Kawasaki Disease

Ho-Chang Kuo
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Ho-Chang Kuo
Kawasaki Disease Center, Department of Pediatrics and College of Medicine
Kaohsiung Chang Gung Memorial Hospital and Chang Gung University
Kaohsiung, Taiwan

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Contents

Introduction and History of Kawasaki Disease

Chih-Lu Wang

Abstract

Kawasaki disease is an acute multisystem vasculitic syndrome of unknown etiology occurring mostly in infants and children younger than 5 years of age especial in Asia countries. In developed countries, Kawasaki disease is currently the leading cause of acquired heart diseases in children. However, it is still a mysterious disease since the first report of Dr. Kawasaki in 1967. In this chapter, we review and summarize the history, epidemiology, infection, genetics, and immune response of this disease.

Keywords

Kawasaki disease · History · Epidemiology
Genetics · Infection · Immune

Kawasaki disease (KD) is an acute febrile multisystem vasculitis of unknown etiology occurring mostly in children with age younger than 5 years old. In developed countries, KD is currently the leading cause of acquired heart diseases in children. However, it still continues to be a mysterious disease [1, 2].

Kawasaki disease (KD) is a small to medium sized vessel vasculitis that affects mainly in young children. Tomisaku Kawasaki observed his first case of KD in January 1961 when he was a staff pediatrician at the Red Cross Hospital in a suburb of Tokyo. The patient, a 4-year-old boy, recovered spontaneously from his illness and was discharged as "diagnosis unknown." Then Dr. Tomisaku Kawasaki published the first English language report of 50 patients with KD in 1974 [3]. Since then, there have been almost 15,000 articles in the literature related to this disease, despite extensive research over the last 50 years, but the etiology of KD, a distinct causative agent, and immunopathogenesis remain an enigma.

Kawasaki disease is characterized by long-term fever, conjunctivitis, diffuse mucosal inflammation, pleomorphic rash, hard edema of the hands and feet associated with peeling of the fingertips, and nonsuppurative neck lymphadenopathy [4]. The most serious complication of KD is acute coronary lesions including myocardial infarction and coronary aneurysm, which is characteristic when identified in the context of compatible febrile illness [5, 6]. To date, there are no specific diagnostic tests for KD. The diagnosis of KD is based on fever ≥5 days, and it meets four of the five clinical criteria listed in Table 1. However, atypical cases of KD are very common (up to around 15% of the total), and the diagnosis should be considered without the full complement of diagnostic criteria [7]. In addition to the diagnostic criteria, a wide range of nonspecific clinical features can be found, including irritability, uveitis, aseptic meningitis, cough, vomiting, diarrhea, abdominal pain, gallbladder, urethritis, joint

C.-L. Wang (✉)
Po-Jen Hospital, Kaohsiung, Taiwan

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Table 1 Diagnostic criteria of Kawasaki disease

Fever persisting at least 5 days with at least four of the five principal clinical features
1. Nonpurulent conjunctivitis, bilateral
2. Cervical lymphadenopathy, >1.5 cm
3. Polymorphous skin rashes
4. Abnormalities of lip or oral mucosa: strawberry tongue, fissured lips, diffuse erythema of oropharynx
5. Abnormalities of extremities: edema of palm and soles, desquamation of finger tips

The diagnosis of Kawasaki disease is considered to be confirmed by the presence of fever and four of the remaining five criteria if other known diseases can be excluded

pain, arthritis, hypoalbuminemia, liver damage, and heart failure [8]. In some countries where newborns are vaccinated with bacillus Calmette–Guerin (BCG), KD can be associated with erythematous induration or even ulceration of BCG scars in one-third of cases [9].

Seasonal change in wind patterns was reported to have a significant association with the epidemics of KD in Japan. Occurrence of disease in epidemiological clusters, seasonal variation, and a very low risk of recurrence suggested that KD may be triggered by infectious agents [5].

Some supportive evidences suggest a genetic basis of KD including familial occurrence of cases, a high risk among siblings, and a high disease prevalence in Northeast Asian populations. Dysregulated innate and adaptive immune responses are also reported in the acute stages of KD. In addition to coronary endothelial dysfunction, wall inflammation and impaired vascular remodeling contribute to the development of coronary artery abnormalities (CAAs) and thrombosis. Genetic aberrations in certain intracellular signaling pathways involving functions of immune effectors are found to be associated with increased susceptibility to KD and development of CAAs [10].

Epidemiology

Kawasaki disease mainly affects young children, mostly under 5 years of age. The risk of boys is 1.5 times higher than that of girls. The epidemiological patterns of different geographical locations vary greatly, and the incidence rate varies with race and season [11]. In the world, Japan has the highest incidence (239/100,000 under 5 years old) [12], followed by South Korea (113.1/100,000) and Taiwan (69–84/100,000) [13]. In these countries, a strong national KD epidemiological survey is conducted every 2–3 years. Four KD epidemics occurred in Japan in 1979, 1982, 1986, and 1998 [14].

The epidemiological surveys in Japan have also reported that compared with the general population, children whose parents or siblings have a history of KD have a higher incidence [15–17].

In the USA, it is reported that the incidence of KD hospitalizations for children under 5 years of age is 19 per 100,000 [18]. However, significant differences between different races have been noted. Compared with whites, Asians [19] and Pacific Islanders have a 2.5 times higher incidence, and blacks have a 1.5 times higher incidence. This is also supported by the fact that Hawaii, which has the largest Asian population in the USA, has the highest incidence of KD in the USA. The average incidence of children under 5 years of age from 1996 to 2006 was 50.4 per 100,000 cases. In Europe, the UK [20] reported an annual incidence of 8.4/100,000 in children below 5 years of age, while in Denmark and the Netherlands, the incidence rate for children under 5 is about 4–5/100,000 [21]. Interestingly, seasonal changes have also been noted in the KD incidence trend. In Japan, the incidence rate is higher in January (winter) and July (summer). Just like in Korea, the incidence rate is higher in the USA in winter and spring. There is no change in regions like Hawaii, which may be due to the tropical climate throughout the year. In Europe, the incidence is highest in winter. Luca and Yeung proposed a hypothesis about this variation [22]. These researchers hypothesized that KD may be caused by an airborne medium in Central Asia, which is then blown to different geographical locations and entered the human body through the respiratory tract to cause KD. Therefore, wind patterns may determine the incidence of

KD in different parts of the world. However, this association must be confirmed by more epidemiological studies on a global scale.

In this chapter, we review and summarize the infection agents, genetic background, and host immune dysregulation, intending to establish a feasible infection–immunogenetic pathogenesis for this mysterious disease.

Is Kawasaki Disease an Infectious Disease?

During the past 50–60 years, identifying of a definitive infectious agent that causes KD has not been possible. Certain intracellular pathogens and superantigens from bacteria have been implicated in the immunopathogenesis of KD. Several lines of evidence support the fact that KD is an infectious disease, such as acute onset of a self-limited illness, increased susceptibility in the younger age groups, and geographic clustering of outbreaks with a seasonal predominance (later winter and early spring). Various bacteria such as *Streptococcus pyogenes*, *Staphylococcus aureus* [23], *Mycoplasma pneumoniae* [24], and *Chlamydia pneumoniae* [25] have been reported from patients with KD. Suspected viral pathogens, especially lymphocyte viruses, such as adenovirus [26], Epstein–Barr virus [27], parvovirus B19, herpes virus 6 [28], parainfluenza type 3 virus, human immunodeficiency virus, measles [29], rotavirus, dengue virus, and varicella [30], have been considered potential causes of KD, but there is no evidence that any one of the agents is guilty. Takahashi and his colleagues used a three-stage screening procedure to identify a new type of lymphotropic virus from the peripheral blood mononuclear cells of patients with KD [31]. This new virus has a broad but low level of homology (25–33% homology) with the African swine fever virus, which replicates in cells of the monocyte-macrophage lineage. In contrast, there are some clues that do not indicate the existence of infectious causes, such as a slowly increasing incidence of KD in different countries without large-scale outbreak and a lack of human-to-human transmission or a common source of infection and similar susceptibility to KD of Japanese who live in a country other than Japan.

Superantigens are related to the immune pathogenesis of KD. Superantigens are a type of microbial proteins or exotoxins that can directly bind to a large number of lymphocytes and antigen-presenting cells and trigger a disproportionate nonspecific immune response [32]. It is now clear that the role of superantigens in the pathology of infectious diseases is more appreciated than before. *Staphylococcus aureus* and *Streptococcus pyogenes* produce at least 19 different superantigens. The range of microorganisms known to produce superantigens has been expanded to include gram-negative bacteria, mycoplasma, viruses, parasites and yeasts. The possible importance of superantigens in KD is implied by its ability to induce coronary arteritis in a mouse model, in which *Lactobacillus casei* cell wall extract induces coronary arteritis that reflects KD in children [33]. Superantigens may directly bind to T cell subpopulations with unique T cell receptors (TCRs) containing variable Vβ chains. Further studies have shown that the quantification of TCR Vβ2 T cells may be valuable for the diagnosis of KD. The combination of superantigens and lymphocytes can induce autoimmune processes by stimulating autoreactive T cells and B cells to produce autoantibodies [34]. It has been suggested that KD in very young infants may be related to passive placental transfer lacking anti–toxic shock syndrome toxin 1 (TSST-1) antibodies, because the average anti-TSST-1 titer of the mothers of KD infants is significantly lower than that of control subjects.

Exogenous superantigens, mainly bacterial toxins and viral antigens, are the source of many diseases. Evidence shows that superantigens are involved in diseases such as KD [35], toxic shock syndrome, and possibly rheumatoid arthritis. Superantigens may come from a variety of common pathogens in the environment. They may induce immunity in most individuals, but they may also cause the characteristic clinical manifestations of KD in some susceptible hosts.

Esper et al. [36] also discovered a new type of human coronavirus named New Haven coro-

navirus (HCoV-NH) in the respiratory secretions of a 6-month-old infant with classic KD. They further detected HCoV-NH positive by reverse transcriptase polymerase chain reaction from 8 of 11 children with KD (72.7%) and 1 of 22 control subjects (4.5%) (Mantel–Haenszel Matching odds ratio, 16.0 (95% confidence interval, 3.4–74.4); $P = 0.0015$). These data indicate that HCoV-NH infection is related to KD. Since the 2020 coronavirus disease 2019 (COVID-19) pandemic, a 30-fold increased incidence of Kawasaki-like disease has been reported. Children with Kawasaki-like disease diagnosed after the SARS-CoV-2 epidemic began to show evidence of immune response to the virus, were older in age, had a higher rate of cardiac involvement, and had more features of macrophage activation syndrome (MAS). The SARS-CoV-2 epidemic was associated with high incidence of a severe form of Kawasaki disease (maybe the KD shock syndrome, KDSS). A similar outbreak of Kawasaki-like disease is expected in some countries of Europe and America affected by the SARS-CoV-2 epidemic. In the midst of the coronavirus disease (COVID-19) pandemic, widespread disease burden affecting patients of all ages all over the world was reported. A case of a 6-month-old infant admitted and diagnosed with classic KD, who also screened positive for COVID-19, in the setting of fever and minimal respiratory symptoms was reported. The patient was treated according to AHA treatment guidelines, with intravenous immunoglobulin (IVIG) and aspirin, and subsequently defervesced with resolution of her clinical symptoms. The patient's initial echocardiogram was normal, and she was discharged within 48 h of completion of her IVIG, with instructions to be quarantined at home for 14 days from the date of her positive test results for COVID-19, which is diagnosed as the multisystem inflammatory syndrome in children (MIS-C), a novel syndrome linked to SARS-CoV-2 in children [37].

Is Kawasaki Disease a Genetic Disease?

The higher incidence of KD in Japan, together with the fact that the incidence among Japanese descendants in the USA is higher than that of other ethnic groups in the USA and the UK, indicates that genetic susceptibility may play an important role in the incidence of KD [38]. There is also evidence that the incidence of KD among siblings is much higher than that of the general population [39]. This further supports the fact that genetic factors cause susceptibility to KD. Hirata et al. [40] reported five episodes of KD in three siblings within 6 years. Two of the three children had recurrent KD and had coronary artery disease, including a giant coronary aneurysm in the youngest sibling. The nonsimultaneous occurrence of the diseases in these three children emphasizes the importance of the genetic basis in the development of KD.

Many genetic polymorphisms are associated with KD in different populations. For example, single-nucleotide polymorphisms in the monocyte chemoattractant protein 1 gene regulatory region [41], methylenetetrahydrofolate reductase, angiotensin I-converting enzyme genotype II82, and SLC11A1 (formerly NRAMP1) gene [42] have been related to KD disease in different populations. The gene products of HLA class I and class II loci cause peptide fragments to be expressed on the surface of cells that bind antigens and initiate an immune response. Studies have shown that KD is also related to certain genetic polymorphisms and major histocompatibility complex alleles. Fildes et al. [39] analyzed HLA types using a standard microcytotoxicity test in 205 KD patients and 500 normal controls, and the results showed that HLA-BW22 is more common in KD patients than in normal controls. Among the subtypes of HLA-BW22 antigen, KD is related to HLA-BW22J2 in Japanese, but not in Caucasians. This fact indicates that there are one or more genes that control the susceptibility of different races to KD. Genetic polymorphisms in the TNF-α gene can affect the magnitude of this cytokine production after inflammatory stimulation. Kamizono et al. [43] demonstrated that peripheral blood mononuclear cells from KD patients with coronary artery disease produced increased amounts of TNF-α in response to bacterial products (such as TSST-1). Quasney et al. [44] showed that the lymphotoxin α +250 A/A genotype is more common in white children with KD than in the control group. The TNF-α-308 A/G genotype is significantly higher in

whites with coronary artery abnormal KD than in Japanese, but not in people with normal echocardiography. Our research in children in Taiwan shows that the immune brake gene cytotoxic T lymphocyte antigen 4 of the +49 A/G polymorphism is significantly related to the severity of KD in men and the occurrence of KD in girls [45]. Onouchi et al. [46] also reported that the CD40L polymorphism of intron 4 (IVS4 +121 A > G) in KD patients with coronary artery disease was more common in boys ($P = 0.030$). This indicates that people of different races with different genders and different genetic alleles may have different susceptibility to the occurrence and severity of KD.

The first-generation KD patients have now reached the reproductive age, so the incidence of the second-generation cases may increase. There have been five cases of second-generation KD; this is essential for analyzing the genetic susceptibility of KD. Lee et al. [47] reported that in the second-generation transmission mode of KD, the same HLA antigens, A24, 9, B25, 5, and DR2, were detected in mothers and daughters.

The prevalence of KD is increasing globally, as is general atopic diseases. Atopic diseases are associated with immunoregulatory abnormalities similar to those observed in acute KD. The results showed that compared with the control group, the family history of allergies in children with a history of KD was significantly more common. Compared with the control group, the incidence of atopic dermatitis and allergic rhinitis in children with KD was significantly higher (about 1.7 times). Furuno et al. [48] showed that in the later stages of the acute phase of KD, there was a greater increase in CD23+ B lymphocytes and serum IgE. It also shows that there is a significant correlation between the occurrence of KD and anti-dust mite specific IgE. There was a decrease in the number of interferon-γ-producing (IFNr), but not interleukin-4 (IL-4)-producing, T cells during the acute stage of KD. Thus, genetic predisposition to KD showed association with atopy [5]. The complex genetics of KD is beginning to be uncovered by the efforts of multinational collaborative groups to determine the genetic influences on disease susceptibility and disease outcome of IVIG resistance and CAA formation. Roughly 65% of the genetic risk for KD susceptibility is accounted for by polymorphisms in calcium signaling pathways, the TGF-beta signaling pathway, and human leukocyte antigens (HLA).

Several susceptible genes have been identified through genome-wide association studies (GWAS) and linkage studies (GWLS) in the past two decades [49]. The genes that are reported to be significant in KD can be classified in four major groups including enhanced T cell activation (ITPKC, ORAI1, STIM1), dysregulated B cell signaling (CD40, BLK, FCGR2A), decreased apoptosis (CASP3), and altered transforming growth factor beta signaling (TGFB2, TGFBR2, MMP, SMAD). Onouchi et al. [50] performed a genome-wide association study (GWAS) of Kawasaki disease in Japanese subjects using data from 428 individuals with Kawasaki disease (cases) and 3379 controls genotyped at 473,803 SNPs, which observed significant associations in the FAM167A-BLK region at 8p22-23, in the human leukocyte antigen (HLA) region at 6p21.3 and in the CD40 region at 20q13. They replicated the association of a functional SNP of FCGR2A identified in a recently reported GWAS of Kawasaki disease. In conclusion, genetic background play important role in the pathogenesis of KD with several genes involved.

Is Kawasaki Disease an Immune-Mediated Disease?

There is no doubt that immune changes, especially the release of a large number of cytokines that cause inflammation of the vascular endothelium, play a vital role in the immune pathogenesis of KD. In the acute stage of KD, activation of numerous immunologic factors including T cell activation [48], cytokine production [51, 52], nitric oxide production [53], autoantibody production, association of allergic diseases [54], and enhanced adhesion molecule expression [41] are well documented. The pathological examination of KD acute coronary arteritis showed that with the accumulation of CD8+ T cells in the vascular lesions, a T lymphocyte-dependent process characterized by transmural infiltration of activated T lymphocytes appeared [55]. Macrophage

activation [56] and changes in T helper cell and regulatory cell functions are also related to the imbalance of immune response in patients with Kawasaki disease.

In our study [53], we found that the plasma nitric oxide (NO) concentration (measured by the total NO metabolite called NOx) of KD patients was higher than that of the non-KD fever control group. The increase of NOx in KD patients is significantly related to the occurrence of coronary artery dilation (>3 mm). After receiving IVIG treatment, the elevated NOx in KD patients was significantly reduced. Inducible but not constitutive NO synthase (NOS) mRNA and protein in monocytes were significantly expressed in acute KD, but they were significantly reduced after IVIG treatment.

CD40 ligand (CD40L, CD154, gp39) is a transmembrane protein structurally related to tumor necrosis factor (TNF)-α, which was originally found on activated CD4+ T cells [57]. Both the membrane-bound and soluble forms of this ligand can interact with CD40, which is constitutively expressed on B cells, macrophages, and endothelial cells, leading to various immune and inflammatory responses [58]. The interaction of CD40L and CD40 on B cells plays a central role in the conversion of IgM to IgG production. CD40L is also present on activated platelets, which induces endothelial cells to secrete chemokines and release tissue factor [59]. Kotowicz et al. showed that the connection of CD40L and CD40 on human endothelial cells can lead to activation of endothelial cells and induce the expression of vascular cell adhesion molecule 1, intracellular adhesion molecule 1 (ICAM-1), and E-selectin, which leads to the recruitment and activation of T cells and neutrophils at sites of inflammation [60]. Mach et al. proved that activated human T cells mediate the contact-dependent expression of matrix metalloproteinases in vascular endothelial cells through CD40–CD40L signal transduction [61]. In addition, the interaction between CD40L and CD40 also involves the regulation of tissue structural cells (including smooth muscle cells), and epithelial cells and fibroblasts. The CD40L–CD40 interaction is undoubtedly involved in chronic inflammatory diseases, including atherosclerosis, systemic lupus erythematosus, and acute coronary syndrome [62]. We established that the expression of CD40L on CD4+ and CD8+ T cells and platelets was significantly increased in KD patients, and decreased 3 days after IVIG administration. During acute KD, the soluble form of CD40L (sCD40L) in the blood is also higher, but, in contrast, the amount of soluble CD40L is not affected by IVIG treatment [63, 64]. We found that the expression of CD40L on CD4+ T cells and platelets, but not on CD8+ T cells, is significantly related to the occurrence of coronary artery dilation, while sCD40L is not. This suggests that CD40L may play an important role in the immune pathogenesis of coronary artery dilation in KD. We believe that the increased expression of CD40L on T cells and platelets associated with increased sCD40L shedding in KD patients can not only trigger immune activation but also contribute to the pathogenesis of the disease's vascular inflammation [65]. We are currently determining whether NO is a mediator of CD40L expression, or whether CD40L mediates NO induction. It has been reported that the expansion of T cells expressing TCR Vβ2 and Vβ6 chains is stimulated by streptococcal and staphylococcal superantigens (such as TSST-1) to promote the immune pathogenesis of KD in a variety of ways. Jabara and Geha [66] showed that TSST-1 promotes CD40L expression on T cells. CD40L is preferentially expressed in the Vβ2 subpopulation of TSST-1 amplified T cells. It also showed that the connection of TSST-1 to Vβ 2-TCR can induce rapid surface expression of CD40L on CD4+ T cells, leading to continuous T cell proliferation and monocyte activation. As mentioned above, the cell wall extract of *Lactobacillus casei* can induce coronary arteritis in mice that mimic KD [67]. Duong et al. showed that *L. casei* cell wall extracts can induce all the characteristics of superantigen-mediated response: significant proliferation of naive T cells; nonclassical major histocompatibility limitations, with different class II molecular presentations of the level of efficiency of this superantigen; the requirement for antigen presentation, but not for processing and stimulating T cells in a nonclonal, TCR

Vβ chain-dependent manner. They proved that the superantigen activity in the cell wall extract of *Lactobacillus casei* is the cause of coronary artery disease [68].

The increase of autoreactive cells associated with continuous immune overactivation may play an important role in the immune pathogenesis of autoimmune diseases including KD. Yi et al. showed a decrease in apoptotic cells and DNA fragmentation in peripheral blood lymphocytes from KD patients compared with normal healthy children. After IVIG treatment, the reduction of apoptotic cells and DNA fragments returned to that of the normal control group, which was accompanied by rapid clinical remission compared with the aspirin treatment group [69]. After 3–5 days of IVIG treatment, the lymphocyte proliferation response also decreased. They believe that the reduction of peripheral blood lymphocyte apoptosis may also be involved in the pathogenesis of KD. The proportion of spontaneous apoptotic polymorphonuclear neutrophils (annexin V positive cells and DNA fragmented cells) in KD patients is significantly lower than that of neutrophils in patients with bacterial or viral infection or normal children. Later these authors also showed that high-dose IVIG treatment of KD can reduce the number of circulating neutrophils by accelerating apoptosis [70]. Inoue et al. pointed out that compared with KD, serum from patients with acute KD significantly increased the expression of ICAM-1 on human umbilical vein endothelial cells [71]. In contrast, KD serum does not induce Fas expression. This indicates that ICAM-1 rather than Fas-mediated activity is related to KD vasculitis. Incomplete KD appears to be more common in infants than in older children, while the laboratory findings of incomplete KD resemble those of classic KD. The cell surface marker of neutrophil, CD177, has been observed to be higher in patients with typical presentation of KD than incomplete form, which may indicate the importance of neutrophil migration, neutrophil chemotaxis, and leukocyte migration in the presentation of clinical KD symptoms and coronary artery involvement [72]. DNA hypomethylation and increased CD177 transcripts in KD when compared to both types of control subjects including fever and nonfever controls. Furthermore, CD177 expression also showed to be related with the typical presentation of KD and IVIG treatment response.

