Kawasaki Disease and Coronary Artery Involvement: A Narrative Review

Kruthiga Rajasekaran 1, Shrimahitha Duraiyarasu 2, Mayowa Adefuye 3, Nisha Manjunatha 4, Vinutna Ganduri 5

1. Research, Rajash Mathiah Medical College & Hospital, Chidambaram, IND 2. Research, K.A.P. Viswanatham Government Medical College, Tiruchirappalli, IND 3. Research, University of Iladon College of Medicine, Iladan, NGA 4. Research, Our Lady of Fatima University College of Medicine, Valenzuela, PHIL 5. Research, Bhaskar Medical College, Hyderabad, IND

Abstract

Kawasaki disease is a systemic vasculitis with a risk of developing coronary artery lesions if left untreated. Kawasaki disease can be diagnosed clinically with classical symptoms (conjunctivitis, rash, lymphadenopathy, mucositis, edema of hands and feet), but predicting the risk of developing coronary artery aneurysm remains challenging. The coronary sequelae of Kawasaki disease have significant morbidity and mortality and are the second most common cause of acquired cardiac disease in children. Several genetic and immune factors are involved in the inflammation of coronary artery lesions in Kawasaki disease.

Introduction And Background

Kawasaki disease, also known as acute febrile mucocutaneous syndrome, is a multi-system inflammatory disorder of the blood vessels that mainly affects infants and children under five years of age [1]. In January 1961, Tomisaku Kawasaki, a Japanese pediatrician, encountered his first case of pediatric vasculitis, and in 1967 he published a study in Japanese with over 50 patients suffering from this syndrome [2]. It is more prevalent in Japan, with an incidence reported of over 200/100000, which is much higher than in Western countries, where it is 4/100000. Kawasaki disease varies significantly by race, with an incidence ranging from over 200/100000 in Japan to only 0.7% in Western countries [3]. The disease has a male predominance with a ratio of 1.5:1 [4]. Some recent studies have stated that the co-expression of five immune genes is involved in the development of Kawasaki disease [5]. In children under five, 80% of Kawasaki cases are reported, while adults account for only 0.7% [4]. The disease has a male predominance with a ratio of 1.5:1 [4,5]. In general, the etiology of Kawasaki disease is unknown, but some studies suggest that the hygiene hypothesis could be a risk factor. Sterile environments, frequent use of antibiotics, sanitizing agents, and formula feeds lead to defective B-cell maturation and low production of immunoglobulins. Dysregulated B cell maturation and differentiation make non-pathogenic triggers pathogenic. This supports the role of immunoglobulins in the treatment of Kawasaki disease [6]. Some recent studies have stated that the co-expression of five immune genes is involved in the development of Kawasaki disease.

Using the Gene Expression Omnibus Database, Kawasaki disease-related databases (GSE18606, GSE68004, GSE73641) were obtained and integrated with samples from 173 Kawasaki patients and 101 samples from regular patients. With the help of CIBERSORT, 22 immune cells were identified in the samples and subjected to differentially expressed gene (DEG) analysis and weighted gene co-expression network analysis (WGCNA). These co-expression networks and Cytoscape 3.5.1's cytoHubba tool helped identify these CXCL8, CCL5, CCR7, CXCR3, and CCR1 genes that play an important role in the pathogenesis of Kawasaki disease.

The classic symptoms of Kawasaki disease include fever lasting more than five days, bilateral non-purulent conjunctivitis, dysmorphic skin rashes, edema of hands and feet, and cervical lymphadenopathy and mucositis. Diagnosis is mainly clinical, with a fever lasting more than five days and any four of the five aforementioned clinical criteria [8]. Patients who do not have classic symptoms but have a fever lasting more than five days and evidence of systemic inflammation such as hypoalbuminemia, elevated platelet count, increased WBC count, amiotransferase elevation, and anemia should have an echocardiogram [9]. There are

Categories: Cardiology, Family/General Practice, Pediatrics
Keywords: aspirin, corticosteroids, kawasaki disease, arteritis, pseudoaneurysms, coronary artery

