[J]. *Atherosclerosis*, 2017, 258: 20-25.
- [35] Alexandra F Freeman,Elizabeth Mannino Avila,Pamela A Shaw, et al. Coronary artery abnormalities in Hyper-IgE syndrome.[J]. *Journal of Clinical Immunology*, 2011, 31(3): 338-45.
- [36] Sandra Hansmann,Elke Lainka,Gerd Horneff, et al. Consensus protocols for the diagnosis and management of the hereditary autoinflammatory syndromes CAPS, TRAPS and MKD/HIDS: a German PRO-KIND initiative.[J]. *Pediatric Rheumatology Online Journal*, 2020, 18(1): 17.
- [37] Ru-Yue Chen,Xiao-Zhong Li,Qiang Lin, et al. Epstein-Barr virus-related hemophagocytic lymphohistiocytosis complicated with coronary artery dilation and acute renal injury in a boy with a novel X-linked inhibitor of apoptosis protein (XIAP) variant: a case report.[J]. *Bmc Pediatrics*, 2020, 20(1): 456.
- [38] Cohen Jeffrey-I,Jaffe Elaine-S,Dale Janet-K, et al. Characterization and treatment of chronic active Epstein-Barr virus disease: a 28-year experience in the United States.[J]. *Blood*, 2011, (22): 5835-49.
- [39] Quintanilla-martinez Leticia,Swerdlow Steven-H,Tousseyn Thomas, et al. New concepts in EBV-associated B, T, and NK cell lymphoproliferative disorders.[J]. *Virchows Archiv : an international journal of pathology*, 2022, (1): 227-244.
- [40] Kimura Hiroshi,Morishima Tsuneo,Kanegane Hirokazu, et al. Prognostic factors for chronic active Epstein-Barr virus infection.[J]. *The Journal of infectious diseases*, 2003, (4): 527-33.
- [41] Muneuchi Jun,Ohga Shouichi,Ishimura Masataka, et al. Cardiovascular complications associated with chronic active Epstein-Barr virus infection.[Z], 2009: 274-81.
- [42] Correction to: Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association.[J]. *Circulation*, 2019, (5): e181-e184.

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