In short, Kawasaki disease has become the main cause of childhood-acquired heart disease in industrialized countries. However, the pathogenesis remains unclear. Recent reports link genetic susceptibility to its causality. Many case reports attributed its occurrence to different sources of infection, but did not find that they were always related, so further research is needed. Immune system disorders are known to occur in Kawasaki disease, but its underlying mechanism is worthy of further study and is currently the subject of research by many researchers. According to treatment, the combination of aspirin and IVIG shows positive results in most acute cases. However, IVIG is of little use in refractory cases. In order to prevent coronary complications, various drugs are being studied and beginning to show positive results, but large-scale prospective studies are still needed to determine the safety and effectiveness of their treatment of refractory KD.

References

1. Burns JC, Kushner HI, Bastian JF, et al. Kawasaki disease: brief history. Pediatrics. 2000;106:e27.
2. Burns JC, Glode MP. Kawasaki syndrome. Lancet. 2004;364:533–44.
3. Kawasaki T, Kosaki F, Osawa S, Shigemitsu I, Yanagawa S. A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. Pediatrics. 1974;54:271–6.
4. 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.
5. Agarwal S, Agrawal DK. Kawasaki disease: etiopathogenesis and novel treatment strategies. Expert Rev Clin Immunol. 2017;13(3):247–58.
6. Newburger JW, Takahashi M, Burns JC. Kawasaki disease. J Am Coll Cardiol. 2016;67(14):1738–49.

7. Hsieh YC, Wu MH, Wang JK, et al. Clinical features of atypical Kawasaki disease. J Microbiol Immunol Infect. 2002;35:57–60.
8. Singh S, Jindal AK, Pilania RK. Diagnosis of Kawasaki disease. Int J Rheum Dis. 2018;21(1):36–44.
9. Hsu YH, Wang YH, Hsu WY, Lee YP. Kawasaki disease characterized by erythema and induration at the Bacillus Calmette–Guérin and purified protein derivative inoculation sites. Pediatr Infect Dis J. 1987;6:576–8.
10. Rife E, Gedalia A. Kawasaki disease: an update. Curr Rheumatol Rep. 2020;22(10):75.
11. Singh S, Vignesh P, Burgner D. The epidemiology of Kawasaki disease: a global update. Arch Dis Child. 2015;100(11):1084–8.
12. Makino N, Nakamura Y, Yashiro M, Ae R, Tsuboi S, Aoyama Y, et al. Descriptive epidemiology of Kawasaki disease in Japan, 2011–2012: from the results of the 22nd nationwide survey. J Epidemiol. 2015;25(3):239–45.
13. Lin MC, Lai MS, Jan SL, Fu YC. Epidemiologic features of Kawasaki disease in acute stages in Taiwan, 1997–2010: effect of different case definitions in claims data analysis. J Chin Med Assoc. 2015;78:121–6.
14. Yanagawa H, Nakamura Y, Yashiro M, et al. Incidence survey of Kawasaki disease in 1997 and 1998 in Japan. Pediatrics. 2001;107:e33.
15. Fujita Y, Nakamura Y, Sakata K, et al. Kawasaki disease in families. Pediatrics. 1989;84:666–9.
16. Kaneko K, Obinata K, Katsumata K, Tawa T, Hosaka A, Yamashiro Y. Kawasaki disease in a father and daughter. Acta Paediatr. 1999;88:791–2.
17. Matsubara T, Furukawa S, Ino T, Tsuji A, Park I, Yabuta K. A sibship with recurrent Kawasaki disease and coronary artery lesion. Acta Paediatr. 1994;83:1002–4.
18. Chang RK. Hospitalizations for Kawasaki disease among children in the United States, 1988–97. Pediatrics. 2002;109:e87.
19. Du ZD, Zhang T, Liang L, et al. Epidemiologic picture of Kawasaki disease in Beijing from 1995 through 1999. Pediatr Infect Dis J. 2002;21: 103–7.
20. Harnden A, Alves B, Sheikh A. Rising incidence of Kawasaki disease in England: analysis of hospital admission data. Br Med J. 2002;324:1424–5.
21. Uehara R, Belay ED. Epidemiology of Kawasaki disease in Asia, Europe, and the United States. J Epidemiol. 2012;22(2):79–85.
22. Luca NJ, Yeung RS. Epidemiology and management of Kawasaki disease. Drugs. 2012;72(8):1029–38.
23. Wann ER, Fehringer AP, Ezepchuk YV, et al. Staphylococcus aureus isolates from patients with Kawasaki disease express high levels of protein A. Infect Immun. 1999;67:4737–43.
24. Wang JN, Wang SM, Liu CC, Wu JM. Mycoplasma pneumoniae infection associated with Kawasaki disease. Acta Paediatr. 2001;90:594–5.
25. Normann E, Naas J, Gnarpe J, Backman H, Gnarpe H. Demonstration of Chlamydia pneumoniae in cardiovascular tissues from children with Kawasaki disease. Pediatr Infect Dis J. 1999;18:72–3.
26. Embil JA, McFarlane ES, Murphy DM, Krause VW, Stewart HB. Adenovirus type 2 isolated from a patient with fatal Kawasaki disease. Can Med Assoc J. 1985;132:1400.
27. Barton M, Melbourne R, Morais P, Christie C. Kawasaki syndrome associated with group A streptococcal and Epstein–Barr virus co-infections. Ann Trop Paediatr. 2002;22:257–60.
28. Hagiwara K, Komura H, Kishi F, Kaji T, Yoshida T. Isolation of human herpesvirus-6 from an infant with Kawasaki disease. Eur J Pediatr. 1992;151:867–8.
29. Kuijpers TW, Herweijer TJ, Scholvinck L, et al. Kawasaki disease associated with measles virus infection in a monozygotic twin. Pediatr Infect Dis J. 2000;19:350–3.
30. Lee DH, Huang HP. Kawasaki disease associated with chickenpox: report of two sibling cases. Acta Paediatr Taiwan. 2004;45:94–6.
31. Takahashi K, Oharaseki T, Yokouchi Y. Update on etio and immunopathogenesis of Kawasaki disease. Curr Opin Rheumatol. 2014;26(1):31–6.
32. Llewelyn M, Cohen J. Superantigens: microbial agents that corrupt immunity. Lancet Infect Dis. 2002;2:156–62.
33. Chan WC, Duong TT, Yeung RS. Presence of IFN-γ does not indicate its necessity for induction of coronary arteritis in an animal model of Kawasaki disease. J Immunol. 2004;173:3492–503.
34. Cunningham MW, Meissner HC, Heuser JS, Pietra BA, Kurahara DK, Leung DY. Anti-human cardiac myosin autoantibodies in Kawasaki syndrome. J Immunol. 1999;163:1060–5.
35. Yarwood JM, Leung DY, Schlievert PM. Evidence for the involvement of bacterial superantigens in psoriasis, atopic dermatitis, and Kawasaki syndrome. FEMS Microbiol Lett. 2000;192:1–7.
36. Esper F, Shapiro ED, Weibel C, et al. Association between a novel human coronavirus and Kawasaki disease. J Infect Dis. 2005;191:499–502.
37. Kabeerdoss J, Pilania RK, Karkhele R, Kumar TS, Danda D, Singh S. Severe COVID-19, multisystem inflammatory syndrome in children, and Kawasaki disease: immunological mechanisms, clinical manifestations and management. Rheumatol Int. 2021;41(1):19–32.
38. Kumrah R, Vignesh P, Rawat A, Singh S. Immunogenetics of Kawasaki disease. Clin Rev Allergy Immunol. 2020;59(1):122–39.
39. Fildes N, Burns JC, Newburger JW, Klitz W, Begovich AB. The HLA class II region and susceptibility to Kawasaki disease. Tissue Antigens. 1992;39:99–101.
40. Hirata S, Nakamura Y, Yanagawa H. Incidence rate of recurrent Kawasaki disease and related risk factors: from the results of nation-wide surveys of Kawasaki disease in Japan. Acta Paediatr. 2001;90:40–4.

41. Jibiki T, Terai M, Shima M, et al. Monocyte chemoattractant protein 1 gene regulatory region polymorphism and serum levels of monocyte chemoattractant protein 1 in Japanese patients with Kawasaki disease. Arthritis Rheum. 2001;44:2211–2.
42. Ouchi K, Suzuki Y, Shirakawa T, Kishi F. Polymorphism of SLC11A1 (formerly NRAMP1) gene confers susceptibility to Kawasaki disease. J Infect Dis. 2003;187:326–9.
43. Kamizono S, Yamada A, Higuchi T, Kato H, Itoh K. Analysis of tumor necrosis factor-α production and polymorphisms of the tumor necrosis factor-α gene in individuals with a history of Kawasaki disease. Pediatr Int. 1999;41:341–5.
44. Quasney MW, Bronstein DE, Cantor RM, et al. Increased frequency of alleles associated with elevated tumor necrosis factor-α levels in children with Kawasaki disease. Pediatr Res. 2001;49:686–90.
45. Wang CL, Wu YT, Ling MW, Chen RF, Liu HC, Yang KD. Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) polymorphism involved in Kawasaki disease. In: 168th academic meeting of The Taiwan Pediatric Association, November 10–13, 2001, Taipei, Taiwan. Abstract 92; 2001. p. 11–16.
46. Onouchi Y, Onoue S, Tamari M, et al. CD40 ligand gene and Kawasaki disease. Eur J Hum Genet. 2004;12(12):1062–8.
47. Lee YC, Kuo HC, Chang JS, et al. Two new susceptibility loci for Kawasaki disease identified through genome-wide association analysis. Nat Genet. 2012;44(5):522–5.
48. Furuno K, Yuge T, Kusuhara K, et al. CD25+CD4+ regulatory T cells in patients with Kawasaki disease. J Pediatr. 2004;145:385–90.
49. 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(1):157–66.
50. Onouchi Y, Ozaki K, Burns JC, et al. A genome-wide association study identifies three new risk loci for Kawasaki disease. Nat Genet. 2012;44(5):517–21.
51. Guo MM, Tseng WN, Ko CH, Pan HM, Hsieh KS, Kuo HC. Th17- and Treg-related cytokine and mRNA expression are associated with acute and resolving Kawasaki disease. Allergy. 2015;70(3):310–8.
52. Kimura J, Takada H, Nomura A, et al. Th1 and Th2 cytokine production is suppressed at the level of transcriptional regulation in Kawasaki disease. Clin Exp Immunol. 2004;137:444–9.
53. Wang CL, Wu YT, Lee JR, Liu HC, Huang LT, Yang KD. Decrease nitric oxide production after intravenous immunoglobulin treatment in patients with Kawasaki disease. J Pediatr. 2002;141:560–5.
54. Huang PY, Huang YH, Guo MM, Chang LS, Kuo HC. Kawasaki disease and allergic diseases. Front Pediatr. 2021;8:614386. https://doi.org/10.3389/fped.2020.614386.
55. Brown TJ, Crawford SE, Cornwall ML, et al. CD8 T lymphocytes and macrophages infiltrate coronary artery aneurysms in acute Kawasaki disease. J Infect Dis. 2001;184:940–3.
56. Muise A, Tallett SE, Silverman ED. Are children with Kawasaki disease and prolonged fever at risk for macrophage activation syndrome? Pediatrics. 2003;112:e495.
57. van Kooten C, Banchereau J. CD40-CD40 ligand. J Leukoc Biol. 2000;67:2–17.
58. Yellin MJ, Brett J, Baum D, et al. Functional interactions of T cells with endothelial cells: the role of CD40L-CD40-mediated signals. J Exp Med. 1995;182:1857–64.
59. Henn V, Slupsky JR, Grafe M, et al. CD40 ligand on activated platelets triggers an inflammatory reaction of endothelial cells. Nature. 1998;391:591–4.
60. Kotowicz K, Dixon GL, Klein NJ, Peters MJ, Callard RE. Biological function of CD40 on human endothelial cells: costimulation with CD40 ligand and interleukin-4 selectively induces expression of vascular cell adhesion molecule-1 and P-selectin resulting in preferential adhesion of lymphocytes. Immunology. 2000;100:441–8.
61. Mach F, Schonbeck U, Fabunmi RP, et al. T lymphocytes induce endothelial cell matrix metalloproteinase expression by a CD40L-dependent mechanism: implications for tubule formation. Am J Pathol. 1999;154:229–38.
62. Aukrust P, Muller F, Ueland T, et al. Enhanced levels of soluble and membrane-bound CD40 ligand in patients with unstable angina: possible reflection of T lymphocyte and platelet involvement in the pathogenesis of acute coronary syndromes. Circulation. 1999;100:614–20.
63. Wang CL, Wu YT, Liu CA, et al. Expression of CD40 ligand on CD4 T cells and platelets correlated to the coronary artery lesion and disease progress in Kawasaki disease. Pediatrics. 2003;111:e140.
64. Kuo HC, Wang CL, Yang KD, Lo MH, Hsieh KS, Li SC, Huang YH. Plasma prostaglandin E2 levels correlated with the prevention of intravenous immunoglobulin resistance and coronary artery lesions formation via CD40L in Kawasaki disease. PLoS One. 2016;11(8):e0161265. https://doi.org/10.1371/journal.pone.0161265.
65. Garlichs CD, Eskafi S, Raaz D, et al. Patients with acute coronary syndromes express enhanced CD40 ligand/CD154 on platelets. Heart. 2001;86:649–55.
66. Jabara HH, Geha RS. The superantigen toxic shock syndrome toxin-1 induces CD40 ligand expression and modulates IgE isotype switching. Int Immunol. 1996;8:1503–10.
67. Tomita S, Myones BL, Shulman ST. In vitro correlates of the L. casei animal model of Kawasaki disease. J Rheumatol. 1993;20:362–7.
68. Duong TT, Silverman ED, Bissessar MV, Yeung RS. Super antigenic activity is responsible for induc-

tion of coronary arteritis in mice: an animal model of Kawasaki disease. Int Immunol. 2003;15:79–89.
69. Yi QJ, Li CR, Yang XQ. Effect of intravenous immunoglobulin on inhibiting peripheral blood lymphocyte apoptosis in acute Kawasaki disease. Acta Paediatr. 2001;90:623–7.
70. Tsujimoto H, Takeshita S, Nakatani K, Kawamura Y, Tokutomi T, Sekine I. Intravenous immunoglobulin therapy induces neutrophil apoptosis in Kawasaki disease. Clin Immunol. 2002;103:161–8.
71. Inoue Y, Kimura H, Kato M, Okada Y, Morikawa A. Sera from patients with Kawasaki disease induces intercellular adhesion molecule-1 but not Fas in human endothelial cells. Int Arch Allergy Immunol. 2001;125:250–5.
72. Huang YH, Lo MH, Cai XY, Liu SF, Kuo HC. Increase expression of CD177 in Kawasaki disease. Pediatr Rheumatol Online J. 2019;17(1):13. https://doi.org/10.1186/s12969-019-0315-8. PMID: 30943984; PMCID: PMC6446352.

Clinical Symptoms of Kawasaki Disease

Ming-Ren Chen

Abstract

Kawasaki disease (KD) was first reported by Japanese professor Tomisaku Kawasaki in 1967 (Arerugi 16:178–222, 1967). Initially he described the disease as "mucocutaneous lymph node syndrome" (Kawasaki et al., Pediatrics 54:271–276, 1974). For years, mucocutaneous lymph node syndrome became Kawasaki syndrome, then termed as Kawasaki disease. The diagnosis of this "disease" is by grouping of several symptoms, and the etiology is not yet established until now. KD is a "syndrome," not a "disease" by definition (Calvo et al., AMIA Annu Symp Proc 2003:802, 2003). With the progression of more and more identifiable etiologies and diagnostic features, hopefully KD will be a real "disease" in the near future. This chapter describes five major symptoms of KD and some unusual and/or atypical clinical manifestations. The cardiovascular complications of KD will be discussed in chapter "Complications of Kawasaki Disease."

The COVID-19 pandemic caused 524 million infections and 6283 thousands death until May 23, 2022. Some COVID-19 associated manifestations again raised concern between KD and COVID-19-associated multisystem inflammatory syndrome in children (MIS-C) (Ravelli and Martini, Ann Rheum Dis 79:993–995, 2020). We also discuss this issue in this chapter.

Keywords

Kawasaki disease · Kawasaki syndrome
Kawasaki disease shock syndrome
Incomplete Kawasaki disease · Kawasaki-like multisystem inflammatory syndrome

Kawasaki disease (KD) is an acute, self-limited febrile illness of unknown cause which predominantly affects children less than 5 years of age, rarely newborn infants [5]. The incidence of KD in Northeast Asian region, including Japan, South Korea, Mainland China, and Taiwan, is 10–30 times higher than that in the USA and Europe. In Taiwan, KD incidence doubled (28.58–60.08 per 100,000) during the period of 1996–2011 [6], or around 69 per 100,000 [7]. The overall cumulative incidence was 2.78‰ [8]. Without timely treatment of IVIG, the coronary artery aneurysms will be 15–25% [9]. KD is now the most common acquired heart disease in children in developed countries. Without pathognomonic tests, the diagnosis depends on the identification of principal clinical symptoms and the exclusion of other clinically similar findings with known causes [10].

M.-R. Chen (✉)
Department of Pediatrics, MacKay Children's Hospital, Taipei, Taiwan

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In 2017, the American Heart Association published the diagnostic criteria for classic KD [11, 12]. Classic KD is diagnosed by fever for at least 5 days (the day of fever onset is taken to be the first day of fever) together with at least four of the five following principal clinical findings.

1. Erythema and fissured lips (Fig. 1), strawberry tongue (Fig. 2), and/or injection of oral and pharyngeal mucosa.
2. Bilateral bulbar conjunctival injection without exudates.
3. Maculopapular skin rashes, diffuse erythroderma, or erythema multiforme-like.
4. Hands (palms) and feet (soles) erythema and indurative edema in acute phase (Fig. 3) and/or periungual desquamation in subacute phase (Fig. 4).

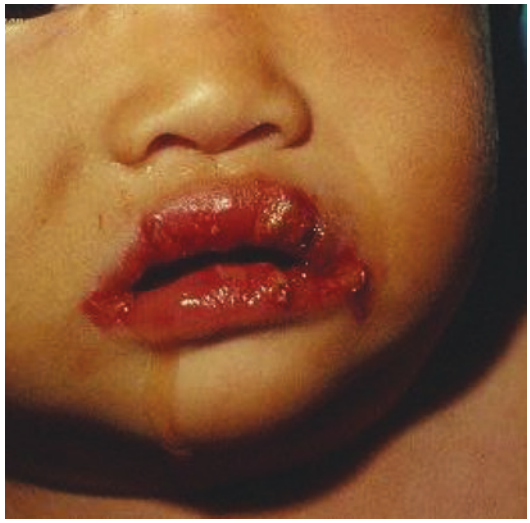

Fig. 1 Fissure lip

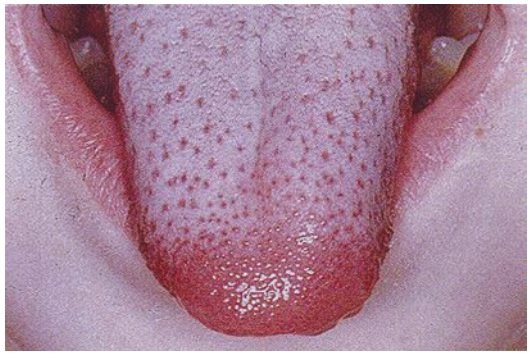

Fig. 2 Strawberry tongue

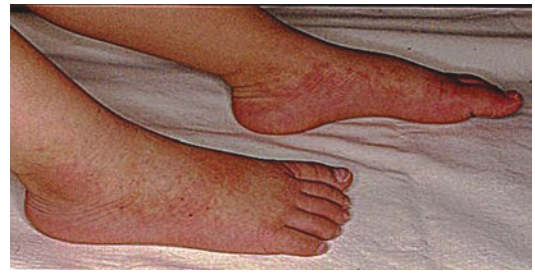

Fig. 3 Feet erythema/indurative edema

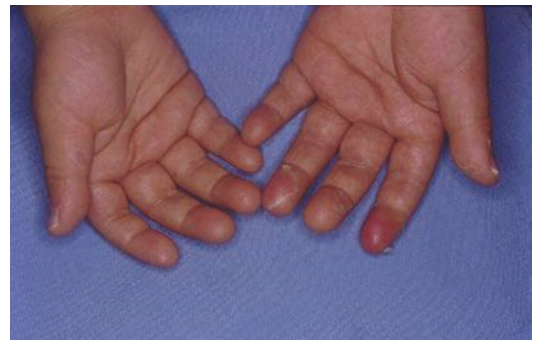

Fig. 4 Peeling over finger tips

5. Cervical lymphadenopathy (≥1.5 cm in diameter), usually unilateral.

In the presence of ≥4 principal clinical features, especially when erythema and swelling of the palms and soles are present, the diagnosis of KD can be made with 4 days of fever. However, some well experienced pediatricians can make the diagnosis with 3 days of fever in rare cases.

One or more principal clinical features may present during the illness but resolve by the time of presentation. If a patient who does not fulfill the criteria of classic KD, incomplete KD should be suspected. If coronary artery abnormalities were noted on echocardiography, most cases will be confirmed as KD.

In laboratory data, white blood cell count is usually normal or elevated with neutrophil predominance; acute phase reactants such as C-reactive protein and erythrocyte sedimentation rate may elevate during the acute phase. Serum sodium and albumin levels are low, liver enzymes are elevated, and patients may have sterile pyuria. Increased platelet count is common in the second week after the onset of fever.

Other clinical findings may involve different systems of our body, including the following: *cardiovascular system* (e.g., myocarditis, pericarditis, valvular regurgitation, shock, coronary artery abnormalities, aneurysms of other medium-sized arteries (Figs. 5, 6, and 7), gangrene of peripheral limbs, dilatation of aortic root), *respiratory system* (e.g., bronchial and interstitial infiltrates on chest radiography), *musculoskeletal system* (e.g., arthritis/or arthralgia), *gastrointestinal system* (e.g., diarrhea, vomiting, abdominal pain, hepatitis, jaundice, hydrops of gallbladder, pancreatitis), *nervous system* (e.g., irritability, aseptic meningitis, facial nerve palsy, sensorineural hearing loss), *genitourinary system* (e.g., urethritis/meatitis, hydrocele), and *others* (e.g., desquamating rash in groin (Fig. 8), retropharyngeal phlegmon, anterior uveitis, and erythema and induration at the Bacillus Calmette–Guerin (BCG) inoculation site (Fig. 9)).