How to cite this article
Rajasekaran K, Duraiyarasu S, Adefuye M, et al. (August 24, 2022) Kawasaki Disease and Coronary Artery Involvement: A Narrative Review. Cureus 14(8): e28358. DOI 10.7759/cureus.28358
serum biomarkers expressed during acute attacks of Kawasaki disease. Lipopolysaccharide binding protein, leucine-rich 2 glycoprotein, and angiotensinogen are examples of these [10]. The mainstay of treatment for Kawasaki disease is aspirin and intravenous immunoglobulins (IVIG), but recent studies have demonstrated the efficacy of corticosteroids plus IVIG and anti-tumor necrosis factor alpha (TNF-α) drugs in managing IVIG-resistant Kawasaki disease [11]. The serious complication of Kawasaki disease is the involvement of the cardiovascular system. These include pericarditis, myocarditis, coronary artery dilatations, and coronary artery aneurysms. These cardiac lesions are the second most common cause of acquired cardiac disease in children [12]. This review article highlights the association between Kawasaki disease and coronary artery lesions by discussing the risk factors and pathophysiology involved in the development of coronary artery lesions and recent advances in treatment modalities to prevent the development of coronary artery lesions as a consequence of Kawasaki disease.

**Review**

**Pathogenesis of coronary artery involvement in Kawasaki disease**

The pathogenesis of Kawasaki disease remains unclear. Several studies were conducted to determine the theory behind the development of Kawasaki disease based on genetic, immunologic, and infectious factors. Several studies found several associations between genetic and immunologic components in an attempt to identify the pathogenesis of coronary artery involvement in Kawasaki disease. The Japan Ministry of Health first proposed the definition of coronary artery aneurysm, defined as the internal diameter of the coronary artery more than 5mm in children less than five years old or more than 4mm in children more than five years old [13].

**Interplay between immune and genetic factors**

Coronary artery aneurysms and coronary artery disease are two major complications of Kawasaki disease. Using isobaric tags for relative and absolute quantitation (iTRAQ) analysis and western blot, five specific proteins were identified, which include mannose-binding lectin 2 (MBL2), complement factor H (CFH), kininogen 1 (KNG1), serpin family C member 1 (SERPINC1) and fibronectin 1 (FN1). Complement factor H, a negative regulator of C3b protein, and mannose-binding lectin 2 regulate cleavage of C2 and C4 proteins. Low complement factor H and mannose binding lectin 2 increase C3b levels and decrease C2 and C4 separation, causing innate inflammation and contributing to coronary artery damage and thrombosis. In contrast with coronary artery disease (CAD), coronary artery aneurysms (CAA) with KNG1 with histidine proline glycoprotein and SERPINC1 have anti-inflammatory and anticoagulant properties, and their low levels cause inflammation and endothelial damage resulting in coronary artery dilatation and aneurysm formation. Fibronectin 1 is an extracellular glycoprotein involved in wound healing and wound processing. Low levels of fibronectin 1 in CAD and CAA are found [14-18].

Transforming growth factor-beta is one such gene that plays a vital role in T cell activation and cardiac remodeling in Kawasaki disease [19]. Transcription growth factor-beta (TGF-beta) is involved in endothelial cell proliferation, migration, apoptosis, angiogenesis, calcification, and fibrosis. The active and latent form of TGF-beta is regulated by two proteins, FURIN and EMILIN (elastin microfibril interfaceter-1). The active form of TGF-beta binds to the TGFBR2 receptor, which recruits TGFBR1 or ACVR1L (activin type 2 like 1), which further phosphorylates the SMAD family of proteins translocates to the nucleus and causes transcription of TGF-beta. Alteration in TGFBR2, TGFBR2, and SMAD5 genes causes continuous transcription and remodeling of coronary endothelial cells and coronary artery aneurysm formation [20].

The most critical gene in the development of coronary artery lesions in Kawasaki disease is the discovery of the inositol 1,4,5-trisphosphate 3-kinase (ITPKC) gene. ITPKC is an important negative regulator of calcium channels and regulates T cells activation. Genetic polymorphisms of ITPKC gene affect its mRNA splicing, translating into an immature and truncated protein. When an antigen binds to the T cell receptor, activation of phospholipase-gamma one results in hydrolysis of phosphatidylinositol 3,4 bisphosphate to IP3 and DAG. Low activity of the mutated ITPKC gene in Kawasaki disease causes continuous phosphorylation of IP3, which binds to the IP3 receptor in the endoplasmic reticulum and causes calcium release into the cytoplasm. The depletion of calcium in the endoplasmic reticulum is sensed by the stromal interaction molecule (STIM), and the empty endoplasmic reticulum also evokes the store-operated calcium entry (SOC) a process through which extracellular calcium enters via ORAI, a calcium-release activated calcium channel located on the plasma membrane. The cytoplasmic calcium binds to calmodulin, and the calcium calmodulin complex results in the activation of calcineurin, which dephosphorylates the nuclear factor of activated T cells (NFAT), results in continuous transcription of genes involved in T cell activation and release of a large number of inflammatory cytokines which mediates inflammation of coronary artery and formation of aneurysms (Figure 1) [21].
Several proteins are involved in the pathogenesis of Kawasaki disease. N-terminal prohormone of brain natriuretic peptide (NT-pro-BNP) is the potential biomarker of myocardial damage that occurred as a sequela of Kawasaki disease [22]. Cardiac troponin and peristin are non-specific markers elevated in the acute stages of Kawasaki disease [23,24]. Tenascin-C is an extracellular glycoprotein upregulated and used to predict the risk of the development of coronary artery aneurysms [25].

Another study proposed the role of regulatory T cells (Tregs) cells in the pathogenesis of Kawasaki disease. CD4+CD25+forkhead box protein 3 (Foxp3+) Tregs are crucial in maintaining immune tolerance. Foxp3 is a transcription factor important for developing Tregs. There are three microRNAs (miRNA) involved in the expression of the Foxp3+ transcription factor. These include miR-155, miR-31, and miR-21. Foxp3+ directly activates miR-155, which binds to suppressors of cytokines signaling (SOCS)-1 mRNA, thereby inhibiting cytokine signaling. It also indirectly regulates signal transducer and activator of transcription (STAT)-5, which binds to the promoter region of Foxp3+ to increase its expression. miR-31 negatively regulates Foxp3+ expression. miR-21 positively regulates Foxp3+ expression (Figure 2).
FIGURE 2: Expression of Foxp3 gene in regulatory T cells. miR-155, miR-31, and miR-21. Foxp3+ directly activates miR-155, which binds to suppressors of cytokines signaling (SOCS)-1 mRNA, thereby inhibiting cytokine signaling. It also indirectly regulates signal transducer and activator of transcription (STAT)-5, which binds to the promoter region of Foxp3+ to increase its expression. miR-31 negatively regulates Foxp3+ expression. miR-21 positively regulates Foxp3+ expression (Figure 1). Interleukin-6, when it binds to its receptor on Treg cells, activates signal transducer and activator of transcription (STAT)-3, which suppresses miR-21. In patients with Kawasaki disease, it is found that low levels of miR-155 and low numbers of Foxp3+ Treg cells and elevated levels of miR-31 and IL-6 are present. Interleukin-6, when bound to its receptor on Treg cells, activates signal transducer and activator of transcription (STAT)-3, which suppresses miR-21. In patients with Kawasaki disease, it is found that low levels of miR-155 and low numbers of Foxp3+ Treg cells, and elevated levels of miR-31 and IL-6 are present [26-29]. Another miRNA (miR-223) plays a role in forming coronary artery aneurysms in Kawasaki disease. Damage to the endothelium of coronary vessels leads to activation of platelets. miR-223 is not native to vascular smooth muscle cells, but the activated platelets deliver miR-223 to vascular smooth muscle cells, which suppress their de-differentiation through platelet-derived growth factor-beta inhibition. Blood samples of platelet from Kawasaki disease patients with coronary artery aneurysms cultured in vitro show low levels of miR-223, causing massive release of matrix metalloproteinases 9, which damages coronary artery endothelium dilatation and leads to aneurysm formation [30].

Homeodomain interacting protein kinase 3 (circHIPK3), zinc finger protein 124 (circ2NF124), WAS protein homolog associated with actin, Golgi membranes, and microtubules pseudogene 1 (circWHAMMP1), SLAIN motif family, member 2 (circSLAIN2), and ataxia telangiectasia mutated (circ ATM) are the circulatory RNAs expressed low in the coronary arteries of untreated Kawasaki disease patients [31]. Urine biomarkers include...
filamin, talin, complement regulator CSMD3, immune pattern recognition receptor mucin, and immune cytokine protease meprin A, all elevated in acute stages of Kawasaki disease [32].