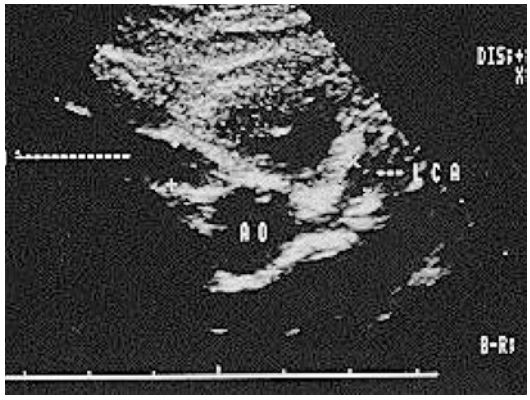

Fig. 5 Aneurysm of coronary artery (echocardiogram)

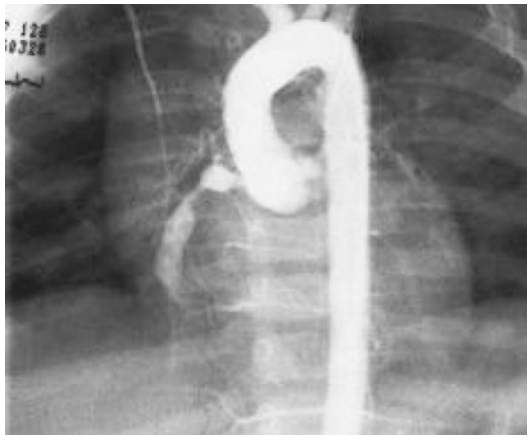

Fig. 6 Right coronary artery aneurysm (aortogram, PA view)

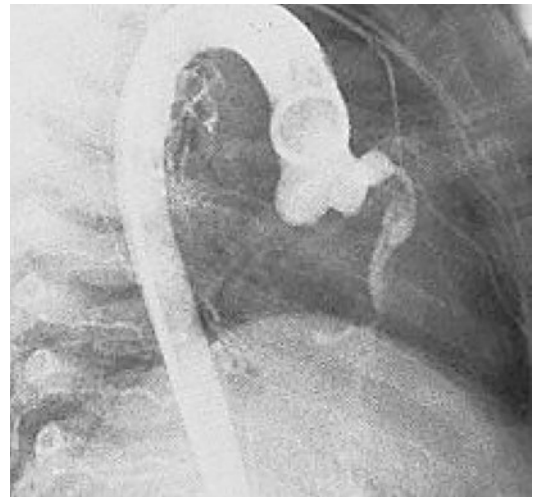

Fig. 7 Right coronary artery aneurysm (aortogram, RAO view)

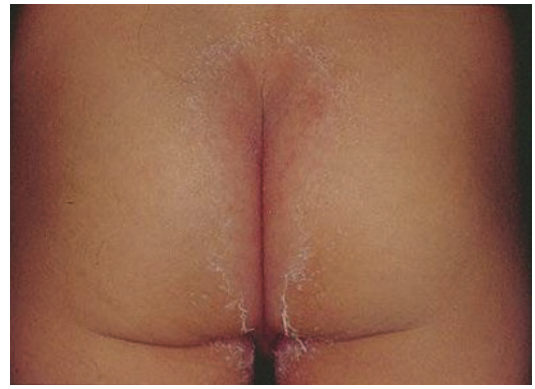

Fig. 8 Desquamation over perianal area

The differential diagnosis includes other infectious and immune disease: measles, other viral infections (adenovirus, enterovirus), staphylococcal and streptococcal toxin-mediated diseases (scarlet fever, toxic shock syndrome), drug hypersensitivity (Stevens–Johnson syndrome), and systemic onset juvenile idiopathic arthritis. For rare patients with epidemiologic risk factors, Rocky Mountain spotted fever or other rickettsial infections, and leptospirosis, should also be ruled out.

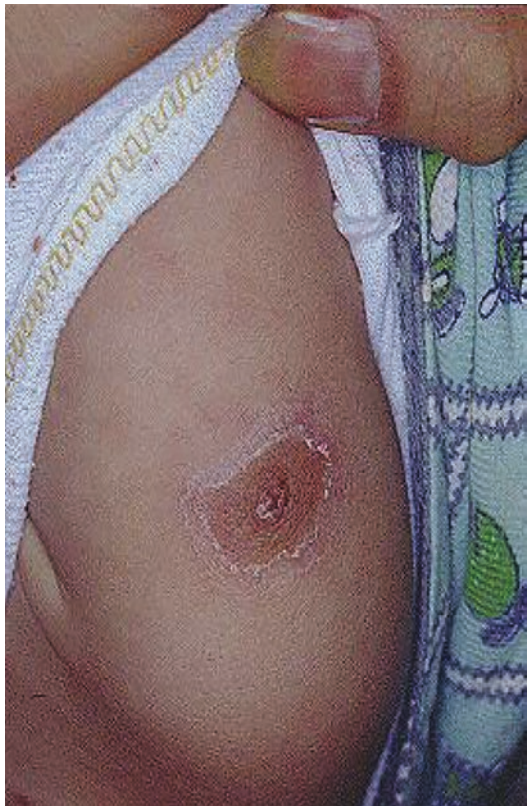

Fig. 9 BCG induration

Clinical Symptoms of Classic KD

Fever

The fever pattern is remittent and spiking, usually >39–40 °C, and persists ≥5 days. Some may continue for 2–3 weeks if no appropriate therapy. It usually resolves within 36 h after IVIG infusion therapy.

Extremity Changes

Erythema and indurative edema appear on palms and soles during acute stage (Fig. 3), sometimes with painful sensation. In the beginning of second or third week of fever, desquamation at periungual regions of fingers or toes (Fig. 4) are noted and may extend to palms and soles. Some patients will develop transverse grooves (Beau line) 1 or 2 months after fever.

Skin Rash

Erythematous skin rashes usually appear in 5 days of fever. The eruptions are typically maculopapular, but frequently polymorphic, and occasionally scarletiform. The skin rashes are generalized appear on the trunk and limbs. It will be more diagnostic in the patients with rashes on inguinal region, associated with early desquamation. Rare cases of psoriatic plaque and pustule had been reported [13]. Patients with atopic dermatitis may have recurrent or severe skin lesion. Bulbous vesicles and petechial rashes are not reported in KD.

Conjunctivitis

Bilateral nonexudative conjunctivitis developed soon after fever. The conjunctival injection spares the limbus (Fig. 10). There are some reported cases of anterior uveitis and subconjunctival hemorrhage [14–16].

Oropharyngeal Changes

The oral changes include red, dry, cracking, peeling, and fissured lips (Fig. 1). Erythema and prominent fungi form papilla show the strawberry tongue (Fig. 2). Oropharynx injection and erythema are prominent, although no ulcer or exudate.

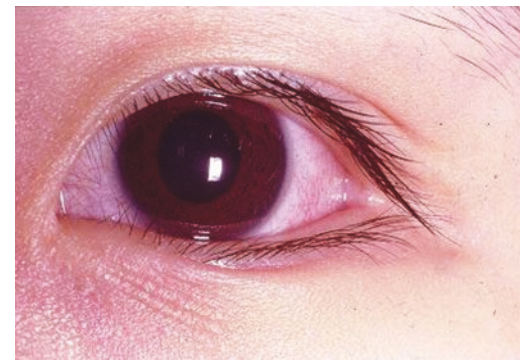

Fig. 10 Conjunctivitis

Cervical Lymphadenopathy

Cervical nonpurulent lymphadenitis is the least-recorded symptom. Usually it is unilateral, located at anterior neck with the diameter ≥1.5 cm. It may be the only symptom of KD and mistaken as bacterial lymphadenitis.

Except for periungual and perianal desquamation (Fig. 8), most of the major symptoms appear during the acute phase.

Incomplete (Atypical) KD

Many ill children do not meet the criteria for complete (typical) Kawasaki disease. However, KD should always be the differential diagnosis once prolonged and unexplained fever occurs in any age group in childhood, especially in those with any of the principal clinical features. If coronary artery aneurysms were identified in such children by echocardiography, the diagnosis of KD is thought to be confirmed. Yet, in most cases of KD, the coronary artery abnormality is not seen until the second week from disease onset. That is, we cannot rule out the diagnosis of KD with a normal echocardiogram in the first week of illness. For infants <6 months old and those without eye or oral mucosal changes, the diagnosis might be delayed.

Incomplete KD may be considered in infants or children who have fever ≥5 days with only two or three clinical symptoms, or fever ≥7 days without known identified causes. Incomplete KD can be made if further laboratory assessment revealed an elevated inflammatory marker (CRP ≥ 3.0 mg/dL and/or ESR ≥ 40 mm/h), combined with a positive echocardiogram result or combined with ≥3 significant abnormal laboratory data of following: anemia of age, thrombocytosis (platelet count ≥450,000/mm^3 after the seventh day of fever), low albumin (≤3.0 g/dL), elevated alanine aminotransferase (ALT), leukocytosis (WBC count ≥15,000/mm^3), and pyuria (urine WBC count ≥10/hpf). Treatment is advised if incomplete KD is considered to be confirmed.

If further laboratory assessment revealed an elevated inflammatory marker (CRP ≥ 3.0 mg/dL and/or ESR ≥ 40 mm/h), without ≥3 significant abnormal laboratory data and negative echocardiogram, or inflammatory marker with CRP < 3.0 mg/dL and ESR < 40 mm/h, serial clinical and laboratory reevaluation on persist febrile patients are required. Once the typical peeling develops, echocardiogram is indicated.

Unusual Manifestation of KD

Some infants may have irritability, aseptic meningitis, culture-negative shock, cervical lymphadenitis unresponsive to antibiotic treatment, and retropharyngeal or parapharyngeal phlegmon unresponsive to antibiotic treatment. These unusual presentations are discussed below.

Skin inoculation site BCG (Fig. 9) [17], or tuberculin skin test reactivity [18], psoriasis [13, 19]. Nail changes such as Beau lines (linear nail creases), transverse orange-brown or red chromonychia, transverse leukonychia (leukonychia striata), pincer nails, and onychomadesis, usually occurring 4–6 weeks after onset of fever [20–23].

In addition to nonsuppurative conjunctivitis, ocular involvement of uveitis was 36.1%, and may be associated with coronary artery dilatation [24].

Gastrointestinal symptoms include diarrhea, vomiting, abdominal pain, hepatitis, hydrops of gallbladder, and pancreatitis. Some manifestation may mimic surgical abdomen, such as pseudo-obstruction or appendicitis. In a cohort of 219 patients with severe surgical conditions, acute abdominal pain/distension, vomiting, hepatomegaly, and jaundice were the most common symptoms at onset. All patients completely recovered, but 50% developed coronary aneurysms despite early intravenous gammaglobulin treatment [25–28].

Neurological involvement was relatively rare, including headache, convulsion, somnolence, irritability, aseptic meningitis, unilateral or bilateral facial palsies, and sensory hearing loss. These rare neurological symptoms may be asso-

ciated with an increased risk of IVIG resistance [29]. The facial palsy appears likely to resolve after acute stage [30–33].

The cervical lymphadenopathy may be confused with bacterial lymphadenitis. KD lymphadenopathy can involve several lymph nodes and cause retropharyngeal edema or even phlegmon. However, bacterial lymphadenitis usually involves solitary lymph node and has echolucent central lesion. Many reported cases showed that KD cervical lymphadenopathy is associated with deep neck inflammation and results in parapharyngeal and retropharyngeal edema and nonsuppurative phlegmon [34, 35].

Cardiovascular involvement of Kawasaki disease includes pericardial effusion, coronary aneurysms, myocarditis, mitral and/or aortic valvular insufficiency, peripheral gangrene [36], and aneurysms of peripheral arteries. The proportion of patients with noncoronary peripheral artery aneurysms was about 2% of all patients with KD. The most common involved arteries were the axillary (18.6%), common iliac (12.4%), and brachial (11.6%) arteries. After 6 months follow-up, 92.9% had some degree of regression, with 80% returning to normal [37].

KD, KDSS (Kawasaki Disease Shock Syndrome), and Multisystem Inflammatory Syndrome in Children (MIS-C)

KDSS is a less common manifestation of KD. However, some reported cases may up to 1/3 of KD. It occurs more in older and male patients. Multisystem involvement with atypical presentation in KDSS is frequent, including more serious skin rash, heart failure, abdominal pain, and neurological symptoms. KDSS is often associated with higher inflammatory markers and more coronary artery complication, and more resistance to immunoglobulin (IVIG). Proportions of leukocytosis, neutrophilia, and hypoalbuminemia are higher, as are that of C-reactive protein, brain natriuretic peptide, and ferroprotein. Mechanical ventilation, inotropes, and albumin infusions are often necessary. An important differential diagnosis is toxic shock syndrome (TSS), especially in the early stage of disease course [38–42].

Multisystem inflammatory syndrome in children (MIS-C), also known as pediatric inflammatory multisystem syndrome, is a new menace to children that is temporally associated with coronavirus disease 2019 (COVID-19) [43]. In the report of WHO and literature [44] the symptoms, laboratory data, and images of MIS-C are similar to KD. Some patients with severe symptoms, even shock, needed resuscitation and ventilator therapy. Such occurrence of Kawasaki-like disease in association with SARS-CoV-2 infection also suggests that KD is not a disease, but rather a syndrome. Recognition of the etiological trigger is important since Kawasaki syndrome secondary to SARS-CoV-2 infection appears to be more severe and requires aggressive treatment [45]. Symptoms of COVID-19 in recent reported cases meet the diagnostic criteria of KD. Older age, more complications of myocardial injury and shock occur in such patients [46–50]. There are some overlapping and different symptoms and signs among KD, KDSS, and MIS-C in regard to age, sex, race, severity of symptoms, and treatment responses [51]. Different aspects of KD, KDSS, and MIS-C need further research and discussion.

References

1. Kawasaki T. [Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children]. Arerugi = [Allergy]. 1967;16(3):178–222.
2. Kawasaki T, Kosaki F, Okawa S, Shigematsu I, Yanagawa H. A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. Pediatrics. 1974;54(3):271–6.
3. Calvo F, Karras BT, Phillips R, Kimball AM, Wolf F. Diagnoses, syndromes, and diseases: a knowledge representation problem. AMIA Annu Symp Proc. 2003;2003:802.
4. Ravelli A, Martini A. Kawasaki disease or Kawasaki syndrome? Ann Rheum Dis. 2020;79(8):993–5.
5. Altammar F, Lang B. Kawasaki disease in the neonate: case report and literature review. Pediatr Rheumatol Online J. 2018;16(1):43.
6. Huang YH, Lin KM, Ho SC, Yan JH, Lo MH, Kuo HC. Increased incidence of Kawasaki disease in Taiwan in recent years: a 15 years nation-

wide population-based cohort study. Front Pediatr. 2019;7:121.
7. Huang WC, Huang LM, Chang IS, Chang LY, Chiang BL, Chen PJ, et al. Epidemiologic features of Kawasaki disease in Taiwan, 2003–2006. Pediatrics. 2009;123(3):e401–5.
8. Wu MH, Lin MT, Chen HC, Kao FY, Huang SK. Postnatal risk of acquiring Kawasaki disease: a nationwide birth cohort database study. J Pediatr. 2017;180:80–6.e2.
9. Kim GB. Reality of Kawasaki disease epidemiology. Korean J Pediatr. 2019;62(8):292–6.
10. Lin MT, Wu MH. The global epidemiology of Kawasaki disease: review and future perspectives. Glob Cardiol Sci Pract. 2017;2017(3):e201720.
11. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, 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(17):e927–99.
12. Research Committee of the Japanese Society of Pediatric C, Cardiac Surgery Committee for Development of Guidelines for Medical Treatment of Acute Kawasaki D. Guidelines for medical treatment of acute Kawasaki disease: report of the Research Committee of the Japanese Society of Pediatric Cardiology and Cardiac Surgery (2012 revised version). Pediatr Int. 2014;56(2):135–58.
13. Eberhard BA, Sundel RP, Newburger JW, Baker A, Fuhlbrigge RC, Burns JC, et al. Psoriatic eruption in Kawasaki disease. J Pediatr. 2000;137(4):578–80.
14. Smith LB, Newburger JW, Burns JC. Kawasaki syndrome and the eye. Pediatr Infect Dis J. 1989;8(2):116–8.
15. Burns JC, Joffe L, Sargent RA, Glode MP. Anterior uveitis associated with Kawasaki syndrome. Pediatr Infect Dis. 1985;4(3):258–61.
16. Ohno S, Miyajima T, Higuchi M, Yoshida A, Matsuda H, Saheki Y, et al. Ocular manifestations of Kawasaki's disease (mucocutaneous lymph node syndrome). Am J Ophthalmol. 1982;93(6):713–7.
17. Yamada H, Ohta H, Hasegawa S, Azuma Y, Hasegawa M, Kadoya R, et al. Two infants with tuberculid associated with Kawasaki disease. Hum Vaccin Immunother. 2016;12(11):2772–6.
18. Bertotto A, Spinozzi F, Vagliasindi C, Radicioni M, De Rosa O, Vaccaro R. Tuberculin skin test reactivity in Kawasaki disease. Pediatr Res. 1997;41(4 Pt 1):560–2.
19. Liao YC, Lee JY. Psoriasis in a 3-month-old infant with Kawasaki disease. Dermatol Online J. 2009;15(11):10.
20. Berard R, Scuccimarri R, Chedeville G. Leukonychia striata in Kawasaki disease. J Pediatr. 2008;152(6):889.
21. George AP, Gaby CE, Broughton RA. Red chromonychia in Kawasaki disease. Pediatr Infect Dis J. 2015;34(6):675–6.
22. Tessarotto L, Rubin G, Bonadies L, Valerio E, Cutrone M. Orange-brown chromonychia and Kawasaki disease: a possible novel association? Pediatr Dermatol. 2015;32(3):e104–5.
23. James R, Burgner D. Orange-brown chromonychia in Kawasaki disease. Arch Dis Child. 2015;100(9):872.
24. Shiari R, Jari M, Karimi S, Salehpour O, Rahmani K, Hassas Yeganeh M, et al. Relationship between ocular involvement and clinical manifestations, laboratory findings, and coronary artery dilatation in Kawasaki disease. Eye (Lond). 2020;34(10):1883–7.
25. Zulian F, Falcini F, Zancan L, Martini G, Secchieri S, Luzzatto C, et al. Acute surgical abdomen as presenting manifestation of Kawasaki disease. J Pediatr. 2003;142(6):731–5.
26. Liebmann LI, Mikelic V, Joh MM, Wilson FM. Hydrops of the gallbladder in an adult with Kawasaki disease. JAMA. 1982;247(6):827–9.
27. Suddleson EA, Reid B, Woolley MM, Takahashi M. Hydrops of the gallbladder associated with Kawasaki syndrome. J Pediatr Surg. 1987;22(10):956–9.
28. Yellamaty V, Steele RW. Kawasaki disease presenting as hydrops of the gallbladder. Clin Pediatr (Phila). 2020;59(4–5):486–9.
29. Liu X, Zhou K, Hua Y, Wu M, Liu L, Shao S, et al. Neurological involvement in Kawasaki disease: a retrospective study. Pediatr Rheumatol Online J. 2020;18(1):61.
30. Bushara K, Wilson A, Rust RS. Facial palsy in Kawasaki syndrome. Pediatr Neurol. 1997; 17(4):362–4.
31. Zhang B, Hao Y, Zhang Y, Yang N, Li H, Liang J. Kawasaki disease manifesting as bilateral facial nerve palsy and meningitis: a case report and literature review. J Int Med Res. 2019;47(8):4014–8.
32. Rodriguez-Gonzalez M, Castellano-Martinez A, Perez-Reviriego AA. Atypical presentation of incomplete Kawasaki disease: a peripheral facial nerve palsy. J Emerg Med. 2018;55(1):118–20.
33. Yu X, Liu X, Wang Y, Lu N, Wang M, Sun L. Kawasaki disease complicating bilateral facial nerve palsy and giant coronary artery aneurysms: a case report. Medicine (Baltimore). 2019;98(7):e14395.
34. Kanegaye JT, Van Cott E, Tremoulet AH, Salgado A, Shimizu C, Kruk P, et al. Lymph-node-first presentation of Kawasaki disease compared with bacterial cervical adenitis and typical Kawasaki disease. J Pediatr. 2013;162(6):1259–63, 63.e1–2.
35. Kato H, Kanematsu M, Kato Z, Teramoto T, Kondo N, Hoshi H. Computed tomographic findings of Kawasaki disease with cervical lymphadenopathy. J Comput Assist Tomogr. 2012;36(1):138–42.
36. Tomita S, Chung K, Mas M, Gidding S, Shulman ST. Peripheral gangrene associated with Kawasaki disease. Clin Infect Dis. 1992;14(1):121–6.
37. Zhao QM, Chu C, Wu L, Liang XC, Sun SN, He L, et al. Systemic artery aneurysms and Kawasaki disease. Pediatrics. 2019;144(6):e20192254.
38. Chen PS, Chi H, Huang FY, Peng CC, Chen MR, Chiu NC. Clinical manifestations of Kawasaki disease

shock syndrome: a case-control study. J Microbiol Immunol Infect. 2015;48(1):43–50.
39. Ma L, Zhang YY, Yu HG. Clinical manifestations of Kawasaki disease shock syndrome. Clin Pediatr (Phila). 2018;57(4):428–35.
40. Gamez-Gonzalez LB, Moribe-Quintero I, Cisneros-Castolo M, Varela-Ortiz J, Munoz-Ramirez M, Garrido-Garcia M, et al. Kawasaki disease shock syndrome: unique and severe subtype of Kawasaki disease. Pediatr Int. 2018;60(9):781–90.
41. Lazea C, Man O, Sur LM, Serban R, Lazar C. Unusual presentation of Kawasaki disease with gastrointestinal and renal manifestations. Ther Clin Risk Manag. 2019;15:1411–6.
42. Dawman L, Kabra SK. Kawasaki disease: unusual clinical manifestations. Indian J Pediatr. 2014;81(4):325–7.
43. Ahmed M, Advani S, Moreira A, Zoretic S, Martinez J, Chorath K, et al. Multisystem inflammatory syndrome in children: a systematic review. EClinicalMedicine. 2020;26:100527.
44. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA. 2020;324(3):259–69.
45. Akca UK, Kesici S, Ozsurekci Y, Aykan HH, Batu ED, Atalay E, et al. Kawasaki-like disease in children with COVID-19. Rheumatol Int. 2020;40(12):2105–15.
46. Toubiana J, Poirault C, Corsia A, Bajolle F, Fourgeaud J, Angoulvant F, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. BMJ. 2020;369:m2094.
47. McCrindle BW, Manlhiot C. SARS-CoV-2-related inflammatory multisystem syndrome in children: different or shared etiology and pathophysiology as Kawasaki disease? JAMA. 2020;324(3):246–8.
48. Singh-Grewal D, Lucas R, McCarthy K, Cheng AC, Wood N, Ostring G, et al. Update on the COVID-19-associated inflammatory syndrome in children and adolescents; paediatric inflammatory multisystem syndrome-temporally associated with SARS-CoV-2. J Paediatr Child Health. 2020;56(8):1173–7.
49. Moreira A. Kawasaki disease linked to COVID-19 in children. Nat Rev Immunol. 2020;20(7):407.
50. Son MBF. Pediatric inflammatory syndrome temporally related to covid-19. BMJ. 2020;369:m2123.
51. Chen MR, Kuo HC, Lee YJ, Chi H, Li SC, Lee HC, et al. Phenotype, susceptibility, autoimmunity, and immunotherapy between Kawasaki disease and coronavirus disease-19 associated multisystem inflammatory syndrome in children. Front Immunol. 2021;12:632890.

Diagnosis of Kawasaki Disease and Development of New Biomarkers

Mindy Ming-Huey Guo

Abstract

Since first described by Dr. Tomisaku Kawasaki in 1961, the clinical diagnosis of Kawasaki disease (KD) has remained relatively unchanged. However, studies have suggested that diagnosis using that original clinical criteria alone may have led to an underdiagnosis of Kawasaki disease. In this chapter, we review widely accepted diagnostic criteria for Kawasaki disease, diagnostic criteria for "atypical" Kawasaki disease, diagnostic pitfalls, and other differential diagnoses. We also review the current literature regarding new biomarkers, scoring systems, and microRNA panels that may aid in the diagnosis of KD.