**Histopathology of coronary artery in Kawasaki disease**

The histopathology of coronary artery lesions was studied in 37 Japanese patients. The arteries studied include the aorta, carotid, celiac, iliac, hepatic, splenic, mesenteric, renal, lumbar arteries, and the venous system. There are six stages of progressive histopathological findings, including degeneration of endothelial cells, edema and degeneration of the media, necrotizing pan arteritis, granuloma formation, scar formation, and aneurysm formation [33]. There is also an occurrence of myocardial fibrosis in Kawasaki disease patients. Since biopsy of the myocardial tissue is practically difficult, a recent innovation called cardiac integrated backscatter analysis is used in identifying myocardial fibrosis [34].

**Diagnosis**

Since the first case of Kawasaki disease was reported by Dr. Tamisaku Kawasaki, the criteria for diagnosis remain clinical. There are many criteria proposed in different years for the diagnosis of Kawasaki disease. Based on Japanese guidelines, in 2002, according to the Kawasaki disease research committee, the diagnosis of Kawasaki disease is made when five of the following six symptoms present: persistent fever lasting more than five days, bilateral conjunctival congestion, mucosal involvement, polymorphous eruptions, peripheral extremities involvement, and acute non-purulent cervical lymphadenopathy [35]. In 2004, The American Heart Association proposed its guidelines. These include fever for five days with any four of the five clinical features (erythema of palms and soles, diffuse polymorphic eruptions, bilateral nonexudative conjunctivitis, mucosal involvement, cervical lymphadenopathy) [9].

Echocardiography plays an important role in identifying cardiac complications in Kawasaki disease. The Japanese Ministry of Health criteria first proposed the initial echocardiographic criteria in 2004, which was modified in 2008, which classified aneurysms as small aneurysms, medium aneurysms, and large aneurysms [36]. In 2017 the American Heart Association classified aneurysms with the help of Z scores (Table 1) [37].

| 2017 AHA classification of coronary artery aneurysms with Z score | 2008 modified Japan Ministry of Health criteria |
|---------------------------------------------------------------|-----------------------------------------------|
| Small aneurysm: ≥2.5 Z score<5 | Small aneurysm: ≤4mm internal diameter of coronary artery |
| Medium aneurysm:≥5 Z score<10 | Medium aneurysm: >4mm to ≤8mm internal diameter of coronary artery |
| Large aneurysm: Z score≥10 | Large aneurysm: >8mm internal diameter of coronary artery |

**TABLE 1: Classification of coronary artery aneurysms in Kawasaki disease**

AHA: American Heart Association.

**Management**

*Standard Therapy*

Aspirin and intravenous immunoglobulins are two drugs conventionally used to treat Kawasaki disease. The initial treatment for Kawasaki disease combines aminosalicylic acid (ASA) with intravenous immunoglobulins [38]. The most important part of treatment in Kawasaki disease is early detection and prevention of cardiac complications, especially coronary artery aneurysms. Several scoring systems were developed to detect the risk of developing coronary artery aneurysms. The Harada scoring system was the first scoring system used to detect coronary artery aneurysms. The factors included in the scoring system are white blood cell count 12,000/mm3, platelet count 350,000/mm3, C-reactive protein, hematocrit 35%, albumin 3.5 g/dL, age ≤ 12 months and male sex. Suppose the child has any four of the fore-mentioned laboratory values within 10 days of illness. In that case, the patient is at risk of developing coronary artery lesions and an indication for immunoglobulins administration [39]. The administration of intravenous immunoglobulins within 10 days of onset of the disease can reduce the risk of the development of coronary artery aneurysms [40]. IVIG suppresses cytokine production, inflammatory markers like CD40L and iNOS, and the provision of anti-idiotypic antibodies [41].

During the initial stages of Kawasaki disease, aspirin should be administered in a high dose (80mg/kg/day) divided every six hours. High-dose aspirin is continued for 14 days during the initial phase of the disease and the child should be fever-free for 48 to 72 hours before stopping high-dose aspirin [42,43]. This high dose of aspirin is followed by a low dose of aspirin (3 to 5 mg/kg daily) for its antiplatelet action and to
prevent cardiac complications [44]. While on aspirin therapy, the child should be monitored for the development of Reye syndrome, especially with high-dose aspirin for a prolonged duration of time [45]. Children at risk of developing resistance to intravenous immunoglobulin treatment are treated with corticosteroids as adjunctive therapy. A meta-analysis, including studies, found that the addition of intravenous methylprednisolone to the standard regimen of Kawasaki disease benefits in preventing coronary artery aneurysms development [46].

**Biological Agents**

Anakinra, an IL-1 antagonist, has been used to manage Kawasaki disease. Several case reports mentioned the introduction of anakinra after the development of coronary artery lesions in Kawasaki disease (Table 2). Guillaume et al. reported a case in 2018 in which an 18-year-old boy with typical Kawasaki disease was treated with IVIG on the sixth day of illness. Methylprednisolone and second dose of IVIG were started after he developed aneurysms on the ninth day of illness; Fever subsided, but aneurysms worsened on the 25th day, and hence anakinra was started on the 25th day of illness. The patient was started on 6mg/kg/day for 10 weeks, reduced to every three days for four weeks with a dose of 6mg/kg/day, and till withdrawal, the patient was administered with 6mg/kg/day but every two days for four weeks. Reduction in C-reactive protein levels and decrease in size of aneurysms after treated with anakinra for 18 weeks as pulse therapy [47].

| Author               | History of patients who developed coronary artery lesions in Kawasaki disease                                                                 | Treatment before starting anakinra                                      |
|---------------------|------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Guillaume et al. [47]| 18-month-old boy with typical Kawasaki disease who developed diffuse fusiform coronary artery aneurysms after seventh day of admission.                                    | IVIG, three boluses of corticosteroids                                  |
| Kone Paul et al. [48]| Reported 11 patients with Kawasaki disease with 7 had coronary artery dilatation and one has myocarditis with Kawasaki disease.              | IVIG                                                                   |
| Lind-Hoist et al. [49]| 12-week-old infant with development of coronary artery aneurysms and pericarditis on day 10 after admission.                                | IVIG, infliximab, Corticosteroids                                      |
| Maggio et al. [50]  | 9-month-old girl with parvovirus infection developed Kawasaki disease and 26 days after treatment for Kawasaki disease developed coronary artery aneurysms. | IVIG                                                                   |
| Gambacorta et al. [51]| 9-month-old boy with refractory classical Kawasaki disease who developed aneurysms.                                                          | IVIG, corticosteroids, infliximab                                      |

**TABLE 2: Case reports of Kawasaki disease treated with anakinra after developing coronary artery lesions**

Kone-Paul et al. reported the use of anakinra in 11 patients. Nine of them had complete Kawasaki disease, and two of them had incomplete Kawasaki disease. They were started on anakinra with a dose range of 2-8mg/kg/day for 15 days after the deterioration of their clinical conditions despite treatment with primary (aspirin and IVIG) and secondary drugs (infliximab, cyclosporine, methotrexate) drugs. Complete resolution of fever and inflammation and reduction in the size of aneurysms were observed in these patients [48].

Lind-Hoist et al. reported atypical Kawasaki disease in a 12-week-old infant, treated with IVIG and aspirin. A refractory form of Kawasaki disease is diagnosed when symptoms worsen after treatment with infliximab and corticosteroids. Anakinra is administered when levels of ferritin, triglycerides, alanine aminotransferases, and hemophagocytosis in the bone marrow are observed and suspicious of macrophage activation syndrome is made and symptoms resolved with increasing doses from 5mg/kg/day to 10mg/kg/day [49].

Maggio et al. reported Kawasaki disease in siblings after being infected with parvovirus. The elder sibling died of coronary artery aneurysms due to Kawasaki disease, and after two years, the younger sibling at nine months of age developed incomplete Kawasaki disease with subsequent coronary artery aneurysm on the 26th day of illness despite treatment with IVIG and administered anakinra with a dose of 4mg/kg/day for 25 days and reported improvement in her clinical conditions and reduction of aneurysm size [50]. Gambacorta et al. reported a case of classical Kawasaki disease in a nine-month-old boy refractory to treatment with IVIG on day nine and day 14, methylprednisolone on day 20, development of coronary artery aneurysms on day 37, and improvement in clinical condition and decrease in z score of aneurysms was observed after starting anakinra with the dosage of 6mg/kg/day on day 40 of illness [51].
Infliximab, TNF-α antagonist, and etanercept, when administered with intravenous immunoglobulins, cause rapid reductions in the level of C-reactive protein and resolution of fever in a few days and a decrease in Z score of coronary artery aneurysms [52]. Etanercept, a TNF-α receptor blocker, when used as a primary drug with aspirin and intravenous immunoglobulins, reduces inflammation of blood vessels leading to resolution of fever, and the combination is well tolerated [53]. The involvement of the NFAT-calcineurin pathway in the pathogenesis of Kawasaki disease leads to the use of calcineurin inhibitors like cyclosporine and tacrolimus in the management of IVIG-resistant Kawasaki disease. These agents decrease the CD4+ T and CD8+ T cell-mediated inflammation in blood vessels [54].