Keywords

Kawasaki disease · Diagnosis · Biomarkers
Echocardiography

M. M.-H. Guo (✉)
Kawasaki Disease Center, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan

Division of Allergy, Immunology and Rheumatology, Department of Pediatrics, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan

College of Medicine, Chang Gung University, Taoyuan, Taiwan
e-mail: mindymhguo@cgmh.org.tw

Clinical Features and Diagnosis of Kawasaki Disease

Kawasaki disease (KD) was first described by Japanese pediatrician Tomisaku Kawasaki in 1961, when he observed a 4-year-old boy who presented with a variety of symptoms, including persistent fever and rash, and he initially referred to it as "acute febrile mucocutaneous lymph node syndrome" (MCLS). Although the new diagnosis was initially met with skepticism, Dr. Kawasaki persevered, and after collecting a series of 50 cases, he published his findings, complete with meticulous hand-drawn diagrams, in a Japanese journal. He outlined the cardinal features of the newly discovered disease to include persistent fever, bilateral conjunctivitis, oral fissures, skin rash, edema of the hands and feet, and cervical lymphadenopathy [1]. Although the original name for this new inflammatory disease was later changed to "Kawasaki disease" in his honor, his original description of the condition remains fairly consistent with current diagnostic criteria.

The most commonly used diagnostic criteria for Kawasaki disease is the American Heart Association's diagnostic criteria, which includes fever for at least 5 days and at least four out of five of the following criteria: bilateral bulbar conjunctival injection, oral mucosa changes (including fissured lips, strawberry tongue, injected pharynx), changes in the peripheral extremities (erythema of the palms and soles, edema of the hands

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and feet in the acute phase, and periungal desquamation in the convalescent phase), a polymorphous rash, and cervical lymphadenopathy (more than 1.5 cm in diameter) [2]. "Kuo's 1-2-3-4-5 mnemonic for Kawasaki disease," an easy way to remember the diagnostic criteria that was created by Dr. Ho-Chang Kuo from Taiwan, is outlined in Table 1. The Japanese Ministry of Health diagnostic criteria for KD differs only slightly in that fever for at least 5 days is not considered an essential criterion. In other words, patients who exhibit all five of the cardinal symptoms but may be afebrile or have fever for less than 5 days may still be diagnosed with KD [3] (Table 1). In a 2017 update of diagnostic guidelines for KD, the American Heart Association also acknowledged the debate regarding fever duration and has stated that KD can still be diagnosed in patients with fever of more than 4 days, who also present with at least four of the five cardinal symptoms, especially if palmar or plantar erythema or edema of the hands and feet (four limbs change) are present (we call this the 4-4-4 rule) [2]. Both diagnostic criteria have been widely accepted in not only research but also clinical settings. It is important to note that the cardinal features of KD may not all present simultaneously and may abate before a proper diagnosis can be made. Therefore, a detailed history and repeated examinations are vital for an accurate and timely diagnosis of KD.

Other symptoms that may be seen in patients with KD but are not included in the diagnostic criteria include arthritis, gastrointestinal involvement, irritability, lethargy, neurological involvement, cough, and rhinorrhea (Table 1). Arthritis, especially of the large joints of the lower extremities (i.e., knees, hips, ankles), can be found in 7.5–25% of patients and is mostly transient and nondeforming [4]. In a survey of 198 patients with KD, other prodromal symptoms occurring in the acute phase of KD include irritability in 50% of patients, vomiting in 44%,

Table 1 Diagnostic criteria for Kawasaki disease

Kawasaki Disease Research Committee (Japanese Ministry of Health) [3]	American Heart Association Guidelines [2]
Principal symptoms (at least five of the following)	*Diagnosis of classic KD*
Fever for ≥5 days Bilateral conjunctival congestion Oral mucosal changes (diffuse injection, strawberry tongue) Polymorphous exanthema Changes in peripheral extremities (initial stage: reddening of the palms and soles; convalescent stage: peeling of the fingertips) Acute nonpurulent cervical lymphadenopathy	Fever for at least 5 days AND at least four of the following five criteria 1. Erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa 2. Bilateral bulbar conjunctival injection without exudate 3. Rash: maculopapular, diffuse erythroderma, or erythema multiforme-like 4. Erythema and edema of the hands and feet in the acute phase and/or periungual desquamation in the subacute phase 5. Cervical lymphadenopathy (≥1.5 cm diameter), usually unilateral
**Patients with four of the principal symptoms can be diagnosed with KD if coronary aneurysm or dilatation is detected by 2D echocardiography or coronary angiography	
Other significant symptoms or findings	*Incomplete Kawasaki disease*
Positive echocardiography findings Gastrointestinal: Hydrops of gallbladder, elevated serum transaminase, abdominal pain Redness and crusting of the BCG site Blood: leukocytosis, thrombocytosis, anemia, hypoalbuminemia, elevated CRP and ESR Pyuria Joint pain or swelling Neurological: cerebrospinal fluid pleocytosis, conscious change, convulsions, facial palsy, paralysis of extremities Respiratory: cough and rhinorrhea	Fulfills all four of the following criteria 1. Fever of 5 days or more 2. At least two classical symptoms of KD 3. CRP ≥ 3.0 mg/dL OR ESR ≥ 40 mm/h 4. At least three of the supplementary laboratory criteria: anemia for age, platelet count of ≥450,000/mm^3 after the seventh day of fever, albumin ≤3.0 g/dL, elevated alanine transaminase, white blood cell count of ≥15,000/mm^3, urine white blood cells ≥10 /high powered field OR a *positive echocardiogram* (see Table 3)

diarrhea in 26%, and abdominal pain in 18% [5]. Abdominal imaging including radiographs or CT scans may show signs of pseudo-obstruction, which is often present before cardinal symptoms become evident [6]. In the COVID-19 pandemic era, when gastric or intestinal symptoms present weeks after confirmed of COVID-19 infection, MIS-C should also be taken into consideration. KD should also be considered in the differential diagnosis of infants and children who present with prolonged fever and unexplained aseptic meningitis. In a review of 1582 patients with KD, 80 (5.1%) patients showed signs of neurological involvement, with lethargy being the most common (50.1%), followed by irritability (26.3%), meningeal irritation (18.8%), convulsions (17.5%), headache (16.3%), bulging fontanelles (8.8%), and facial palsy (1.3%) [7]. Furthermore, Kawasaki disease shock syndrome (KDSS) is a rare but severe manifestation of KD associated with shock, hypotension, impaired left ventricular systolic function, mitral regurgitation, consumptive coagulopathy, and increased risk of coronary artery lesions and IVIG resistance [8]. Due to clinical similarities including rash, fever, and shock, patients with Kawasaki disease shock syndrome may be misdiagnosed with toxic shock syndrome [9]. KD may also present as cervical lymphadenitis and have adjacent cellulitis and phlegmon mimicking bacterial adenitis [10], especially in children less than 6 months old or more than 4 years old [11]. The possibility of KD should be considered in infants and children presenting with prolonged fever, cervical lymphadenitis, and retropharyngeal or parapharyngeal phlegmon and who do not respond to antibiotic therapy [2].

In regions such as Taiwan or Japan where vaccination schedules routinely include the bacillus Calmette–Guerin (BCG) vaccination, induration and erythema or crusting around the BCG vaccination can be found in up to 50% of patients diagnosed with KD and may aid in the diagnosis of KD, especially in children younger than 3 years old [12, 13]. In a previous study of 34 patients diagnosed with Kawasaki disease, induration around the BCG site was characterized into three common patterns: a targetoid bull's eye pattern centered around the BCG site; homogeneous erythema surrounding the BCG site; or a whitish patch at the BCG inoculation site. Patients who presented with a targetoid bull's eye pattern around the BCG site at the time of KD diagnosis were associated with a higher risk of coronary artery dilatation [14]. In patients who had received the BCG vaccine but only fulfilled four of the principal symptoms established by Japanese guidelines (see Table 1 for details), erythema, induration, or crusting around the BCG may provide an additional clue highly suggestive of a KD diagnosis. Erythema of the BCG vaccination site is relatively specific to the diagnosis of KD, although measles infection was also reported to be associated with BCG induration in a previous case report [15].

Our research team recently developed a wireless optical monitoring system that utilized a tri-wavelength light source (700, 910, and 950 nm) and a light detector to determine the degree of edema in the palms and soles of febrile patients suspected of having KD. In our pilot study of 123 patients, KD patients had significantly greater relative peripheral edema and lower total hemoglobin concentrations detected via the optical monitoring system when compared to the febrile controls. Additional studies are being conducted to establish benchmark parameters and optimal cutoff values for the diagnosis of KD. We are optimistic that wireless optical monitoring can provide an additional noninvasive diagnostic aid, especially in patients suspected of having KD but who do not fulfill the clinical criteria [16].

Diagnosis of Incomplete (or Atypical) Kawasaki Disease

As many as 10–15% of KD patients whose diagnosis is confirmed by echocardiogram do not fulfil the aforementioned criteria [17], especially in infants younger than 1 year old [18, 19]. In 2004, the American Heart Association established guidelines to aid in diagnosis of incomplete KD. Treatment for patients with incomplete KD should be given to those patients who fulfill all four of the following criteria: (1) fever of 5 days

or more; (2) two or three clinical symptoms of KD; (3) elevated C-reactive protein (CRP) level of more than 3.0 mg/dL or an erythrocyte sedimentation rate (ESR) of more than 40 mm/h; and (4) at least three of the supplementary laboratory criteria (anemia for age, platelet count of ≥450,000/mm^3 after the seventh day of fever, albumin ≤3.0 g/dL, elevated alanine transaminase, white blood cell count of ≥15,000/mm^3, urine white blood cells ≥10/high powered field) or a positive echocardiogram (Table 1) [20]. Furthermore, in patients with 5 or more days of fever and two or three of the cardinal symptoms of KD, serial clinical and laboratory follow-up is recommended if fever persists, and additional echocardiography is also recommended if periungal peeling of the fingers and toes occurs. Positive 2D echocardiography findings are listed in Table 2 and are discussed in section "Echocardiographic Findings That Aid in the Diagnosis of Kawasaki Disease."

That KD may be more difficult to diagnose in infants and in older children is an important consideration. Infants younger than 6 months of age are more likely to present with incomplete KD and thus receive IVIG therapy later and have a higher risk of coronary artery involvement, even in those who receive IVIG therapy within 10 days of disease onset [21, 22]. KD is equally difficult to diagnose in children older than 10 years old. In a review of 113 patients with Kawasaki disease, the cardinal KD symptoms of patients who were more than 5 years old appeared later in the clinical course and were prone to have more severe signs of inflammation, including a longer duration of fever and higher levels of ESR; such patients were also more likely to require additional therapy along with IVIG. Interestingly, older children were also more likely to have cervical lymphadenopathy when compared to children younger than 5 years old (85.0% vs. 51.6%) [23].

Table 2 Kuo's 1-2-3-4-5 mnemonic for Kawasaki disease

Number	Mnemonic	Clinical features
1	Refers to symptoms occurring in "One mouth"	Strawberry tongue, oral fissures, injected pharynx, and other signs of oropharyngeal mucosa inflammation
2	Referring to bilateral conjunctivitis seen in the "Two eyes"	Bilateral nonsuppurative conjunctivitis
3	Referring to the "Three fingers" required to palpate for cervical lymphadenopathy	Cervical lymph node enlargement of >1.5 cm in diameter of at least one lymph node
4	Referring to changes in "Four peripheral extremities"	Erythema of the palms and soles, edema of the hands and feet in the acute phase, and periungal desquamation in the convalescent phase
5	Refers to the multiple areas of the *polymorphous rash*	

The differential diagnosis for patients presenting with symptoms similar to those seen in Kawasaki disease include childhood infectious exanthems, drug reactions, or systemic juvenile idiopathic arthritis. Several viral illnesses, including measles, adenovirus, and Epstein–Barr Virus (EBV) infections, share the clinical features of fever, rash, and mucocutaneous inflammation similar to KD [2]. However, the presence of exudative conjunctivitis (seen in adenovirus), discrete whitish lesions of the oral mucosa (i.e., Koplik spots, seen in measles), or generalized lymphadenopathy (more commonly seen in EBV) should prompt an alternative diagnosis, as these symptoms are less commonly seen in patients with KD. Moreover, patients with adenovirus, measles, or EBV often lack the cardinal extremity changes like palmar plantar erythema or swelling more often seen in KD. Scarlet fever and toxic shock syndrome, which are both caused by toxins produced by group A streptococcal infection may also mimic KD, although the presence of overt exudative pharyngitis is much more indicative of streptococcal pharyngitis and not common in KD. Drug reactions or Stevens–Johnson's syndrome may also mimic KD, but the presence of blisters, bullae, or a vesicular rash makes the diagnosis of KD less likely. Likewise, patients with systemic juvenile idiopathic arthritis may also present with fever, rash, and joint pain similar to KD but will often lack other signs of mucosal inflammation, including oral mucosa

or conjunctiva. Recognizing that KD may also occur in tandem with both bacterial and viral infections is vital [24, 25]. Therefore, confirmation of a bacterial or viral infection does not necessarily preclude a KD diagnosis.

Echocardiographic Findings That Aid in the Diagnosis of Kawasaki Disease

Echocardiography should be performed on all patients with suspected or confirmed KD as soon as possible, not only to aid in the diagnosis of KD but also to establish a baseline of echocardiographic parameters for future follow-up. Evaluation should include visualization of all the main segments of the coronary artery, as well as monitoring of ventricular wall motion, ejection fraction, valvular regurgitation, and the presence of pericardial effusion. Use of a high-frequency transducer is strongly recommended in both infants and older children, as it enables better visualization of the coronary arteries [2]. In terms of natural history, coronary artery lesions may progress to their maximal diameter 4–6 weeks after the onset of KD and may then regress over a period of 1–2 years. Therefore, a normal echocardiogram in the first week of disease onset does not exclude a diagnosis of KD, and serial examinations (maybe every other day) are suggested in the case of a high index of suspicion.

Measurement of coronary artery internal diameter is crucial and can either be categorized in absolute dimensions (Japanese criteria) [3, 26] or be adjusted according to patient body weight and size (American Heart Association Guidelines) [2]. According to Japanese guidelines, coronary arteries are considered to be abnormally dilated if the internal diameter exceeds 3 mm in a child younger than 5 years old or 4 mm in a child older than 5 years old. Coronary artery dilatations can be classified as small (3–4 mm in children younger than 5 years old; >4 mm or if the internal diameter is <1.5 times of an adjacent segment in children older than 5 years old), medium (internal diameter of 4–8 mm in children younger than 5 years old; 1.5–4 times the size of an adjacent segment in children older than 5 years old), giant (internal diameter larger than 8 mm in children younger than 5 years old, or if it measures >4 times that of an adjacent segment in children older than 5 years old) (Table 3). However, grading coronary artery size according to absolute measurements and age does not take into account differences in body size or height and may thus underestimate the degree of coronary artery involvement in up to 27% of patients with KD [27]. Therefore, significant efforts have been made to normalize coronary artery dimensions across age and weight groups using regression modeling of normal coronary artery diameter

Table 3 Echocardiography findings in Kawasaki disease

American Heart Association Guidelines [2]
Positive findings for Kawasaki disease include the following
1. Left anterior descending coronary artery or right coronary artery with a *Z*-score ≥2.5
2. Coronary artery aneurysm
3. ≥Three of the following suggestive features: decreased left ventricular function, mitral regurgitation, pericardial effusion, or *Z* scores in the left anterior descending coronary artery or right coronary artery of 2–2.5
Z-score classification of coronary artery lesions
1. Dilatation only: *Z*-score 2–2.5
2. Small aneurysm: *Z*-score to ≥2.5–5
3. Medium aneurysm: *Z*-score ≥5–10, and absolute measurement <8 mm
4. Large aneurysm: *Z*-score ≥10, or absolute measurement ≥8 mm
Japan Circulation Society [26, 63]
Classification of coronary aneurysms during the acute phase
1. Small aneurysms or dilatation Children <5 years old: localized dilatation >3 mm but within ≤4 mm internal diameter Children ≥5 years old: localized dilatation >4 mm or if the internal diameter of a segment measures <1.5 times that of an adjacent segment
2. Medium aneurysms Children <5 years old: an internal diameter from >4 to <8 mm Children ≥5 years of age: internal diameter of a segment measures 1.5–4 times that of an adjacent segment
3. Giant aneurysms Children <5 years old: aneurysms with an internal diameter of ≥8 mm Children ≥5 years of age: the internal diameter of a segment measures >4 times that of an adjacent segment

measurements to body surface area. *Z*-score, or the number of standard deviations away from the mean, has been adopted as the basis for scoring coronary artery diameters according to the American Heart Association guidelines. Coronary artery diameters are normal if *Z*-scores are less than 2 and are considered to have dilatation only if *Z*-scores are 2–2.5; small aneurysms have a *Z*-score of 2.5–5, medium aneurysms have a *Z*-score of 5–10 and an absolute measurement of less than 8 mm, and large or giant aneurysms have a *Z*-score of more than 10 or an absolute measurement of more than 8 mm [2].

Many methods have been adopted to derive *Z*-scores from coronary artery measurements in normal children in different countries and ethnic populations over time and thus may differ with regard to how body surface area is calculated and the regression model used to fit coronary artery measurements to body surface area. One of the largest studies was performed by Kobayashi et al., in which coronary artery diameters were prospectively collected in 3815 healthy Japanese children and then statistically normalized to body surface area (Haycock method: body surface area = 0.024265 × height (cm) 0.3964 × weight (kg) 0.5378) using a lambda–mu–sigma regression model [28] (available online: http://raise.umin.jp/zsp/calculator/). In a study of 412 Taiwanese children under 6 years of age, the Debois method was used to estimate body surface area, and exponential regression was performed to normalize coronary artery measurements against body surface area [29]. An online calculator is also available at http://www.tspc.org.tw/service/z_score.asp. It is important to note that small differences in coronary artery measurements on 2D echocardiogram may be amplified by translating absolute measurements into *Z*-scores. In addition, use of different *Z*-score systems derived from different normalized datasets may result in differences in size classifications, especially when coronary artery measurements are large.

Other findings associated with KD that can be found on echocardiography include pericarditis, pericardial effusion, and valvular regurgitation (especially of the mitral and aortic valves) [2]. Left ventricular systolic dysfunction and aortic dilatation can be found in up to 20% and 8% of patients with KD, respectively, in the acute phase of KD, and both are associated with coronary artery dilatation [30].

Development of New Biomarkers to Aid in the Diagnosis of Kawasaki Disease

Many inflammatory markers, such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) values, and white blood cell and platelet counts, may assist in the diagnosis of KD when evaluated alongside clinical symptoms. However, these inflammatory markers are mostly nonspecific and may also be elevated by other infectious or inflammatory diseases. For example, in a study of 114 patients suspected of KD, an ESR level of ≥40 mm/h was found to have a sensitivity of 90.5% but a specificity of only 66.6% [31]. Because of this, patients with indeterminant KD symptoms are difficult to differentiate from patients with febrile illnesses of other causes, especially in a primary care setting. Recently, researchers at Stanford University have developed two novel scoring systems to differentiate between KD and febrile illnesses of other causes. The first scoring system published in 2013 used five clinical symptoms and 12 laboratory data points to stratify febrile patients into low (negative predictive value of >95%), intermediate, and high (positive predictive value of >95%) risk groups [32]. However, even after stratification, 20–30% of febrile patients remained unstratified; therefore, a second algorithm encompassing 18 clinical and laboratory data points was developed, and patients were stratified again using data-mining models to increase detection of KD among febrile patients [33]. In our study group, we tried to develop a more simplified scoring system that can adequately differentiate between febrile and KD patients. In an analysis of 6310 febrile patients and 485 patients with KD, we developed a scoring system of eight laboratory criteria, with the highest scores being attributed to eosinophil percentage of >1.5%, CRP of >24 mg/L, and alanine aminotransferase level of >30 U/L [34].

Other investigations into immunological biomarkers related to KD have shed light on the possible immunopathogenesis of the disease. Previous studies have found that acute Kawasaki disease is associated with elevation of both Th1 cytokines like IL-6, TNF-a, and IFN-r and Th2 cytokines like IL-4, IL-5, and IL-31 [35, 36]. In a previous study, we found that KD patients with lower Th2 cytokines like IL-5 had a higher risk of developing coronary artery lesions, thus suggesting that Th-2 responses may have a protective effect against coronary artery lesion development [36].

B-type natriuretic peptide (BNP) and its inactive cleavage product N-terminal prohormone of brain natriuretic peptide (NT-proBNP) are currently the most extensively studied proteomic biomarkers for KD. BNP is produced by ventricular cardiomyocytes in response to stretching ventricles due to increased ventricular blood volume or myocardial ischemia and is a well-established biomarker for both congestive heart failure and coronary artery diseases [37]. The accuracy of NT-proBNP as a diagnostic biomarker for differentiating KD from other febrile illnesses was recently reviewed in a meta-analysis of six studies that included 279 patients with KD. This biomarker had a pooled sensitivity of 89% and a pooled specificity of 72%, making it a specific, though modestly sensitive, test for diagnosing KD [38]. No cutoff values are universally recognized at this point, which may be partially attributed to the age-specific changes in NT-proBNP levels. NT-proBNP levels are highest in the first days after birth, decrease sharply in the first few weeks of life, and then gradually decline with age [39].

Our research team has recently attempted to use *Escherichia coli* (*E. coli*) proteome microarrays as a novel diagnostic platform for diagnosing Kawasaki disease. *E. coli* proteome microarrays consist of nearly 4200 purified *E. coli* proteins and are used to test the presence of anti-*E. coli* protein IgG and IgM antibodies within patients' serum [40]. Current theories regarding the etiology and pathogenesis of KD suggest that KD may be the result of an overreactive immune response to a common environmental or infectious trigger, but a universally recognized infectious trigger has yet to be identified [41]. Case reports have identified *E. coli* and other gram-negative pathogens, such as *Klebsiella oxytoca*, as possible infectious triggers of KD [42, 43]. Furthermore, studies focused on the gastrointestinal microbiota of KD patients have found higher numbers of both gram-positive and heat shock protein producing Gram-negative bacteria in the stools of children with KD [44]. *E. coli* is also a common gut bacterium and participates in the development of immune homeostasis and autoimmunity in young children [45]. Overall, these studies suggest that *E. coli* may be a relevant pathogen associated with the development of KD. Therefore, we have hypothesized that patients with KD have specific anti-*E. coli* antibody profiles, thus indicating the role *E. coli* may play in the pathogenesis of KD. In a pilot study using a training set of 20 patients with KD and 20 febrile controls, a core set of 20 *E. coli* proteins was identified that could accurately predict a KD diagnosis in our blind testing set of an additional 40 febrile patients (Area under ROC curve: 0.75) [46]. *E. coli* proteome microarrays have already been used in previous studies to identify specific antibody profiles in other diseases, such as inflammatory bowel disease [47] and bipolar disorder [48]. Since only 125 picoliters of serum was used in our microarray testing, *E. coli* proteome microarrays may be a novel method for screening and diagnosing KD.

MicroRNAs are small noncoding RNA that are about 22 nucleotides long and regulate gene expression through the complementary binding of target mRNAs or the 3′ untranslated region (3′ UTR), thus disrupting the translation of mRNA into product proteins. MiRNAs can be found in all types of blood cells within circulation, including leukocytes, erythrocytes, and platelets. One recent study has suggested that exosomes containing miRNAs can be found within circulating plasma and may participate in distant cell-to-cell cross talk and gene regulation. Plasma microRNAs are relatively stable, even when subjected to changes in pH or temperature (e.g., freeze–thaw cycle), thus making them ideal candidates as diagnostic biomarkers in the future [49].

Many of the microRNAs identified in the serum of KD patients' target genes may alter

the growth and function of vascular endothelial cells. MicroRNA miR-233 is one of the most abundantly expressed microRNAs present in the serum of KD patients [50]. Bone marrow-derived cells, such as leukocytes and platelets, secrete miR-233 in the serum, which then enters vascular endothelial cells. Targets for miR-233 include such genes as IGF1R and IL-6ST [51]. MiR-233-3p directly targets IL-6ST 3′ untranslatable regions (UTR) and inhibits IL-6 expression, an important inflammatory cytokine in KD, which subsequently decreases the important expression transcription factors p-STAT3 and NF-kB p65. In one KD mouse model, injection with miR-233-3p alleviates vascular endothelial destruction and inhibits the expression of IL-6, as well as the vascular adhesion molecules E-selectin and ICAM-1 [52].

Other microRNAs have been found to inhibit vascular cell proliferation (i.e., miR-27b) or induce apoptosis (i.e., miR-186, miR-125-5p). The upregulation of miR-27b in an endothelial cell line suppresses the TGF-b pathway and endothelial cell proliferation and migration by upregulating SMAD7 [53]. Serum miR-186 has been found to induce the apoptosis of endothelial cells by inhibiting SMAD6 and activating the MAPK pathway [54]. Likewise, miR-125-5p induced the apoptosis of endothelial cells by inhibiting MKK7 and activating Caspase-3 [55]. MicroRNAs may also contribute to coronary artery remodeling and fibrosis via the promotion of connective tissue growth factor (CTGF). Serum from KD patients KD have lower levels of miR-483, which targets the untranslated region of CTGF. The knockdown of miR-483 in endothelial cells enhances CTGF expression [56].

Certain miRNAs have also been found to be associated with prognostic outcomes. In a study of 102 KD patients and 18 healthy controls, KD patients who were IVIG-resistant had markedly higher levels of miR-200c and miR-371-5p [57]. CAL development has been shown to be associated with the upregulation of miR-92a-3p, miR-let-7i-3p, miR-145-5p, and miR-320a [58, 59]. Transfection of miR-145-5p and miR-320a into the monocyte cell line THP-1 increased the expression of inflammatory cytokines IL-6 and TNF-α in the supernatant. Furthermore, the immunohistochemical staining of a coronary artery sample obtained from a 4-year-old boy with KD who died on the tenth day of fever due to the rupture of a coronary artery aneurysm showed increased staining of miR-145-5p and miR320a in the endothelial cells of the coronary artery [60].

The identification of single miRNAs is probably not as useful as finding an entire miRNA expression profile for the diagnosis of KD because approximately 60% of protein encoding genes are probably simultaneously regulated by multiple miRNAs [61]. In our study of 50 patients with KD (31 used as a training set and the remaining 19 used as a validation set), miRNAs extracted from peripheral leukocytes underwent next-generation sequencing, which enabled us to identify 10 miRNAs. This panel of ten miRNAs was then used as a screening panel for KD diagnosis within the validation set and was found to have a sensitivity of 83.3% and a specificity of 92.5%. We encourage both researchers and clinicians to submit ΔCt values of the ten miRNAs included in our panel to our Kawasaki Disease Detection Platform website, which is accessible via http://formosa3.nchc.org.tw:50190/KDP/index.php. Our website can than predict the probability of KD according to the submitted miRNA expression levels of a certain patient [62]. Our miRNA panel has already been patented in Taiwan and the USA to differentiate KD from other febrile diseases (Kawasaki Disease Diagnosis Kit, patent number I598586); patents in other countries are currently pending.

Conclusion

Increasing KD awareness, early and precise diagnosis (through echocardiography, AHA supplemental criteria, 4-4-4 rule, and BCG induration), and biomarker development will help with the early detection and treatment of KD.

References

1. Kawasaki T. [Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children]. Arerugi. 1967;16(3):178–222.
2. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, 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(17):e927–99.
3. Ayusawa M, Sonobe T, Uemura S, Ogawa S, Nakamura Y, Kiyosawa N, et al. Revision of diagnostic guidelines for Kawasaki disease (the 5th revised edition). Pediatr Int. 2005;47(2):232–4.
4. Gong GW, McCrindle BW, Ching JC, Yeung RS. Arthritis presenting during the acute phase of Kawasaki disease. J Pediatr. 2006;148(6):800–5.
5. Baker AL, Lu M, Minich LL, Atz AM, Klein GL, Korsin R, et al. Associated symptoms in the ten days before diagnosis of Kawasaki disease. J Pediatr. 2009;154(4):592–5.e2.
6. Colomba C, La Placa S, Saporito L, Corsello G, Ciccia F, Medaglia A, et al. Intestinal involvement in Kawasaki disease. J Pediatr. 2018;202:186–93.
7. Liu X, Zhou K, Hua Y, Wu M, Liu L, Shao S, et al. Neurological involvement in Kawasaki disease: a retrospective study. Pediatr Rheumatol Online J. 2020;18(1):61.
8. Kanegaye JT, Wilder MS, Molkara D, Frazer JR, Pancheri J, Tremoulet AH, et al. Recognition of a Kawasaki disease shock syndrome. Pediatrics. 2009;123(5):e783–9.
9. Gamez-Gonzalez LB, Moribe-Quintero I, Cisneros-Castolo M, Varela-Ortiz J, Munoz-Ramirez M, Garrido-Garcia M, et al. Kawasaki disease shock syndrome: unique and severe subtype of Kawasaki disease. Pediatr Int. 2018;60(9):781–90.
10. Rossi Fde S, Silva MF, Kozu KT, Camargo LF, Rossi FF, Silva CA, et al. Extensive cervical lymphadenitis mimicking bacterial adenitis as the first presentation of Kawasaki disease. Einstein (Sao Paulo). 2015;13(3):426–9.
11. Kao HT, Huang YC, Lin TY. Kawasaki disease presenting as cervical lymphadenitis or deep neck infection. Otolaryngol Head Neck Surg. 2001;124(4):468–70.
12. Wang CL, Wu YT, Liu CA, Kuo HC, Yang KD. Kawasaki disease: infection, immunity and genetics. Pediatr Infect Dis J. 2005;24(11):998–1004.
13. Uehara R, Igarashi H, Yashiro M, Nakamura Y, Yanagawa H. Kawasaki disease patients with redness or crust formation at the Bacille Calmette–Guerin inoculation site. Pediatr Infect Dis J. 2010;29(5):430–3.
14. Tseng HC, Ho JC, Guo MM, Lo MH, Hsieh KS, Tsai WC, et al. Bull's eye dermatoscopy pattern at bacillus Calmette–Guerin inoculation site correlates with systemic involvements in patients with Kawasaki disease. J Dermatol. 2016;43(9):1044–50.
15. Muthuvelu S, Lim KS, Huang LY, Chin ST, Mohan A. Measles infection causing Bacillus Calmette–Guerin reactivation: a case report. BMC Pediatr. 2019;19(1):251.
16. Kuo HC, Lo CC, Lin PX, Kao CC, Huang YH, Lin BS. Wireless optical monitoring system identifies limb induration characteristics in patients with Kawasaki disease. J Allergy Clin Immunol. 2018;142(2):710–1.
17. Fukushige J, Takahashi N, Ueda Y, Ueda K. Incidence and clinical features of incomplete Kawasaki disease. Acta Paediatr. 1994;83(10):1057–60.
18. Yeom JS, Woo HO, Park JS, Park ES, Seo JH, Youn HS. Kawasaki disease in infants. Korean J Pediatr. 2013;56(9):377–82.
19. Rosenfeld EA, Corydon KE, Shulman ST. Kawasaki disease in infants less than one year of age. J Pediatr. 1995;126(4):524–9.
20. Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, 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(17):2747–71.
21. Chang FY, Hwang B, Chen SJ, Lee PC, Meng CC, Lu JH. Characteristics of Kawasaki disease in infants younger than six months of age. Pediatr Infect Dis J. 2006;25(3):241–4.
22. Salgado AP, Ashouri N, Berry EK, Sun X, Jain S, Burns JC, et al. High risk of coronary artery aneurysms in infants younger than 6 months of age with Kawasaki disease. J Pediatr. 2017;185:112–6.e1.
23. Cai Z, Zuo R, Liu Y. Characteristics of Kawasaki disease in older children. Clin Pediatr (Phila). 2011;50(10):952–6.
24. Chang LY, Lu CY, Shao PL, Lee PI, Lin MT, Fan TY, et al. Viral infections associated with Kawasaki disease. J Formos Med Assoc. 2014;113(3):148–54.
25. Huang SM, Huang SH, Weng KP, Chien KJ, Lin CC, Huang YF. Update on association between Kawasaki disease and infection. J Chin Med Assoc. 2019;82(3):172–4.
26. Group JCSJW. Guidelines for diagnosis and management of cardiovascular sequelae in Kawasaki disease (JCS 2013). Digest version. Circ J. 2014;78(10):2521–62.
27. de Zorzi A, Colan SD, Gauvreau K, Baker AL, Sundel RP, Newburger JW. Coronary artery dimensions may be misclassified as normal in Kawasaki disease. J Pediatr. 1998;133(2):254–8.
28. Kobayashi T, Fuse S, Sakamoto N, Mikami M, Ogawa S, Hamaoka K, et al. A new Z score curve of the coronary arterial internal diameter using the Lambda-Mu-Sigma method in a pediatric population. J Am Soc Echocardiogr. 2016;29(8):794–801.e29.
29. Lin MT, Chang CH, Hsieh WC, Chang CE, Chang YM, Chen YC, et al. Coronary diameters in Taiwanese

children younger than 6 years old: Z-score regression equations derived from body surface area. Acta Cardiol Sin. 2014;30(4):266–73.
30. Tsuda E, Singhal M. Role of imaging studies in Kawasaki disease. Int J Rheum Dis. 2018;21(1):56–63.
31. Chaiyarak K, Durongpisitkul K, Atta T, Soongswang J, Laohaprasitiporn D, Nana A. Clinical manifestations of Kawasaki disease: what are the significant parameters? Asian Pac J Allergy Immunol. 2009;27(2–3):131–6.
32. Ling XB, Kanegaye JT, Ji J, Peng S, Sato Y, Tremoulet A, et al. Point-of-care differentiation of Kawasaki disease from other febrile illnesses. J Pediatr. 2013;162(1):183–8.e3.
33. Hao S, Jin B, Tan Z, Li Z, Ji J, Hu G, et al. A classification tool for differentiation of Kawasaki disease from other febrile illnesses. J Pediatr. 2016;176:114–20.e8.
34. Tsai CM, Chu CH, Liu X, Weng KP, Liu SF, Huang YH, et al. A novel score system of blood tests for differentiating Kawasaki disease from febrile children. PLoS One. 2021;16(1):e0244721.
35. Wang Y, Wang W, Gong F, Fu S, Zhang Q, Hu J, et al. Evaluation of intravenous immunoglobulin resistance and coronary artery lesions in relation to Th1/Th2 cytokine profiles in patients with Kawasaki disease. Arthritis Rheum. 2013;65(3):805–14.
36. Kuo HC, Wang CL, Liang CD, Yu HR, Huang CF, Wang L, et al. Association of lower eosinophil-related T helper 2 (Th2) cytokines with coronary artery lesions in Kawasaki disease. Pediatr Allergy Immunol. 2009;20(3):266–72.
37. de Lemos JA, McGuire DK, Drazner MH. B-type natriuretic peptide in cardiovascular disease. Lancet. 2003;362(9380):316–22.
38. Lin KH, Chang SS, Yu CW, Lin SC, Liu SC, Chao HY, et al. Usefulness of natriuretic peptide for the diagnosis of Kawasaki disease: a systematic review and meta-analysis. BMJ Open. 2015;5(4):e006703.
39. Nir A, Lindinger A, Rauh M, Bar-Oz B, Laer S, Schwachtgen L, et al. NT-pro-B-type natriuretic peptide in infants and children: reference values based on combined data from four studies. Pediatr Cardiol. 2009;30(1):3–8.
40. Chen CS, Korobkova E, Chen H, Zhu J, Jian X, Tao SC, et al. A proteome chip approach reveals new DNA damage recognition activities in Escherichia coli. Nat Methods. 2008;5(1):69–74.
41. Esposito S, Polinori I, Rigante D. The gut microbiota-host partnership as a potential driver of Kawasaki syndrome. Front Pediatr. 2019;7:124.
42. Watanabe T. Pyuria in patients with Kawasaki disease. World J Clin Pediatr. 2015;4(2):25–9.
43. Husain EH, Al-Rashid M. Kawasaki disease in association with urinary tract infection. Indian Pediatr. 2011;48(10):808–9.
44. Nagata S, Yamashiro Y, Ohtsuka Y, Shimizu T, Sakurai Y, Misawa S, et al. Heat shock proteins and superantigenic properties of bacteria from the gastrointestinal tract of patients with Kawasaki disease. Immunology. 2009;128(4):511–20.
45. Wu HJ, Wu E. The role of gut microbiota in immune homeostasis and autoimmunity. Gut Microbes. 2012;3(1):4–14.
46. Kuo HC, Huang YH, Chung FH, Chen PC, Sung TC, Chen YW, et al. Antibody profiling of Kawasaki disease using Escherichia coli proteome microarrays. Mol Cell Proteomics. 2018;17(3):472–81.
47. Chen CS, Sullivan S, Anderson T, Tan AC, Alex PJ, Brant SR, et al. Identification of novel serological biomarkers for inflammatory bowel disease using Escherichia coli proteome chip. Mol Cell Proteomics. 2009;8(8):1765–76.
48. Chen PC, Syu GD, Chung KH, Ho YH, Chung FH, Chen PH, et al. Antibody profiling of bipolar disorder using Escherichia coli proteome microarrays. Mol Cell Proteomics. 2015;14(3):510–8.
49. Faruq O, Vecchione A. microRNA: diagnostic perspective. Front Med (Lausanne). 2015;2:51.
50. Chen Y, Ding YY, Ren Y, Cao L, Xu QQ, Sun L, et al. Identification of differentially expressed microRNAs in acute Kawasaki disease. Mol Med Rep. 2018;17(1):932–8.
51. Chu M, Wu R, Qin S, Hua W, Shan Z, Rong X, et al. Bone marrow-derived microRNA-223 works as an endocrine genetic signal in vascular endothelial cells and participates in vascular injury from Kawasaki disease. J Am Heart Assoc. 2017;6(2):e004878.
52. Wang X, Ding YY, Chen Y, Xu QQ, Qian GH, Qian WG, et al. MiR-223-3p alleviates vascular endothelial injury by targeting IL6ST in Kawasaki disease. Front Pediatr. 2019;7:288.
53. Rong X, Ge D, Shen D, Chen X, Wang X, Zhang L, et al. miR-27b suppresses endothelial cell proliferation and migration by targeting Smad7 in Kawasaki disease. Cell Physiol Biochem. 2018;48(4):1804–14.
54. Wu R, Shen D, Sohun H, Ge D, Chen X, Wang X, et al. miR186, a serum microRNA, induces endothelial cell apoptosis by targeting SMAD6 in Kawasaki disease. Int J Mol Med. 2018;41(4):1899–908.
55. Wu MH, Lin MT, Chen HC, Kao FY, Huang SK. Postnatal risk of acquiring Kawasaki disease: a nationwide birth cohort database study. J Pediatr. 2017;180:80–6.e2.
56. He M, Chen Z, Martin M, Zhang J, Sangwung P, Woo B, et al. miR-483 targeting of CTGF suppresses endothelial-to-mesenchymal transition: therapeutic implications in Kawasaki disease. Circ Res. 2017;120(2):354–65.
57. Zhang W, Wang Y, Zeng Y, Hu L, Zou G. Serum miR-200c and miR-371-5p as the useful diagnostic biomarkers and therapeutic targets in Kawasaki disease. Biomed Res Int. 2017;2017:8257862.
58. Rong X, Jia L, Hong L, Pan L, Xue X, Zhang C, et al. Serum miR-92a-3p as a new potential biomarker for diagnosis of Kawasaki disease with coronary artery lesions. J Cardiovasc Transl Res. 2017;10(1):1–8.
59. Wang YF, Lian XL, Zhong JY, Su SX, Xu YF, Xie XF, et al. Serum exosomal microRNA let-7i-3p as

candidate diagnostic biomarker for Kawasaki disease patients with coronary artery aneurysm. IUBMB Life. 2019;71(7):891–900.
60. Nakaoka H, Hirono K, Yamamoto S, Takasaki I, Takahashi K, Kinoshita K, et al. MicroRNA-145-5p and microRNA-320a encapsulated in endothelial microparticles contribute to the progression of vasculitis in acute Kawasaki disease. Sci Rep. 2018;8(1):1016.
61. Friedman RC, Farh KK, Burge CB, Bartel DP. Most mammalian mRNAs are conserved targets of microRNAs. Genome Res. 2009;19(1):92–105.
62. Kuo HC, Hsieh KS, Ming-Huey Guo M, Weng KP, Ger LP, Chan WC, et al. Next-generation sequencing identifies micro-RNA-based biomarker panel for Kawasaki disease. J Allergy Clin Immunol. 2016;138(4):1227–30.
63. Ogata S, Tremoulet AH, Sato Y, Ueda K, Shimizu C, Sun X, et al. Coronary artery outcomes among children with Kawasaki disease in the United States and Japan. Int J Cardiol. 2013;168(4):3825–8.

Treatment of Kawasaki Disease

Ling-Sai Chang

Abstract

The goal of treating acute Kawasaki disease (KD) is to treat inflammation and reduce cardiovascular sequelae by reducing the inflammation of the coronary arteries. We reviewed the clinical studies that focused on the efficacy of medications used for KD. Intravenous immunoglobulin (IVIG) is the standard treatments for KD. Some studies have the use of adjunctive corticosteroids in selective patients with KD. Corticosteroids were found to lower the progression of aneurysms in patients with *Z* scores ≥2.5. The efficacies of corticosteroids in KD remain controversial. Biologics, including etanercept and infliximab, have also been reported to exert benefits in patients with coronary artery abnormalities. Clinical trials with larger sample sizes are warranted to examine the efficacy of medications and clarify the role of acetylsalicylic acid in traditional treatments in KD.

Keywords

Coronary artery aneurysm · Corticosteroids Intravenous immunoglobulin · Kawasaki disease · Vasculitis · Treatment

L.-S. Chang (✉)
Kawasaki Disease Center and Department of Pediatrics, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan
e-mail: 8702034@cgmh.org.tw

Intravenous Immunoglobulin

The American Heart Association (AHA) proposed the guidelines for the diagnosis and management of Kawasaki disease (KD) in 2004 based on the evidence including the summary provided by the meta-analysis published in the Cochrane in 2003 and the guideline was updated in 2017 [1–3]. Intravenous immunoglobulin (IVIG) is pooled from serum IgG. High-dose IVIG was applied in the therapy of KD in Japan in 1984 [4]. Then, Newburger et al. conducted a multicenter, randomized controlled trial study (RCT) confirmed that a single high dose IVIG can, indeed, reduce the coronary-artery abnormalities to <5% in then the USA [5]. Since then, KD is considered a nonfatal disease with good prognosis. There are many ways to use IVIG at the beginning, covering IVIG 400 mg/kg daily, for 5 days, or for 3–4 days, IVIG 1 g/kg for 1 or 2 days, IVIG 200 mg/kg per day for 5 consecutive days, IVIG 50–100 mg/kg for 5 days, or IVIG 2 g/kg [3]. Statistical analysis points out that prevalence of coronary artery abnormalities in KD is highly dependent on IVIG dose [3, 6]. The 2004 and 2017 treatment guidelines recommend IVIG 2 g/kg as a single infusion, usually given over 10–12 h [1, 2]. IVIG should be administered within 7 days of fever, and give it as soon as possible after the diagnosis of KD before developing histological arteritis. In a cohort study in Japan from 2011 to 2012, among 20,933 KD patients,

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patients with IVIG administered after 7 days of fever were prone to developing coronary artery dilations compared to those with IVIG before 7 days (odds ratio: 1.66) [7]. IVIG started ≦4 days of symptoms did not reduce the formation of coronary artery dilations. KD is considered a self-limited disease because the patient will go away from fever without treatment [8]. In a retrospective study, among 293 KD patients who had a fever for 5–10 days, the risk of coronary aneurysms after 1 month was significantly higher in 37 patients without IVIG treatment than that of patients who received IVIG (18.9% vs. 5.1%) [8]. Especially in patients younger than 1 year old and with elevated white blood cells, they were a high-risk group for coronary aneurysms. A retrospective study in Japan found that among 968 patients with KD, 71 patients had initial spontaneous defervescence within 7 days. If there was no abnormal coronary artery findings and persistent inflammation, the prognosis was relatively benign [9]. The current treatment recommendations are KD patients including those with spontaneous defervescence need IVIG treatment. However, we need further research to distinguish between high-risk groups and low-risk groups that do not require IVIG treatment for patients with spontaneous defervescence.

The high dose of IVIG has the effect of regulating immunity by lowering the high-affinity receptor FcγRI and ameliorating the inflammation of KD. At the same time, it also reduces the expression of FcγRII and other low-affinity receptors [10, 11]. IVIG also avoids autoimmunity caused by the combination of autoantibodies and Fcγ receptors [12]. The role of IVIG also includes enhancing the activity of regulatory T cells, inhibiting the production of antibodies and inflammation, and balancing type 1/type 2 inflammations [13–16]. The monoclonal antibodies against IgG Fc-dependent pathways have been undergoing clinical studies one after another [12, 17].

Serious adverse effects after treatment with IVIG are quite rare [18]. In 2017, Ibrahim et al. presented a patient with KD who developed transfusion-related acute lung injury after immunoglobulin infusion [19]. The patient's condition resolved with supportive care. Kemmotsu et al. conducted a retrospective analysis, 10-year period study in KD patients treated with high dose IVIG. They observed that acute treatment with high dose IVIG was related to aseptic meningitis in 4 out of 384 patients [20]. Mention of immediate reaction after infusion, one small-sample, cross-sectional study on high dose IVIG treatment reported one child developed skin rash in the 11 pediatric patients with KD [21]. A case series conducted at a tertiary care pediatric hospital identified five KD patients with severe anemia requiring transfusion with incidence of 0.36% [22].

Acetylsalicylic Acid

Before IVIG therapy has been established as the standard treatment for KD and the invention of cardiac ultrasound, acetylsalicylic acid was once believed to reduce the mortality of KD due to its effect on thrombotic occlusion of a coronary artery [23]. High-dose acetylsalicylic acid was applied from 80 to 100 mg/kg/day in the USA to 30–50 mg/kg/day in Japan, poses anti-inflammatory effect by blocking arachidonic acid producing prostaglandin E2, and converted to low-dose acetylsalicylic acid 3–5 mg/kg/day which had antiplatelet function by blocking cyclooxygenase producing thromboxane A2 48 h after defervescence for 6–8 weeks [24]. KD patients with coronary artery abnormalities are recommended to be treated until the cardiac ultrasound is normal and the inflammation index is completely improved.