Coronary artery aneurysm risks stratification and follow-up strategies

Another important consideration in the treatment of Kawasaki disease is the prevention of cardiac complications. In 2017 The American Heart Association (AHA) proposed effective follow-up strategies for early detection and prevention of cardiac complications of Kawasaki disease (Figure 3).

Coronary artery aneurysms are one of the triggers for acute coronary syndrome as a complication of Kawasaki disease. Damage to vascular endothelium causes thrombus formation and can present as acute myocardial infarction. Patients should be monitored periodically with ECG, echocardiogram, and CT/MR angiography based on risk assessment to prevent this. Pharmacological interventions such as lipid-lowering drugs (statins) and anti-platelets like aspirin or clopidogrel should be advised [39].

Limitations

This is the generalized review of the pathogenesis, diagnosis, prevention, and treatment protocols for managing coronary artery lesions in Kawasaki disease. This article does not include the contraindications of drugs and patient-specific management of coronary artery lesions in Kawasaki disease. Therefore, each patient should be evaluated thoroughly and managed according to their history, clinical examination, and laboratory findings in clinical practice.

Conclusions

Coronary artery lesions in Kawasaki disease are associated with significant morbidity and mortality. Although there are many interrelated mechanisms between genetic, immune, and infectious factors in the pathogenesis of coronary artery involvement in Kawasaki disease, the significant etiology has yet to be pinpointed. Echocardiogram, Harada scoring system, and biomarkers like NT-Pro-BNP help identify the risk of developing coronary artery aneurysms. The combination of aspirin with intravenous immunoglobulins, corticosteroids, and biological agents like IL-1 antagonist reduces coronary consequences in Kawasaki disease. Although, as mentioned above, diagnostic and treatment strategies help prevent and treat coronary
Additional Information