Despite the lack of evidence provided by RCT, in contrast, traditional high-dose acetylsalicylic acid was considered to have no significant therapeutic effect in a 10-year retrospective study with 260 KD children [24, 25]. But it is still necessary to understand the preventive effect of low-dose aspirin on coronary artery lesions [26]. Kuo et al. designed a multi-center, randomized controlled, evaluator-blinded trial to compare the difference of coronary artery lesions between the two groups (IVIG alone vs. IVIG plus high-dose acetylsalicylic acid at acute stage) 1 month later [27].

Kuo et al. found that high-dose acetylsalicylic acid was associated with anemia [28]. The previ-

ous study involving 609 KD patients in Taiwan showed high dose acetylsalicylic acid posed no appreciable benefit in preventing the IVIG treatment failure, the formation of coronary artery lesions, or shortening the length of hospital stay. The use of acetylsalicylic acid is most prone to side effects of the digestive system (5.3% among 910 KD patients) in a retrospective study with large sample size [29]. Bleeding in the upper and lower gastrointestinal tract and abnormal liver function have been reported, and symptoms of abdominal discomfort may appear under the treatment of acetylsalicylic acid [30].

Adjuvant Therapy: Corticosteroids

Before knowing which way to treat KD, corticosteroids alone in the treatment of acute KD increased the incidence of coronary artery lesions (CAL) [23]. However, the current goal of precision medicine is to use adjuvant therapy for patients who are predicted to respond poorly to IVIG treatment. Two meta-analyses (one is limited to RCT and the other is not limited to) try to distinguish the effect of corticosteroids in KD [31, 32]. In selected high-risk patients with KD, initial combination with corticosteroids can reduce coronary artery abnormalities [33]. A 35-year retrospective analysis in the USA found that adjuvant therapy can effectively increase the CAL regression rate [34]. When 121 children diagnosed KD with a Z score ≥ 2.5 and <10, treatment plus corticosteroids or infliximab compared with IVIG alone can reduce the deterioration of coronary artery abnormalities [35]. Newburger and colleagues investigated the efficacy of initial methylprednisolone pulse therapy (30 mg/kg) combined with following IVIG in nonselective KD patients. This RCT found coadministration of methylprednisolone and IVIG cannot decrease the risk of coronary artery abnormalities [36].

Studies have investigated the use of initial adjunctive prednisolone with respect to its treatment effect in patients with severe KD in Japan. However, the results of these trials are conflicting.

Kobayashi and colleagues conducted an RCT called RAISE study and evaluated the efficacy of adjunctive initial prednisolone in selected high-risk KD patients evaluated by Kobayashi score [37]. They found that the effect of additional prednisolone was significant for coronary artery abnormalities (4/125 patients in combination group vs. 28/123 patients in standard group, $p < 0.0001$). Analysis of large-scale data from nationwide epidemiologic KD surveys which cannot identified the severity score found significantly decreased risk (estimated risk ratio 0.53) of coronary artery abnormality (74/1593 in combination treatment group with corticosteroids added to initial standard treatment vs. 140/1593 in IVIG group) and the requirement of retreatment for treatment failure (estimated risk ratio 0.65; 225/1593 in combination treatment group with corticosteroids added to initial standard treatment vs. 234/1593 in controls) [38, 39]. However, a Post RAISE study with a multicenter, prospective cohort design did not find different coronary outcomes between patients predicted IVIG resistance using Kobayashi score treated with combination treatment consisting of prednisolone and IVIG and placebo group [40].

Because the design of risk score varies from race to race, it also affects the clinical use of corticosteroids and related research [38, 41]. Since the therapeutic effect is equivalent to secondary IVIG, corticosteroids are also considered an option for refractory KD [42, 43].

Adjuvant Therapy: Biologics

Tumor necrosis factor α (TNFα) is a well-known biomarker for KD. TNFα mediates endothelial cell activation and is involved in the CAL development [44]. Due to the breakthrough development of monoclonal antibodies, strong specificity can avoid systemic immunosuppression and other associated comorbidities [45]. Among the 16 refractory KD patients, 13 patients under infliximab were found to resolve their fever in a small series in 2005 [46]. A phase 3 RCT enrolled 196 patients and demonstrated no additional benefit of treatment resistance for the addition of infliximab, biologics as the format of chimeric murine/human IgG1, produced by hybridoma, to primary treatment in acute KD [47]. However, a meta-analysis for five RCTs with 494 participants

reported anti-TNFα has beneficial effects on treatment resistance [48]. The reduced transcripts of peptidase inhibitor-3, matrix metalloproteinase-8, chemokine receptor-2, and pentraxin-3 related to IVIG resistance after infliximab treatment support the use of infliximab in KD patients with IVIG resistance [49].

Another anti-TNF synthetic biologic, etanercept, binds only soluble TNF. A double-blind multicenter controlled trial on unselected KD patients who were treated with primary adjuvant etanercept demonstrated benefit in IVIG resistance in patients >1 year. It also has favorable effects on ameliorating coronary artery dilation in patients with baseline abnormalities (Z score > 2.5, $n = 22$ in etanercept group compared with $n = 24$ in placebo group $p = 0.03$) [50].

Adjuvant Treatments: Cyclosporin

Cyclosporin is a calcineurin inhibitor and then suppressed the activation of T cells by negative regulation of nuclear factor of activated T cells (NFAT) pathway, following signal transmission with functional polymorphism of *Inositol 1,4,5-trisphosphate 3-kinase C (ITPKC)* associated with the susceptibility and aneurysm formation in KD patients [51]. The high-risk *ITPKC* genotype involved in treatment failure is associated with the higher baseline and activated intracellular calcium and inflammatory biomarkers including IL-1β [52]. A phase 3 RCT collected 175 participants with Kobayashi risk score scale ≧5 points [53]. Combined primary therapy with IVIG and ciclosporin resulted in significantly lower incidence of CAL than IVIG group (12 [14%] of 86 patients; 27 [31%] of 87 patients; $p = 0.010$) [54].

Adjuvant Treatments: Clarithromycin

Immunological and epidemiological evidence strongly suggests characteristics of infectious disease for KD [55, 56]. *Mycoplasma pneumoniae* is the secondary bacterial etiology of pediatric pneumonia in Taiwan and may have association with KD and cardiac outcome [57, 58]. A retrospective Korean survey found 37 cases in 152 tested KD patients showed positive mycoplasma antibodies [59]. Current research cannot confirm that *Mycoplasma pneumoniae* is a possible trigger of KD or just a mere coincidental association [60].

Clarithromycin is a 14-membered ring macrolide with anti-inflammatory activity for respiratory tract infections in children [61]. In a phase 2 RCT involving nonselective patients with KD, IVIG plus clarithromycin showed the efficacy of improving relapse rate of patients (5/40 patients in additional clarithromycin group versus 12/39 patients in control group, $p = 0.046$) [61].

Second-Line Therapy of Refractory Kawasaki Disease

Refractory KD or IVIG resistance was defined as KD patients with fever ≥36 h and <7 days after the completion of their first IVIG treatment [1]. Ten to 20% of KD patients do not respond to gold standard treatment and have an increased risk of cardiovascular sequelae. Currently, there is no consensus regarding optimal adjunctive primary and second-line therapeutics for KD, especially in high-risk patients and patients with complications. Most patients still receive secondary IVIG treatment among more than 300 patients [43]. A meta-analysis identified no significant difference in the effect of intravenous pulse methylprednisolone, infliximab, or secondary IVIG on CAL [42]. Caution is still required in the use of intravenous pulse methylprednisolone due to the higher fever recurrence, higher rehospitalization rate and the higher CAL found in long-term follow-up in the methylprednisolone group [62, 63]. Infliximab's ability to reduce fever is even better than secondary IVIG [43]. The ongoing multicenter phase 3 RCT compares the therapeutic effects of infliximab and secondary IVIG on refractory KD [64]. The IL (interleukin)-1 pathway plays a significant role in KD pathogenesis. In the experimental mouse model of KD, it was found that both IL-1α and IL-1β can cause myocarditis and the

formation of aneurysm, which can be improved by anti-inflammatory drugs anakinra [52, 65]. In a phase 2, open-label study involving 16 patients with IVIG-resistant KD, anakinra, IL-1 inhibitors, showed clinical efficacy [66]. Only one patient stopped treatment because of swelling at the injection site. Highly invasive treatment of plasma exchange increases the risk of treatment. Plasma exchange is a therapeutic option (Class IIb; Level of Evidence C) reserved for patients failed to all other choices for refractory KD [1].

References

1. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, Baker AL, Jackson MA, Takahashi M, Shah PB, Kobayashi T, Wu MH, Saji TT, Pahl E. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation. 2017;135(17):e927–99. https://doi.org/10.1161/cir.0000000000000484.
2. Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, Shulman ST, Bolger AF, Ferrieri P, Baltimore RS, Wilson WR, Baddour LM, Levison ME, Pallasch TJ, Falace DA, Taubert KA. 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(17):2747–71. https://doi.org/10.1161/01.CIR.0000145143.19711.78.
3. Oates-Whitehead RM, Baumer JH, Haines L, Love S, Maconochie IK, Gupta A, Roman K, Dua JS, Flynn I. Intravenous immunoglobulin for the treatment of Kawasaki disease in children. Cochrane Database Syst Rev. 2003;(4):CD004000. https://doi.org/10.1002/14651858.Cd004000.
4. Furusho K, Sato K, Soeda T, Matsumoto H, Okabe T, Hirota T, Kawada S. High-dose intravenous gammaglobulin for Kawasaki disease. Lancet (London, England). 1983;2(8363):1359. https://doi.org/10.1016/s0140-6736(83)91109-1.
5. Newburger JW, Takahashi M, Burns JC, Beiser AS, Chung KJ, Duffy CE, Glode MP, Mason WH, Reddy V, Sanders SP, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. N Engl J Med. 1986;315(6):341–7. https://doi.org/10.1056/nejm198608073150601.
6. Terai M, Shulman ST. Prevalence of coronary artery abnormalities in Kawasaki disease is highly dependent on gamma globulin dose but independent of salicylate dose. J Pediatr. 1997;131(6):888–93. https://doi.org/10.1016/S0022-3476(97)70038-6.
7. Kuwabara M, Yashiro M, Ae R, Yanagawa H, Nakamura Y. The effects of early intravenous immunoglobulin therapy for Kawasaki disease: the 22nd nationwide survey in Japan. Int J Cardiol. 2018;269:334–8. https://doi.org/10.1016/j.ijcard.2018.07.092.
8. Hu YC, Liu HM, Lin MT, Chen CA, Chiu SN, Lu CW, Chang LY, Wang JK, Wu MH. Outcomes of Kawasaki disease children with spontaneous defervescence within 10 days. Front Pediatr. 2019;7:158. https://doi.org/10.3389/fped.2019.00158.
9. Takahashi T, Sakakibara H, Morikawa Y, Miura M. Development of coronary artery lesions in indolent kawasaki disease following initial spontaneous defervescence: a retrospective cohort study. Pediatr Rheumatol. 2015;13(1):44. https://doi.org/10.1186/s12969-015-0042-8.
10. Chang LS, Lo MH, Li SC, Yang MY, Hsieh KS, Kuo HC. The effect of FcγRIIA and FcγRIIB on coronary artery lesion formation and intravenous immunoglobulin treatment responses in children with Kawasaki disease. Oncotarget. 2017;8(2):2044–52. https://doi.org/10.18632/oncotarget.13489.
11. Chang LS, Ming-Huey Guo M, Lo MH, Kuo HC. Identification of increased expression of activating Fc receptors and novel findings regarding distinct IgE and IgM receptors in Kawasaki disease. Pediatr Res. 2021;89(1):191–7. https://doi.org/10.1038/s41390-019-0707-y.
12. Shock A, Humphreys D, Nimmerjahn F. Dissecting the mechanism of action of intravenous immunoglobulin in human autoimmune disease: lessons from therapeutic modalities targeting Fcγ receptors. J Allergy Clin Immunol. 2020;146(3):492–500. https://doi.org/10.1016/j.jaci.2020.06.036.
13. 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(4):560–5. https://doi.org/10.1067/mpd.2002.127505.
14. Wang CL, Wu YT, Liu CA, Lin MW, Lee CJ, Huang LT, Yang KD. Expression of CD40 ligand on CD4+ T-cells and platelets correlated to the coronary artery lesion and disease progress in Kawasaki disease. Pediatrics. 2003;111(2):E140–7. https://doi.org/10.1542/peds.111.2.e140.
15. Kuo HC, Wang CL, Liang CD, Yu HR, Chen HH, Wang L, Yang KD. Persistent monocytosis after intravenous immunoglobulin therapy correlated with the development of coronary artery lesions in patients with Kawasaki disease. J Microbiol Immunol Infect. 2007;40(5):395–400.
16. Shimizu C, Jain S, Davila S, Hibberd ML, Lin KO, Molkara D, Frazer JR, Sun S, Baker AL, Newburger JW, Rowley AH, Shulman ST, Burgner D, Breunis WB, Kuijpers TW, Wright VJ, Levin M, Eleftherohorinou H, Coin L, Popper SJ, Relman DA, Fury W, Lin C, Mellis S, Tremoulet AH, Burns JC. Transforming growth factor-beta signaling pathway in patients with Kawasaki disease. Circ

Cardiovasc Genet. 2011;4(1):16–25. https://doi.org/10.1161/circgenetics.110.940858.
17. Fitzpatrick EA, Wang J, Strome SE. Engineering of Fc multimers as a protein therapy for autoimmune disease. Front Immunol. 2020;11:496. https://doi.org/10.3389/fimmu.2020.00496.
18. Guo Y, Tian X, Wang X, Xiao Z. Adverse effects of immunoglobulin therapy. Front Immunol. 2018;9:1299. https://doi.org/10.3389/fimmu.2018.01299.
19. Ibrahim J, Al Amri A, Ghatasheh G. Transfusion-related acute lung injury after immunoglobulin infusion for Kawasaki disease: a case report and literature review. Glob Pediatr Health. 2017;4:2333794x17746545. https://doi.org/10.1177/2333794x17746545.
20. Kemmotsu Y, Nakayama T, Matsuura H, Saji T. Clinical characteristics of aseptic meningitis induced by intravenous immunoglobulin in patients with Kawasaki disease. Pediatr Rheumatol Online J. 2011;9:28. https://doi.org/10.1186/1546-0096-9-28.
21. Kaba S, Keskindemirci G, Aydogmus C, Siraneci R, Erol Cipe F. Immediate adverse reactions to intravenous immunoglobulin in children: a single center experience. Eur Ann Allergy Clin Immunol. 2017;49(1):11–4.
22. Luban NL, Wong EC, Henrich Lobo R, Pary P, Duke S. Intravenous immunoglobulin-related hemolysis in patients treated for Kawasaki disease. Transfusion. 2015;55(Suppl 2):S90–4. https://doi.org/10.1111/trf.13089.
23. Kato H, Koike S, Yokoyama T. Kawasaki disease: effect of treatment on coronary artery involvement. Pediatrics. 1979;63(2):175–9.
24. Chang LS, Hsu YW, Lu CC, Lo MH, Hsieh KS, Li SC, Chang WC, Kuo HC. CYP2E1 gene polymorphisms related to the formation of coronary artery lesions in Kawasaki disease. Pediatr Infect Dis J. 2017;36(11):1039–43. https://doi.org/10.1097/inf.0000000000001657.
25. Platt B, Belarski E, Manaloor J, Ofner S, Carroll AE, John CC, Wood JB. Comparison of risk of recrudescent fever in children with Kawasaki disease treated with intravenous immunoglobulin and low-dose vs high-dose aspirin. JAMA Netw Open. 2020;3(1):e1918565. https://doi.org/10.1001/jamanetworkopen.2019.18565.
26. Chiang MH, Liu HE, Wang JL. Low-dose or no aspirin administration in acute-phase Kawasaki disease: a meta-analysis and systematic review. Arch Dis Child. 2021;106(7):662–8. https://doi.org/10.1136/archdischild-2019-318245.
27. Kuo HC, Guo MMH, Lo MH, Hsieh KS, Huang YH. Effectiveness of intravenous immunoglobulin alone and intravenous immunoglobulin combined with high-dose aspirin in the acute stage of Kawasaki disease: study protocol for a randomized controlled trial. BMC Pediatr. 2018;18(1):200. https://doi.org/10.1186/s12887-018-1180-1.
28. Kuo HC, Lo MH, Hsieh KS, Guo MM, Huang YH. High-dose aspirin is associated with anemia and does not confer benefit to disease outcomes in Kawasaki disease. PLoS One. 2015;10(12):e0144603. https://doi.org/10.1371/journal.pone.0144603.
29. Huang X, Huang P, Zhang L, Xie X, Xia S, Gong F, Yuan J, Jin L. Is aspirin necessary in the acute phase of Kawasaki disease? J Paediatr Child Health. 2018;54(6):661–4. https://doi.org/10.1111/jpc.13816.
30. Zheng X, Yue P, Liu L, Tang C, Ma F, Zhang Y, Wang C, Duan H, Zhou K, Hua Y, Wu G, Li Y. Efficacy between low and high dose aspirin for the initial treatment of Kawasaki disease: current evidence based on a meta-analysis. PLoS One. 2019;14(5):e0217274. https://doi.org/10.1371/journal.pone.0217274.
31. Wardle AJ, Connolly GM, Seager MJ, Tulloh RM. Corticosteroids for the treatment of Kawasaki disease in children. Cochrane Database Syst Rev. 2017;(1):Cd011188. https://doi.org/10.1002/14651858.CD011188.pub2.
32. Chen S, Dong Y, Kiuchi MG, Wang J, Li R, Ling Z, Zhou T, Wang Z, Martinek M, Purerfellner H, Liu S, Krucoff MW. Coronary artery complication in Kawasaki disease and the importance of early intervention: a systematic review and meta-analysis. JAMA Pediatr. 2016;170(12):1156–63. https://doi.org/10.1001/jamapediatrics.2016.2055.
33. Chang LS, Kuo HC. The role of corticosteroids in the treatment of Kawasaki disease. Expert Rev Anti-Infect Ther. 2020;18(2):155–64. https://doi.org/10.1080/14787210.2020.1713752.
34. Friedman KG, Gauvreau K, Hamaoka-Okamoto A, Tang A, Berry E, Tremoulet AH, Mahavadi VS, Baker A, de Ferranti SD, Fulton DR, Burns JC, Newburger JW. Coronary artery aneurysms in Kawasaki disease: risk factors for progressive disease and adverse cardiac events in the US population. J Am Heart Assoc. 2016;5(9):e003289. https://doi.org/10.1161/jaha.116.003289.
35. Dionne A, Burns JC, Dahdah N, Tremoulet AH, Gauvreau K, de Ferranti SD, Baker AL, Son MB, Gould P, Fournier A, Newburger JW, Friedman KG. Treatment intensification in patients with Kawasaki disease and coronary aneurysm at diagnosis. Pediatrics. 2019;143(6):e20183341. https://doi.org/10.1542/peds.2018-3341.
36. Newburger JW, Sleeper LA, McCrindle BW, Minich LL, Gersony W, Vetter VL, Atz AM, Li JS, Takahashi M, Baker AL, Colan SD, Mitchell PD, Klein GL, Sundel RP. Randomized trial of pulsed corticosteroid therapy for primary treatment of Kawasaki disease. N Engl J Med. 2007;356(7):663–75. https://doi.org/10.1056/NEJMoa061235.
37. Kobayashi T, Saji T, Otani T, Takeuchi K, Nakamura T, Arakawa H, Kato T, Hara T, Hamaoka K, Ogawa S, Miura M, Nomura Y, Fuse S, Ichida F, Seki M, Fukazawa R, Ogawa C, Furuno K, Tokunaga H, Takatsuki S, Hara S, Morikawa A. Efficacy of immunoglobulin plus prednisolone for prevention

of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial. Lancet (London, England). 2012;379(9826):1613–20. https://doi.org/10.1016/s0140-6736(11)61930-2.

38. Ae R, Abrams JY, Maddox RA, Schonberger LB, Nakamura Y, Kuwabara M, Makino N, Matsubara Y, Kosami K, Sasahara T, Belay ED. Corticosteroids added to initial intravenous immunoglobulin treatment for the prevention of coronary artery abnormalities in high-risk patients with Kawasaki disease. J Am Heart Assoc. 2020;9(17):e015308. https://doi.org/10.1161/jaha.119.015308.
39. Burns JC. Revisiting once again steroids for the treatment of acute Kawasaki disease. J Am Heart Assoc. 2020;9(17):e018300. https://doi.org/10.1161/jaha.120.018300.
40. Miyata K, Kaneko T, Morikawa Y, Sakakibara H, Matsushima T, Misawa M, Takahashi T, Nakazawa M, Tamame T, Tsuchihashi T, Yamashita Y, Obonai T, Chiga M, Hori N, Komiyama O, Yamagishi H, Miura M. Efficacy and safety of intravenous immunoglobulin plus prednisolone therapy in patients with Kawasaki disease (Post RAISE): a multicentre, prospective cohort study. Lancet Child Adolesc Health. 2018;2(12):855–62. https://doi.org/10.1016/s2352-4642(18)30293-1.
41. Son MBF, Gauvreau K, Tremoulet AH, Lo M, Baker AL, de Ferranti S, Dedeoglu F, Sundel RP, Friedman KG, Burns JC, Newburger JW. Risk model development and validation for prediction of coronary artery aneurysms in Kawasaki disease in a North American population. J Am Heart Assoc. 2019;8(11):e011319. https://doi.org/10.1161/jaha.118.011319.
42. Chan H, Chi H, You H, Wang M, Zhang G, Yang H, Li Q. Indirect-comparison meta-analysis of treatment options for patients with refractory Kawasaki disease. BMC Pediatr. 2019;19(1):158. https://doi.org/10.1186/s12887-019-1504-9.
43. Crayne CB, Mitchell C, Beukelman T. Comparison of second-line therapy in IVIg-refractory Kawasaki disease: a systematic review. Pediatr Rheumatol Online J. 2019;17(1):77. https://doi.org/10.1186/s12969-019-0380-z.
44. Chaudhary H, Nameirakpam J, Kumrah R, Pandiarajan V, Suri D, Rawat A, Singh S. Biomarkers for Kawasaki disease: clinical utility and the challenges ahead. Front Pediatr. 2019;7:242. https://doi.org/10.3389/fped.2019.00242.
45. Lu RM, Hwang YC, Liu IJ, Lee CC, Tsai HZ, Li HJ, Wu HC. Development of therapeutic antibodies for the treatment of diseases. J Biomed Sci. 2020;27(1):1. https://doi.org/10.1186/s12929-019-0592-z.
46. Burns JC, Mason WH, Hauger SB, Janai H, Bastian JF, Wohrley JD, Balfour I, Shen CA, Michel ED, Shulman ST, Melish ME. Infliximab treatment for refractory Kawasaki syndrome. J Pediatr. 2005;146(5):662–7. https://doi.org/10.1016/j.jpeds.2004.12.022.
47. Tremoulet AH, Jain S, Jaggi P, Jimenez-Fernandez S, Pancheri JM, Sun X, Kanegaye JT, Kovalchin JP, Printz BF, Ramilo O, Burns JC. Infliximab for intensification of primary therapy for Kawasaki disease: a phase 3 randomised, double-blind, placebo-controlled trial. Lancet. 2014;383(9930):1731–8. https://doi.org/10.1016/S0140-6736(13)62298-9.
48. Yamaji N, da Silva Lopes K, Shoda T, Ishitsuka K, Kobayashi T, Ota E, Mori R. TNF-α blockers for the treatment of Kawasaki disease in children. Cochrane Database Syst Rev. 2019;8(8):Cd012448. https://doi.org/10.1002/14651858.CD012448.pub2.
49. Ogihara Y, Ogata S, Nomoto K, Ebato T, Sato K, Kokubo K, Kobayashi H, Ishii M. Transcriptional regulation by infliximab therapy in Kawasaki disease patients with immunoglobulin resistance. Pediatr Res. 2014;76(3):287–93. https://doi.org/10.1038/pr.2014.92.
50. Portman MA, Dahdah NS, Slee A, Olson AK, Choueiter NF, Soriano BD, Buddhe S, Altman CA. Etanercept with IVIg for acute Kawasaki disease: a randomized controlled trial. Pediatrics. 2019;143(6):e20183675. https://doi.org/10.1542/peds.2018-3675.
51. Kuo HC, Yang KD, Juo SH, Liang CD, Chen WC, Wang YS, Lee CH, Hsi E, Yu HR, Woon PY, Lin IC, Huang CF, Hwang DY, Lee CP, Lin LY, Chang WP, Chang WC. ITPKC single nucleotide polymorphism associated with the Kawasaki disease in a Taiwanese population. PLoS One. 2011;6(4):e17370. https://doi.org/10.1371/journal.pone.0017370.
52. Dusser P, Koné-Paut I. IL-1 inhibition may have an important role in treating refractory Kawasaki disease. Front Pharmacol. 2017;8:163. https://doi.org/10.3389/fphar.2017.00163.
53. Aoyagi R, Hamada H, Sato Y, Suzuki H, Onouchi Y, Ebata R, Nagashima K, Terauchi M, Terai M, Hanaoka H, Hata A. Study protocol for a phase III multicentre, randomised, open-label, blinded-end point trial to evaluate the efficacy and safety of immunoglobulin plus cyclosporin A in patients with severe Kawasaki disease (KAICA Trial). BMJ Open. 2015;5(12):e009562. https://doi.org/10.1136/bmjopen-2015-009562.
54. Erratum: Efficacy of primary treatment with immunoglobulin plus ciclosporin for prevention of coronary artery abnormalities in patients with Kawasaki disease predicted to be at increased risk of non-response to intravenous immunoglobulin (KAICA): a randomised controlled, open-label, blinded-endpoints, phase 3 trial (Lancet. 2019;393(10176):1128–37. PII: S0140673618320038. DOI: https://doi.org/10.1016/S0140-6736(18)32003-8). Lancet. 2019;393(10180):1504. https://doi.org/10.1016/S0140-6736(19)30810-4.
55. Kuo HC, Pan CT, Huang YH, Huang FC, Lin YS, Li SC, Huang LH. Global investigation of immune repertoire suggests Kawasaki disease has infectious cause. Circ J. 2019;83(10):2070–8. https://doi.org/10.1253/circj.CJ-19-0206.
56. Huang YH, Lin KM, Ho SC, Yan JH, Lo MH, Kuo HC. Increased incidence of Kawasaki

disease in Taiwan in recent years: a 15 years nationwide population-based cohort study. Front Pediatr. 2019;7:121. https://doi.org/10.3389/fped.2019.00121.
57. Chi H, Huang YC, Liu CC, Chang KY, Huang YC, Lin HC, Chang LY, Ho YH, Tsao KC, Mu JJ, Huang LM, Hsieh YC. Characteristics and etiology of hospitalized pediatric community-acquired pneumonia in Taiwan. J Formos Med Assoc. 2020;119(10):1490–9. https://doi.org/10.1016/j.jfma.2020.07.014.
58. Tang Y, Gao X, Shen J, Sun L, Yan W. Epidemiological and clinical characteristics of Kawasaki disease and factors associated with coronary artery abnormalities in east China: nine years experience. J Trop Pediatr. 2016;62(2):86–93. https://doi.org/10.1093/tropej/fmv077.
59. Park HR, Han MY, Yoon KL, Cha SH, Moon SK, Jung HW. Mycoplasma infection as a cause of persistent fever after intravenous immunoglobulin treatment of patients with Kawasaki disease: frequency and clinical impact. Infect Chemother. 2017;49(1):38–43. https://doi.org/10.3947/ic.2017.49.1.38.
60. Vitale EA, La Torre F, Calcagno G, Infricciori G, Fede C, Conti G, Chimenz R, Falcini F. Mycoplasma pneumoniae: a possible trigger of kawasaki disease or a mere coincidental association? Report of the first four Italian cases. Minerva Pediatr. 2010;62(6):605–7.
61. Nanishi E, Nishio H, Takada H, Yamamura K, Fukazawa M, Furuno K, Mizuno Y, Saigo K, Kadoya R, Ohbuchi N, Onoe Y, Yamashita H, Nakayama H, Hara T, Ohno T, Takahashi Y, Hatae K, Harada T, Shimose T, Kishimoto J, Ohga S, Hara T. Clarithromycin plus intravenous immunoglobulin therapy can reduce the relapse rate of Kawasaki disease: a phase 2, open-label, randomized control study. J Am Heart Assoc. 2017;6(7):e005370. https://doi.org/10.1161/jaha.116.005370.
62. Wang Z, Chen F, Wang Y, Li W, Xie X, Liu P, Zhang X, Zhang L, Huang P. Methylprednisolone pulse therapy or additional IVIG for patients with IVIG-resistant Kawasaki disease. J Immunol Res. 2020;2020:4175821. https://doi.org/10.1155/2020/4175821.
63. Furukawa T, Kishiro M, Akimoto K, Nagata S, Shimizu T, Yamashiro Y. Effects of steroid pulse therapy on immunoglobulin-resistant Kawasaki disease. Arch Dis Child. 2008;93(2):142–6. https://doi.org/10.1136/adc.2007.126144.
64. Roberts SC, Jain S, Tremoulet AH, Kim KK, Burns JC, Anand V, Anderson M, Ang J, Ansusinha E, Arditi M, Ashouri N, Bartlett A, Chatterjee A, DeBiasi R, Dekker C, DeZure C, Didion L, Dominguez S, El Feghaly R, Erdem G, Halasa N, Harahsheh A, Jackson MA, Jaggi P, Jain S, Jone PN, Kaushik N, Kurio G, Lillian A, Lloyd D, Manaloor J, McNelis A, Michalik DE, Newburger J, Newcomer C, Perkins T, Portman M, Romero J, Ronis T, Rowley A, Schneider K, Schuster J, Tejtel SKS, Sharma K, Simonsen K, Szmuszkovicz J, Truong D, Wood J, Yeh S. The Kawasaki Disease Comparative Effectiveness (KIDCARE) trial: a phase III, randomized trial of second intravenous immunoglobulin versus infliximab for resistant Kawasaki disease. Contemp Clin Trials. 2019;79:98–103. https://doi.org/10.1016/j.cct.2019.02.008.
65. Gorelik M, Lee Y, Abe M, Andrews T, Davis L, Patterson J, Chen S, Crother TR, Aune GJ, Noval Rivas M, Arditi M. IL-1 receptor antagonist, anakinra, prevents myocardial dysfunction in a mouse model of Kawasaki disease vasculitis and myocarditis. Clin Exp Immunol. 2019;198(1):101–10. https://doi.org/10.1111/cei.13314.
66. Koné-Paut I, Tellier S, Belot A, Brochard K, Guitton C, Marie I, Meinzer U, Cherqaoui B, Galeotti C, Boukhedouni N, Agostini H, Arditi M, Lambert V, Piedvache C. Phase II open label study of anakinra in intravenous immunoglobulin-resistant Kawasaki disease. Arthritis Rheumatol. 2021;73(1):151–61. https://doi.org/10.1002/art.41481.

Precision Medicine and Big Data Research of Kawasaki Disease

Ming-Chih Lin

Abstract

Big data has now been applied to solve questions that clinical rials cannot be performed due to technical and ethical reasons, length of follow-up, or cost. In Kawasaki disease, it has been commonly applied to estimate the incidence, complication rate, and recurrent rate. Insurance claim data was usually used as the data source. However, the validity of physicians' coding has seldom been checked. The incidence, recurrent rate, and recurrence rate were significantly overestimated while using main diagnosis code alone. Moreover, the peak season may also been misinterpreted. To solve this problem, adding immunoglobulin prescription along with the main diagnosis code to define acute episodes can help to reduce misclassification. A randomized controlled trial for head-to-head comparison between different immunoglobulin is almost impossible. A nationwide longitudinal follow-up study from National Health Insurance claim data can solve this problem. The effectiveness of immunoglobulin may differ among different manufacturing processes. Beta-propiolactonation causes a higher risk of treatment failure and prolonged use of antiplatelet agents or anticoagulants. Acidification for storage may cause more coronary aneurysms. Early immunoglobulin therapy may induce a higher recurrence rate. Using big data to perform a two-generation study gives us further insight into the pathogenesis of Kawasaki disease. The inherited tendency toward immune disorder was proved to be a key factor for the pathogenesis. In the era of precision medicine, a precise biomarker will be developed for diagnosis and monitoring therapeutic effect. Through understanding the genetic contribution to Kawasaki disease, we could ultimately prevent the disease or its sequelae.

Keywords

Big data · Incidence · Immunoglobulin
Genetic predisposition

Big Data and Precision Medicine

"Big data" once referred to available information which increases rapidly in volume, variety, and velocity. However, the terms "data analytics" and "data science" have now been considered for the same [1]. Electronic health record has been widely applied for clinical care, billing, and auditing. It rapidly rises in size. It can be used to general evidence on a large scale at virtually zero cost [2]. Most importantly, it can solve certain

M.-C. Lin (✉)
Children's Medical Center, Taichung Veterans General Hospital, Taichung, Taiwan
e-mail: mingclin@vghtc.gov.tw

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questions that clinical trials cannot be performed due to technical and ethical reasons, length of follow-up, or cost.

Using Big Data for Kawasaki Disease Incidence Estimation

Kawasaki disease is now the most common cause of acquired heart disease in children in most industrialized countries [3–11]. Its complications can range from temporary changes in the coronary arteries, small coronary aneurysms to huge coronary aneurysms [12, 13]. Therefore, estimating the incidence of Kawasaki disease is very important for understanding the burden of the disease and formulating policies.

The incidence rate of different countries has been published many times in the literature. Japan has the highest incidence rate. Its incidence rate is increasing year by year. In 2009, it was 206.2 per 100,000 children under the age of five, and in 2010 it reached 239.6 [11, 14]. South Korea has the second place, around 69 [10]. There is no national survey literature published in China, and the regional incidence rate has been published. In Beijing, it is about 40.9–55.1 [3], and Hong Kong is about 39 [15]. The state of Hawaii in the USA is about 45.2–47.7 [16, 17], and the rest of the USA is about 9.4–17.3 [17–21]. Other European and American predominantly white countries are also in this range [5, 8, 22]. It can be concluded that it has a high incidence in Northeast Asia, and is related to the genes of Northeast Asians, and its high incidence does not disappear due to immigration, as can be seen from the Hawaii report [16, 17].

Most of these published reports come from secondary claim databases or from questionnaire surveys. Only a few countries such as New Zealand have a nationwide login system [5].

The Validity of Claim Data

In most studies, inpatients with an International Classification of Diseases, ninth Revision (ICD9) of 446.1 or tenth Revision (ICD10) of M30.3 as the main diagnosis are regarded as confirmed patients. There are only two reports from those assessing the correctness of the diagnosis. One is a Japanese questionnaire. The researcher compared the inconsistencies between the two questionnaires as a reliability assessment and asked the information provider to correct the inconsistencies. The degree of inconsistence was not described [11]. The other report from Georgia reviewed the medical record to determine the accuracy of the diagnosis, but it did not describe the actual inconsistency [22].

The main reasons why these studies lack reliability and validity analysis are as follows: (1) There is no laboratory gold standard for diagnosis of Kawasaki disease, such as pathological slices, so research on sensitivity and specificity is actually quite difficult to conduct. (2) The secondary database often involves the issue of patient privacy. Anonymous analysis is required, which makes it impossible to analyze the validity of the diagnosis. (3) To check the validity of a national-level huge database will consume a lot of manpower and material resources. (4) Researchers generally believe that the probability of error in such claim data is relatively low, especially for special diagnoses such as Kawasaki disease.

If we use the incidence estimation of Taiwan as example. The statistics of questionnaire survey of contract hospitals by the Taiwan Society of Pediatric Cardiology is 54.9 per 100,000 child-years of children under the age of five. However, the analysis of the national health insurance claim data is 66–69 [7, 23, 24]. The possible reasons for the discrepancy between the results reported by these two sources are as follows: (1) The hospital questionnaire survey is regarded as incomplete and will omit some. At the same time, it will repeatedly calculate the patients referred between hospitals. On the one hand, it may be underestimated, and on the other hand, it may be overestimated. IF the accuracy has not been reviewed and evaluated by medical records, it is quite difficult to control the direction of error. (2) Because National Health Insurance (NHI) has been implemented in Taiwan since 1996 and covers more than 99% of Taiwan population, the epidemiological information analyzed from

the health insurance database is considered to be more complete and more reliable at the same time [25, 26]. However, most reports only analyzed the inpatient files using the International Classification of Diseases coding. Such an analysis may overestimate the incidence of the disease. The reasons are as follows: (1) Physicians are likely to classify Kawasaki disease as the main diagnosis even if the patient is not hospitalized due to an acute attack of Kawasaki disease, such as for angiography, coronary interventional therapy, and computer tomography. (2) In order to avoid peer review, doctors often list Kawasaki disease as the main diagnosis, so that patients can undergo expensive examinations, such as cardiac ultrasound. (3) Kawasaki disease has been listed as one catastrophic disease by the National Health Insurance life-long. When Kawasaki disease patients are admitted due to other diseases such as pneumonia and gastroenteritis, doctors often list Kawasaki disease as the main diagnosis to help patients avoid copayment.

Complication Rate Estimation

Kawasaki disease is an acute systemic vasculitis that mainly occurs in infants and young children. Before high-dose immunoglobulin therapy was widely used to treat this disease, the reported complication rate (coronary artery hemangioma) was as high as 15–25% [27, 28]. Coronary artery aneurysm can cause myocardial infarction, sudden death, or ischemic heart disease. Even using high-dose immunoglobulin therapy, about 5% of patients will still develop coronary aneurysms, and 1% of them will develop giant aneurysms [29–31].

In Taiwan, it has been reported that between 2003 and 2006, the incidence of coronary aneurysms in all age groups ranged from 6% to 35%, and the older the age, the higher the complication rate [7]. It seems that the treatment effect in Taiwan seems to be inferior to that of foreign countries, especially the USA and Japan. But if we study the authors' research method carefully, we will find that there are errors in the method of study. Since the authors of this article use the National Health Insurance database for analysis, if a child has Kawasaki disease at an early age, the doctor is likely to hospitalize the patient for examination at school age. At this time, the admission diagnosis code will naturally include the main diagnosis of Kawasaki disease and the secondary diagnosis code of coronary aneurysm. However, this does not mean that these are acute patients. Although there are similar reports in the USA, and age is a risk factor for coronary aneurysm [32], the complication rate of up to 35% in some age groups is still significantly overestimated.

Recurrence Rates

In Taiwan, the recurrence rate of Kawasaki disease was published by Huang et al. using the national health insurance secondary declaration data, which is about 1.5% [7]. In comparison with approximately 3–3.6% by the questionnaire survey in Japan, the recurrence rate in Taiwan is significantly lower [11, 14]. However, the research method has several problems: (1) Because the authors only analyzed the claim data from 2003 to 2006, the patients in 2005 and 2006 must have insufficient tracking time, which led to the phenomenon of censoring (lost follow-up) in a considerable number of patients. (2) The authors used only the main diagnosis code to define the incidence of acute attacks of Kawasaki disease, which is quite unreliable and dangerous. The doctor may give the main diagnosis Kawasaki disease in order to avoid peer review, or the patient may not have an acute attack at all, but is just admitted to the hospital for follow-up diagnosis and treatment. These may make the recurrence rate of Kawasaki disease overestimated. On the one hand, it may be underestimated, and on the other hand, it may be overestimated. So it is quite difficult to control the direction of error.

How to Estimate the Incidence Accurately by Big Data

Because the immunoglobulin therapy is covered by Taiwan National Health Insurance, almost all

patients with acute Kawasaki disease receive it. By defining Kawasaki disease incidence case as the main diagnosis of Kawasaki disease (ICD9 446.1, ICD10 M30.3) and receiving immunoglobulin therapy, the problem of misclassification can be greatly reduced. From 1997 to 2008, when estimated by the inpatients with diagnosis code, the annual incidence rate in Taiwan is approximately 48.5–78.3 per 100,000 children under 5 years of age. When using the main diagnosis code plus immunoglobulin therapy to define the incidence rate, the incidence rate is approximately 21.5–63.9 annually. The overall difference in the estimated incidence of the two case definition methods is about 1.6:1. During the Taiwan SARS (severe acute respiratory syndrome) outbreak in 2003, the difference was even higher, 2.31–2.46:1. By defining acute Kawasaki disease as the main diagnosis code plus immunoglobulin therapy, the incidence rate significantly reduced by quarantine [33]. It fulfilled the superantigen theory and the initial reports during the COVID-19 outbreak [33, 34].

For the recurrence rate estimation, it can be seen that if acute admission is defined by the main diagnosis code alone, as many as 1.11% of patients can be hospitalized up to three times. On the other hand, while defining incidence cases by the main diagnosis code plus immunoglobulin therapy, only 0.04% of patients have had more than three treatments, which is more in line with the general clinical experience. Only very few patients will relapse more than twice. In the comparison of survival analysis with two different definition methods, the gap between the two is statistically significant. The 5-year cumulative recurrence rates were 3.2% by the main diagnosis code alone and 1.1% by the main diagnosis code plus immunoglobulin therapy [33].

Head-to-Head Comparison of Different Immunoglobulins from Big Data Research

Intravenous immunoglobulins are the most important medicine for treating Kawasaki disease. However, immunoglobulins are extracted from the blood of many donors. Although the World Health Organization has certain regulations for the manufacture of immunoglobulins (at least 1000 donors are required, 90% of the IgG must be preserved intact, and the subclassification must be consistent with normality, it is necessary to screen for the known viruses, hepatitis B, hepatitis C, and human immunodeficiency virus, etc.) [35]. However, immunoglobulins of different brands are different in terms of manufacturing process, purification method, IgA concentration, and storage method [35–40]. These slight differences have led to some reports of side effects and complications, such as reports of severe allergic immune reactions due to higher IgA or IgM components [39, 41], or the spread of hepatitis caused by process problems [42, 43].

In terms of efficacy, in a 1995 retrospective paired study published in the USA (n = 45), the authors compared the efficacy of two brands, Venoglobulin I and Iveegam, and found that Iveegam had shorter fever days and less side effects [44]. The actual reason is not deduced by the authors, but the retrospective matching study and the limited number of patients have restricted the empirical value of the research.

In a study published in 2006, comparing the efficacy of four immunoglobulins, including Venoglobulin S, Gamimune, Intraglobin F, and SNBTSPF Center CBSF, the authors found that Intraglobin F had a higher treatment failure rate. The authors concluded that it was due to enzyme processing, which in turn causes the Fc portion of immunoglobulin to be changed. It may affect the binding of Fc portion and macrophage, and change the release of interleukin-1, thereby affecting the immunoregulatory efficacy [38]. The number of cases in this study is large enough, but because it is a single hospital, the collection of the four groups of patients was not in the same age, and the number of patients in each group was quite different, and there was a lack of long-term follow-up data. In a report by Kuo et al. in 2007, there was no difference between the labels. However, the authors only used eosinophils as the endpoint, and the number of patients was limited [45, 46].

In 2010, Manlhiot et al. compared Ivvegam (nonacidic solution) and Gamimune (acidic solution), and found that Gamimune has a lower

treatment failure rate, shorter hospital stays, but a higher incidence of coronary aneurysms [40]. The authors' inference is that Gamimune is stored in an acidic solution, and large amounts of injection will affect the tension of the blood vessels, especially when the coronary arteries are inflamed. The elastin may be damaged, which causes more coronary aneurysms [47–49].

A randomized controlled trial for head-to-head comparison between different brands of immunoglobulin is almost impossible in Kawasaki disease because immunoglobulin therapy is a well-recognized therapy for Kawasaki disease. In these circumstances, a nationwide longitudinal follow-up study from National Health Insurance claim data can solve this problem. Lin et al. enrolled children under 2 years of age who received immunoglobulin therapy for the first time with the main diagnosis of Kawasaki disease. The authors concluded that the effectiveness of immunoglobulin may differ among different manufacturing processes. Beta-propiolactonation causes a higher risk of treatment failure and prolonged use of antiplatelet agents or anticoagulants. Acidification for storage may cause more coronary aneurysms [50].

Comparing Timing of Immunoglobulin Therapy by Big Data

For the timing of IVIG treatment, physicians mostly follow the guidelines endorsed by the American Heart Association and American Academy of Pediatrics in 2004 and 2017 [51, 52]. It was suggested that IVIG should be given within the 10 days after the first fever episode, if possible, within 7 days. However, whether earlier treatment before day 5 of illness can prevent cardiac sequelae than treatment between days 5 and 7 has no definite answers. Two researches have even reported that it may increase the need for IVIG retreatment [52]. One is a questionnaire study from Japan [53]. The other is a single-institution research in Hong Kong [54]. Nonetheless, better coronary outcomes by earlier IVIG therapy has ever been reported [55].

Using Taiwan NHIRD big data, by defining febrile duration as the date of acetaminophen (ATC code N02BE) or nonsteroidal anti-inflammatory drugs (ATC code M01A) prescription and the date of admission, early IVIG therapy did not demonstrate any better outcomes. On the other hand, it might induce a higher recurrence rate in the long-term follow-up [56].

Genetic Predisposition to Kawasaki Disease from the Perspective of Big Data

Genetic susceptibility and immune dysregulation play important roles in Kawasaki disease pathogenesis [57–59]. Genetic susceptibility linked to genes associated with the immune system has also been reported [51, 60, 61]. Children of Kawasaki disease have a tendency to develop atopy diseases [62, 63]. However, it is still not answered whether Kawasaki disease causes immune disorder later in life or inherited susceptibility toward immune disorders causes Kawasaki disease. When linking claim data of National Health Insurance of Taiwan and Taiwan Maternal and Child Health Database (MCHD), a longitudinal transgenerational population-based study can be done. It concludes that children of mothers with immune disorders tend to have a higher risk of Kawasaki disease [64]. This study provides a strong evidence that inherited tendency toward immune disorder is a key factor for Kawasaki disease pathogenesis. This kind of two-generation study could not be performed unless using big data as the source of analysis [65].