Disclosures
Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Agarwal S, Agrawal DK: Kawasaki disease: etiopathogenesis and novel treatment strategies . Expert Rev Clin Immunol. 2017, 13:247-58. 10.1080/1744666X.2017.1352165
2. Burn J: History of the worldwide emergence of Kawasaki disease . Int J Rheum Dis. 2018, 21:13-5. 10.1111/1756-185X.15214
3. Takahashi K, Ohara-seki T, Yokouchi Y: Pathogenesis of Kawasaki disease . Clin Exp Immunol. 2011, 164 Suppl 1:20-2. 10.1111/j.1365-2249.2011.04561.x
4. Makino N, Nakamura Y, Yashiro M, et al.: Epidemiological observations of Kawasaki disease in Japan, 2013-2014. Pediatr Int. 2018, 60:581-7. 10.1111/ped.13544
5. Holman RC, Belay ED, Christensen KY, Folkema AM, Steiner CA, Schonberger LB: Hospitalizations for Kawasaki syndrome among children in the United States, 1997-2007. Pediatr Infect Dis J 2010, 29:483-8. 10.1097/INF.0b013e3181f8705
6. Lee JK: Hygiene hypothesis as the etiology of Kawasaki disease: dysregulation of early b cell development . Int J Mol Sci. 2021, 22:10.3390/ijms222212354
7. Nie H, Wang S, Wu Q, Xue D, Zhou W: Five immune-gene-signatures participate in the development and pathogenesis of Kawasaki disease. Immun Inflamm Dis. 2021, 9:157-66. 10.1002/iind.3.573
8. Kuo HC, Yang KD, Chang WC, Gei LP, Hsieh KS: Kawasaki disease: an update on diagnosis and treatment . Pediatr Neonatol. 2012, 53:4-11. 10.1161/j.pedn.2011.11.005
9. Newburger JW, Takahashi M, Gerber MA, et al.: Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation. 2004, 110:2747-71. 10.1161/01.CIR.0000145143.19711.78
10. Kimura Y, Yasunagamichi M, Ito Y, et al.: Identification of candidate diagnostic serum biomarkers for Kawasaki disease using proteomic analysis. Sci Rep. 2017, 7:4372. 10.1038/srep4372
11. Eleftheriou D, Levin M, Shingadia D, Tullio B, Klein NJ, Brogan PA: Management of Kawasaki disease. Arch Dis Child. 2014, 99:74-85. 10.1136/archdischild-2012-302841
12. Chang LS, Lin YJ, Yan IH, Guo MM, Lo MH, Kuo HC: Neutrophil-to-lymphocyte ratio and scoring system for predicting coronary artery lesions of Kawasaki disease. BMC Pediatr. 2020, 20:398. 10.1186/s12887-020-02285-5
13. Research Committee on Kawasaki Disease: Report of the Subcommittee on Standardization of Diagnostic Criteria and Reporting of Coronary Artery Lesions in Kawasaki Disease. Ministry of Health and Welfare, Tokyo; 1984.
14. Perkins SJ, Fang KW, Khan S: Molecular interactions between complement factor h and its hepaparin and heparan sulfate ligands. Front Immunol. 2014, 5:126. 10.3389/fimmu.2014.00126
15. Bizzevedl MH, Geissler J, Weverling GJ, Kuipers IM, Lam J, Ottenkamp J, Kuijpers TW: The phenotypic and genetic assessment of antithrombin deficiency. Int J Lab Hematol. 2011, 33:227-37. 10.1111/j.1751-553X.2011.01307.x
16. Obuwoha H, Okada T, Nozu K, et al.: Identification of mutations in FNI leading to glomerulopathy with fibronectin deposits. Pediatr Nephrol. 2016, 31:1459-67. 10.1007/s00467-016-3568-7
17. Kuo HC, Chang WC: Genetic polymorphisms in Kawasaki disease . Acta Pharmacol Sin. 2011, 32:1193-8. 10.1038/aps.2011.93
18. Shimizu C, Jain S, Davila S, et al.: Transforming growth factor-beta signaling pathway in patients with Kawasaki disease. Circ Cardiovasc Genet. 2011, 4:16-25. 10.1161/CIRCGENETICS.110.940858
19. Macian F: NFAT proteins: key regulators of T-cell development and function. Nat Rev Immunol. 2005, 5:472-84. 10.1038/nr1632
20. Reddy M, Singh S, Rawat A, Sharma A, Suri D, Rohit MK: Pro-brain natriuretic peptide (ProBNP) levels in North Indian children with Kawasaki disease. Rheumatol Int. 2016, 36:551-9. 10.1007/s00296-016-4540-6
21. Reindel R, Kim KY, Baker SC, et al.: Periostin is upregulated in coronary arteriopathy in Kawasaki disease and is a potential diagnostic biomarker. Pediatr Infect Dis J. 2014, 33:659-61. 10.1097/INF.0000000000000253
22. Yu HR, Kuo HC, Huang EY, et al.: Plasma clusterin levels in predicting the occurrence of coronary artery lesions in patients with Kawasaki disease. Pediatr Cardiol. 2010, 31:1151-6. 10.1007/s00246-010-9769-7
23. Yokouchi Y, Ohara-seki T, Enomoto Y, Sato W, Imanaka-Yoshida K, Takahashi K: Expression of tenasin C in cardiovascular lesions of Kawasaki disease. Cardiovasc Pathol. 2019, 38:25-30.
immunoglobulin-resistant Kawasaki disease

Tremoulet AH, Pancoast P, Franco A, et al.: Choueiter NF, Olson AK, Shen DD, Portman MA: 6736(13)62298-9

phase 3 randomized, double-blind, placebo-controlled trial

Tremoulet AH, Jain S, Jaggi P, et al.: refractory Kawasaki disease treated with anakinra

Gambacorta A, Buonsenso D, De Rosa G, et al.: 019-2028-5

Maggio MC, Cimaz R, Alaimo A, Comparato C, Di Lisi D, Corsello G: syndrome caused by refractory Kawasaki disease in an infant

Lind-Holst M, Hartling UB, Christensen AE: disease: a retrospective cases series

Kone-Paut I, Cimaz R, Herberg J, et al.: Guillaume MP, Reumaux H, Dubouy F: The clinical diagnosis and management of Kawasaki disease: a review and update . Curr Infect Dis Rep. 2016, 18:32. 10.1007/s11908-016-0558-5

Xiao Er Ke Yi Xue Hui Za Zhi. 1992, 33:67-71.

Lee JH, Hung HY, Huang FY: asprin

Catella-Lawson F, Reilly MP, Kapoor SC, et al.: Inj Immunol. 2009, 182:2578-82. 10.4049/injmmlmn08003162

Zhu FH, Ang JY: 10.4049/jimmunol.0803162

miR-155 contributes to the development of regulatory T cells by targeting SOCS1 protein

Lu LF, Thai TH, Calado DP, et al.: Analysis of circular RNAs in the coronary arteries of patients with Kawasaki disease

Olivito B, Bottoni B, Simonini G, et al.: The clinical diagnosis and management of Kawasaki disease (JCS 2008)—digest version

Kohlihaas S, Garden OA, Scudamore C, Turner M, Okkenhaug K, Vigorito E: Cutting edge: the Foxp3 target

Lu LF, Thai TH, Calado DP, et al.: 10.1186/s12947-016-0046-7

J Pediatr. 2019, 127:855-73. 10.1161/CIRCRESAHA.120.316951

Kim YK: Analysis of circular RNAs in the coronary arteries of patients with Kawasaki disease . J Lipid Atheroscler. 2019, 8:50-7. 10.1299/jlta.2019.8.1.50

Fildes N, Burnt JC, Newburger JW, Kitzis W, Bogovich AB: The HLA class II region and susceptibility to Kawasaki disease. Tissue Antigens. 1992, 39:99-101. 10.1111/j.1365-2407.1992.tb01915.x

Amano S, Hazama F, Hamashima Y: Pathology of Kawasaki disease: I. pathology and morphogenesis of the vascular changes. Jpn Circ J. 1979, 43:633-45. 10.1253/jjcm.43.633

Rahbari-Manesh AA, Salamati P, Ghofarian J, Zekvat M: Relationship between ESR, CRP, platelet count and coronary artery disease in Kawasaki disease. Iran J Pediatr. 2019, 15:139-44. 10.3389/fped.2019.00242

Ayuawsa M, Sonobe T, Uemura S, et al.: Revision of diagnostic guidelines for Kawasaki disease (the 5th revised edition). Pediatr. Int. 2005, 47:232-4. 10.1111/j.1442-2005.2005.00205.x

Xie L, Wang R, Huang M, Zhang Y, Shen J, Xiao T: Quantitative evaluation of myocardial fibrosis by cardiac integrated backscatter analysis in Kawasaki disease. Cardiovasc Ultrasound. 2016, 14:5. 10.1186/s12947-016-0046-7

ICS Joint Working Group: Guidelines for diagnosis and management of cardiovascular sequelae in Kawasaki disease (ICS 2008) – digest version. Circ J. 2010, 74:1989-2020. 10.1259/circj.1989-2020

McCrindle BW, Rowley AH, Newburger JW, et al.: Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation. 2017, 135:e927-99. 10.1161/CIR.0000000000000484

Harada K: Intravascular gamma-globulin treatment in Kawasaki disease . Acta Paediatr Jpn. 1991, 33:805-10. 10.1111/j.1442-2005.1991.tb02612.x

Furusho K, Kamiya T, Nakano H, et al.: High-dose intravenous gammaglobulin for Kawasaki disease. Lancet. 1984, 2:1055-8. 10.1016/s0140-6736(84)91504-6

Wang CL, Wu YT, Lee CJ, Liu HC, Huang LT, Yang KD: Decreased nitric oxide production after intravenous immunoglobulin treatment in patients with Kawasaki disease. J Pediatr. 2002, 141:560-5. 10.1067/mpd.2002.127505

Klassen TP, Rowe PC, Gañañ A: Economic evaluation of intravenous immune globulin therapy for Kawasaki syndrome. J Pediatr. 1995, 122:558-42. 10.1016/s0022-3476(05)85352-2

Zhu FH, Ang YL: The clinical diagnosis and management of Kawasaki disease: a review and update . Curr Opin Pediatr. 2019, 31:850-9. 10.1097/MOP.0000000000001674

Devy S, Haas M, Flocard H, et al.: Calcineurin inhibitor treatment of intravenous immunoglobulin therapy in Kawasaki disease. J Pediatr. 2014, 164:633-40. 10.1016/j.jpeds.2012.02.048