Future Perspectives for Precision Medicine for Kawasaki Disease

Researchers are eager to find new biomarkers for Kawasaki disease to improve the diagnosis accuracy and therapeutic effect. For example, INF-r-inducible protein 10 (IP-10) has been found to have high area under the receiver operating characteristic (ROC) curve values for diagnosis of Kawasaki disease. Moreover, IP-10 level can be

applied for monitoring immunoglobulin therapy efficacy [66]. Along with other new biomarkers, physicians can have more precise information for diagnosis and treatment [66–68].

The susceptibility of genetic Kawasaki disease has been widely studied in recent years, in studies such as ITPKC by sibling linkage analysis [69]; NAALADL2 and ZFHX2 in Caucasian patients [70]; COPB2 and ERAP1 in Han patients [71, 72]; and CD40, BLK, and FCGR2A in Japanese patients by genome-wide association study (GWAS) [73, 74]. Based on these findings, researchers need to clarify the interaction between these genetic susceptibilities. Furthermore, the association with infectious agents should be studied from the perspective of the superantigen theory [75].

In the era of precision medicine, owing to the rapid development of biotechnology, we can optimistically expect precise biomarkers for diagnosis and for monitoring therapeutic effects of Kawasaki disease. Moreover, by understanding the genetic contributions to Kawasaki disease, we can ultimately prevent the disease or its sequelae [76].

References

1. Hulsen T, Jamuar SS, Moody AR, et al. From big data to precision medicine. Front Med (Lausanne). 2019;6:34.
2. Hemingway H, Asselbergs FW, Danesh J, et al. Big data from electronic health records for early and late translational cardiovascular research: challenges and potential. Eur Heart J. 2018;39(16):1481–95.
3. Du ZD, Zhao D, Du J, et al. Epidemiologic study on Kawasaki disease in Beijing from 2000 through 2004. Pediatr Infect Dis J. 2007;26(5):449–51.
4. Fischer TK, Holman RC, Yorita KL, Belay ED, Melbye M, Koch A. Kawasaki syndrome in Denmark. Pediatr Infect Dis J. 2007;26(5):411–5.
5. Heaton P, Wilson N, Nicholson R, Doran J, Parsons A, Aiken G. Kawasaki disease in New Zealand. J Paediatr Child Health. 2006;42(4):184–90.
6. 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(6):483–8.
7. Huang WC, Huang LM, Chang IS, et al. Epidemiologic features of Kawasaki disease in Taiwan, 2003–2006. Pediatrics. 2009;123(3):e401–5.
8. Lynch M, Holman RC, Mulligan A, Belay ED, Schonberger LB. Kawasaki syndrome hospitalizations in Ireland, 1996 through 2000. Pediatr Infect Dis J. 2003;22(11):959–63.
9. Porcalla AR, Sable CA, Patel KM, Martin GR, Singh N. The epidemiology of Kawasaki disease in an urban hospital: does African American race protect against coronary artery aneurysms? Pediatr Cardiol. 2005;26(6):775–81.
10. Park YW, Han JW, Park IS, et al. Kawasaki disease in Korea, 2003–2005. Pediatr Infect Dis J. 2007;26(9):821–3.
11. Yanagawa H, Nakamura Y, Yashiro M, Uehara R, Oki I, Kayaba K. Incidence of Kawasaki disease in Japan: the nationwide surveys of 1999–2002. Pediatr Int. 2006;48(4):356–61.
12. Lin MC, Hsu CM, Fu YC. Giant coronary aneurysms developed in a child of Kawasaki disease with only 3 days of fever. Cardiol Young. 2010;20(3):339–41.
13. Senzaki H. Long-term outcome of Kawasaki disease. Circulation. 2008;118(25):2763–72.
14. Nakamura Y, Yashiro M, Uehara R, et al. Epidemiologic features of Kawasaki disease in Japan: results of the 2009–2010 nationwide survey. J Epidemiol. 2012;22(3):216–21.
15. Ng YM, Sung RY, So LY, et al. Kawasaki disease in Hong Kong, 1994 to 2000. Hong Kong Med J. 2005;11(5):331–5.
16. Holman RC, Curns AT, Belay ED, et al. Kawasaki syndrome in Hawaii. Pediatr Infect Dis J. 2005;24(5):429–33.
17. Holman RC, Shahriari A, Effler PV, Belay ED, Schonberger LB. Kawasaki syndrome hospitalizations among children in Hawaii and Connecticut. Arch Pediatr Adolesc Med. 2000;154(8):804–8.
18. Belay ED, Holman RC, Clarke MJ, et al. The incidence of Kawasaki syndrome in West Coast health maintenance organizations. Pediatr Infect Dis J. 2000;19(9):828–32.
19. Belay ED, Holman RC, Maddox RA, Foster DA, Schonberger LB. Kawasaki syndrome hospitalizations and associated costs in the United States. Public Health Rep. 2003;118(5):464–9.
20. Holman RC, Belay ED, Curns AT, Schonberger LB, Steiner C. Kawasaki syndrome hospitalizations among children in the United States, 1988–1997. Pediatrics. 2003;111(2):448.
21. Holman RC, Curns AT, Belay ED, Steiner CA, Schonberger LB. Kawasaki syndrome hospitalizations in the United States, 1997 and 2000. Pediatrics. 2003;112(3 Pt 1):495–501.
22. Gibbons RV, Parashar UD, Holman RC, et al. An evaluation of hospitalizations for Kawasaki syndrome in Georgia. Arch Pediatr Adolesc Med. 2002;156(5):492–6.
23. Chang LY, Chang IS, Lu CY, et al. Epidemiologic features of Kawasaki disease in Taiwan, 1996–2002. Pediatrics. 2004;114(6):e678–82.
24. Lue HC, Philip S, Chen MR, Wang JK, Wu MH. Surveillance of Kawasaki disease in Taiwan

and review of the literature. Acta Paediatr Taiwan. 2004;45(1):8–14.
25. Wen CP, Tsai SP, Chung WS. A 10-year experience with universal health insurance in Taiwan: measuring changes in health and health disparity. Ann Intern Med. 2008;148(4):258–67.
26. Lin MC, Lai MS. Pediatricians' role in caring for preschool children in Taiwan under the national health insurance program. J Formos Med Assoc. 2009;108(11):849–55.
27. Dajani AS, Taubert KA, Gerber MA, et al. Diagnosis and therapy of Kawasaki disease in children. Circulation. 1993;87(5):1776–80.
28. Kato H, Sugimura T, Akagi T, et al. Long-term consequences of Kawasaki disease. A 10- to 21-year follow-up study of 594 patients. Circulation. 1996;94(6):1379–85.
29. Dajani AS, Taubert KA, Takahashi M, et al. Guidelines for long-term management of patients with Kawasaki disease. Report from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation. 1994;89(2):916–22.
30. Durongpisitkul K, Gururaj VJ, Park JM, Martin CF. The prevention of coronary artery aneurysm in Kawasaki disease: a meta-analysis on the efficacy of aspirin and immunoglobulin treatment. Pediatrics. 1995;96(6):1057–61.
31. Terai M, Shulman ST. Prevalence of coronary artery abnormalities in Kawasaki disease is highly dependent on gamma globulin dose but independent of salicylate dose. J Pediatr. 1997;131(6):888–93.
32. Belay ED, Maddox RA, Holman RC, Curns AT, Ballah K, Schonberger LB. Kawasaki syndrome and risk factors for coronary artery abnormalities: United States, 1994–2003. Pediatr Infect Dis J. 2006;25(3):245–9.
33. Lin MC, Lai MS, Jan SL, Fu YC. Epidemiologic features of Kawasaki disease in acute stages in Taiwan, 1997–2010: effect of different case definitions in claims data analysis. J Chin Med Assoc. 2015;78(2):121–6.
34. Kang J-M, Kim Y-E, Huh K, et al. Reduction in Kawasaki disease after nonpharmaceutical interventions in the COVID-19 era: a nationwide observational study in Korea. Circulation. 2021;143(25):2508–10.
35. Bonilla F, Geha R. Intravenous immunoglobulin therapy. In: Austen KF, editor. Therapeutic immunology. 2nd ed. Malden: Blackwell Science; 2001. p. 264–86.
36. Gelfand EW. Differences between IGIV products: impact on clinical outcome. Int Immunopharmacol. 2006;6(4):592–9.
37. Stiehm ER. Lessons from Kawasaki disease: all brands of IVIG are not equal. J Pediatr. 2006;148(1):6–8.
38. Tsai MH, Huang YC, Yen MH, et al. Clinical responses of patients with Kawasaki disease to different brands of intravenous immunoglobulin. J Pediatr. 2006;148(1):38–43.
39. Manlhiot C, Tyrrell PN, Liang L, Atkinson AR, Lau W, Feldman BM. Safety of intravenous immunoglobulin in the treatment of juvenile dermatomyositis: adverse reactions are associated with immunoglobulin A content. Pediatrics. 2008;121(3):e626–30.
40. Manlhiot C, Yeung RS, Chahal N, McCrindle BW. Intravenous immunoglobulin preparation type: association with outcomes for patients with acute Kawasaki disease. Pediatr Allergy Immunol. 2010;21(3):515–21.
41. Rieben R, Roos A, Muizert Y, Tinguely C, Gerritsen AF, Daha MR. Immunoglobulin M-enriched human intravenous immunoglobulin prevents complement activation in vitro and in vivo in a rat model of acute inflammation. Blood. 1999;93(3):942–51.
42. Centers for Disease Control and Prevention (CDC). Outbreak of hepatitis C associated with intravenous immunoglobulin administration—United States, October 1993–June 1994. MMWR Morb Mortal Wkly Rep. 1994;43(28):505–9.
43. Greenbaum BH. Differences in immunoglobulin preparations for intravenous use: a comparison of six products. Am J Pediatr Hematol Oncol. 1990;12(4):490–6.
44. Rosenfeld EA, Shulman ST, Corydon KE, Mason W, Takahashi M, Kuroda C. Comparative safety and efficacy of two immune globulin products in Kawasaki disease. J Pediatr. 1995;126(6):1000–3.
45. Khan S, Dore PC, Sewell WA. Both patient characteristics and IVIG product-specific mechanisms may affect eosinophils in immunoglobulin-treated Kawasaki disease. Pediatr Allergy Immunol. 2008;19(2):186–7.
46. Kuo HC, Wang CL, Wang L, Yu HR, Yang KD. Patient characteristics and intravenous immunoglobulin product may affect eosinophils in Kawasaki disease. Pediatr Allergy Immunol. 2008;19(2):184–5.
47. Lau AC, Duong TT, Ito S, Yeung RS. Matrix metalloproteinase 9 activity leads to elastin breakdown in an animal model of Kawasaki disease. Arthritis Rheum. 2008;58(3):854–63.
48. Lau AC, Rosenberg H, Duong TT, McCrindle BW, Yeung RS. Elastolytic matrix metalloproteinases and coronary outcome in children with Kawasaki disease. Pediatr Res. 2007;61(6):710–5.
49. Rowley AH, Shulman ST, Spike BT, Mask CA, Baker SC. Oligoclonal IgA response in the vascular wall in acute Kawasaki disease. J Immunol. 2001;166(2):1334–43.
50. Lin M-C, Fu Y-C, Jan S-L, Lai M-S. Comparative effectiveness of intravenous immunoglobulin for children with Kawasaki disease: a nationwide cohort study. PLoS One. 2013;8(5):e63399.
51. 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(17):e927–99.
52. 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(17):2747–71.

53. Muta H, Ishii M, Egami K, et al. Early intravenous gamma-globulin treatment for Kawasaki disease: the nationwide surveys in Japan. J Pediatr. 2004;144(4):496–9.
54. Fong NC, Hui YW, Li CK, Chiu MC. Evaluation of the efficacy of treatment of Kawasaki disease before day 5 of illness. Pediatr Cardiol. 2004;25(1):31–4.
55. Tse SM, Silverman ED, McCrindle BW, Yeung RS. Early treatment with intravenous immunoglobulin in patients with Kawasaki disease. J Pediatr. 2002;140(4):450–5.
56. Ho CL, Fu YC, Lin MC, Jan SL. Early immunoglobulin therapy and outcomes in Kawasaki disease: a nationwide cohort study. Medicine (Baltimore). 2015;94(39):e1544.
57. Takahashi K, Oharaseki T, Yokouchi Y. Update on etio and immunopathogenesis of Kawasaki disease. Curr Opin Rheumatol. 2014;26(1):31–6.
58. Menikou S, Langford PR, Levin M. Kawasaki disease: the role of immune complexes revisited. Front Immunol. 2019;10:1156.
59. Sakurai Y. Autoimmune aspects of Kawasaki disease. J Investig Allergol Clin Immunol. 2019;29(4):251–61.
60. Xie X, Shi X, Liu M. The roles of genetic factors in Kawasaki disease: a systematic review and meta-analysis of genetic association studies. Pediatr Cardiol. 2018;39(2):207–25.
61. Onouchi Y. The genetics of Kawasaki disease. Int J Rheum Dis. 2018;21(1):26–30.
62. Kuo HC, Chang WC, Yang KD, et al. Kawasaki disease and subsequent risk of allergic diseases: a population-based matched cohort study. BMC Pediatr. 2013;13:38.
63. Tsai YJ, Lin CH, Fu LS, Fu YC, Lin MC, Jan SL. The association between Kawasaki disease and allergic diseases, from infancy to school age. Allergy Asthma Proc. 2013;34(5):467–72.
64. Chu HW, Lin CH, Lin MC, Hsu YC. Increased risk of Kawasaki disease in infants born of mothers with immune disorders. Front Pediatr. 2021;9:659598.
65. Chang C-L, Lin M-C, Lin C-H, Ko T-M. Maternal and perinatal factors associated with Kawasaki disease among offspring in Taiwan. JAMA Netw Open. 2021;4(3):e213233.
66. Ko TM, Kuo HC, Chang JS, et al. CXCL10/IP-10 is a biomarker and mediator for Kawasaki disease. Circ Res. 2015;116(5):876–83.
67. Dahdah N, Siles A, Fournier A, et al. Natriuretic peptide as an adjunctive diagnostic test in the acute phase of Kawasaki disease. Pediatr Cardiol. 2009;30(6):810–7.
68. Ye Q, Shao WX, Shang SQ, Zhou MM. Value of the N-terminal of prohormone brain natriuretic peptide in diagnosis of Kawasaki disease. Int J Cardiol. 2015;178:5–7.
69. Onouchi Y, Gunji T, Burns JC, et al. ITPKC functional polymorphism associated with Kawasaki disease susceptibility and formation of coronary artery aneurysms. Nat Genet. 2008;40(1):35–42.
70. Burgner D, Davila S, Breunis WB, et al. A genome-wide association study identifies novel and functionally related susceptibility Loci for Kawasaki disease. PLoS Genet. 2009;5(1):e1000319.
71. Lee YC, Kuo HC, Chang JS, et al. Two new susceptibility loci for Kawasaki disease identified through genome-wide association analysis. Nat Genet. 2012;44(5):522–5.
72. Tsai FJ, Lee YC, Chang JS, et al. Identification of novel susceptibility Loci for Kawasaki disease in a Han chinese population by a genome-wide association study. PLoS One. 2011;6(2):e16853.
73. Khor CC, Davila S, Breunis WB, et al. Genome-wide association study identifies FCGR2A as a susceptibility locus for Kawasaki disease. Nat Genet. 2011;43(12):1241–6.
74. Khor CC, Davila S, Shimizu C, et al. Genome-wide linkage and association mapping identify susceptibility alleles in ABCC4 for Kawasaki disease. J Med Genet. 2011;48(7):467–72.
75. Suenaga T, Suzuki H, Shibuta S, Takeuchi T, Yoshikawa N. Detection of multiple superantigen genes in stools of patients with Kawasaki disease. J Pediatr. 2009;155(2):266–70.
76. KO TM; Chen YR; Wu JY. Precision medicine for kawasaki disease. Medical Research Archives, [S.l.], 2015;2(1). ISSN 2375-1924. Available at: https://esmed.org/MRA/mra/article/view/282. Date accessed: 14 may 2022.

Complication of Kawasaki Disease

Ken-Pen Weng

Abstract

Kawasaki disease (KD) is frequently complicated by the development of coronary artery lesions (CALs) and recognized as the leading cause of acquired heart disease in children. The incidence of CALS is about 15–25% of untreated KD children and 4% of those after intravenous immunoglobulin (IVIG) therapy. Other rare and less severe complications of KD may include aneurysms of medium-sized aneurysms, peripheral gangrene, peripheral facial nerve palsy, and sensorineural hearing loss. Cardiac complications of COVID-19 infection related KD are not rare, including ventricular dysfunction, coronary artery dilation and aneurysms, arrhythmia, and conduction abnormalities. Approximately 7.8–38.3% of children will have IVIG resistance and are at increased risk for development of CALs. The mechanism of IVIG resistance in KD still remains unknown and requires further study.

Keywords

Kawasaki disease · Coronary artery lesions
Intravenous immunoglobulin

K.-P. Weng (✉)
Congenital Structural Heart Disease Center, Department of Pediatrics, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan
e-mail: kpweng@vghks.gov.tw

CAA

Kawasaki disease (KD) is frequently complicated by the development of coronary artery lesions (CALs) and recognized as the leading cause of acquired heart disease in children [1]. The incidence of CALS is about 15–25% of untreated KD children [2] and 4% of those after intravenous immunoglobulin (IVIG) therapy [1, 3]. Other rare and less severe complications of KD may include aneurysms of medium sized aneurysms, peripheral gangrene, peripheral facial nerve palsy, and sensorineural hearing loss [1].

CALs during the acute stage of KD range from dilation only to aneurysms of various numbers, sizes, and characteristics. In acute stage of KD, most patients with CALs will have dilation only (Z score of <2.5). Dilation resolves within 4–8 weeks in the majority. Patients with severe CALs are few and usually asymptomatic initially, but symptoms of myocardial ischemia may develop in the case of subsequent coronary artery stenosis. McCrindle et al. reported that the risks of luminal narrowing, thrombosis, and major adverse cardiovascular complications were nearly completely confined to those with Z scores ≥10 [4]. In acute stage of KD, rare cases of rupture of a coronary artery aneurysm or severe myocardial infarction have been reported [5]. Other medium-sized artery aneurysm may occur rarely in the axillary, subclavian, brachial, femoral, iliac, and splanchnic arteries, and others [6, 7]. A classifi-

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cation of CALs based on *Z* scores [1] is recommended as follows: (1) No involvement: Always <2; (2) Dilation only: 2 to <2.5; (3) Small aneurysm: ≥2.5 to <5; (4) Medium aneurysm: ≥5 to <10, and absolute dimension <8 mm (5). Large or giant aneurysm: ≥10, or absolute dimension ≥8 mm.

Many previous research works have identified potential predictors of CAL development in KD including demographic, clinical, and laboratory variables. The identified predictors of poor coronary outcome in KD patients were as follows: IVIG resistance, anemia, hypoalbuminemia, leukocytosis with predominant neutrophil count, high C-reactive protein (CRP) level, male sex, and age younger than 1 year or older than 6 years [8–13]. Weng et al.'s study showed that the risk factors of acute CALs included neutrophil count, second dose of IVIG treatment, and platelet count, while those of chronic CALs contained age, first dose of IVIG treatment, and band count [14]. Popper et al.'s research suggested that neutrophil activation state and apoptosis might contribute to the pathogenesis of KD [15]. An influx of neutrophils develops in the early stage (7–9 days after KD onset), with a rapid transition to large mononuclear cells in concert with lymphocytes and immunoglobulin A plasma cells [16, 17]. Damage of the internal elastic lamina with subsequent fibroblastic proliferation occurs at this stage, leading to the formation and development of arteritis in KD. Beiser et al. designed an instrument to predict the potential risk of CALs among KD patients [9]. They constructed a sequential risk classification instrument based on easily measured baseline laboratory data and body temperature, including neutrophil count, and demonstrated that all low-risk patients based on this instrument did not develop CALs [9]. Masuda et al. reported male sex, recurrent KD, IVIG administration at 1–4 days of illness and ≥8 days after KD onset, detection of CA dilatations and aneurysms at initial echocardiography, and resistance to IVIG treatment were significantly associated with giant CA aneurysm complications identified after acute KD [18]. Further studies are required to elucidate the risk factors of CALs in KD.

Children with COVID-19 infection are usually mild, but may suffer from a severe inflammatory disease similar to KD a few weeks later [19]. The etiology remains unknown and postulated to be a dysregulated inflammatory response to COVID-19 infection. Typical KD often affects Asian children younger than 8 years, but COVID-19 infection related KD (multisystem inflammatory syndrome in children (MIS-C)) more affects black and Hispanic children with the mean age of 9–11 years [1, 20]. The most common symptoms of COVID-19 infection related KD are prolonged fever and gastrointestinal symptoms. Cardiac complications are not rare, including ventricular dysfunction, coronary artery dilation and aneurysms, arrhythmia, and conduction abnormalities. The potential risk of KD like inflammation and subsequent cardiac complication in children with COVID-19 infection cannot be overemphasized.

IVIG Resistance

IVIG resistance is defined as persistent or recrudescent fever at least 36 hours and <7 days after completion of first IVIG infusion. Approximately 7.8–38.3% of children will have IVIG resistance and are at increased risk for development of coronary artery abnormalities [21–26]. The mechanism of IVIG in reducing inflammation of KD is still not clear. Five possible mechanisms are suggested as follows: blocking Fc receptor, neutralizing a toxin produced by the infectious agent or the causative agents, immunomodulating effect, inducing suppressor activity, and modulating the production of cytokines and cytokine antagonists [27]. Some genetic factors such as polymorphisms in the Fc gamma receptors and IL-1B may play a role in IVIG resistance [28, 29]. IVIG could downregulate IL-1α, IL-1β, and upregulate IL-1Ra production in vitro [30]. Previous researches demonstrated that IVIG influences the production and release of IL-1 in KD patients [31, 32]. Persistence of circulating cytokines is related to IVIG resistance in KD patients [33]. Weng et al.' results may support the hypothesis that modulation of IL-1 production plays an important

role in the development of IVIG resistance [29]. The mechanism of IVIG resistance in KD still remains unknown and requires further study.

A number of previous research works have identified demographic and laboratory data, including age, illness day, platelet count, erythrocyte sedimentation rate (ESR), concentrations of hemoglobin, C-reactive protein (CRP), lactate dehydrogenase, alanine aminotransferase (ALT), initial IVIG treatment before the fifth day of illness, and recurrent KD as predictors of IVIG resistance [11, 23–26, 34–36]. Based on the abovementioned factors, several scoring systems for IVIG resistance have been constructed [11, 23–26, 34]. Fukunishi et al. showed that patients with a CRP >10 mg/dl, LDH >590 IU/L, and/or hemoglobin level <10 g/dl are considered nonresponsive to IVIG [23]. Anemia with hemoglobin <10 g/dl, high neutrophil count (>75%), high band count, and hypoalbuminemia were associated with retreatment with a second dose of IVIG according to Durongpisitkul et al.'s report [24]. For identifying IVIG resistance among KD patients, Kobayashi et al. established a seven-variable logistic model with high sensitivity and specificity as follows: day of illness at initial treatment, age in months, neutrophil count, platelet count, aspartate aminotransferase (AST), sodium (Na), and CRP [11]. Sano et al. demonstrated that KD patients with at least two of three predictors (CRP $\geq$ 7.0 mg, total bilirubin $\geq$ 0.9 mg, or AST $\geq$ 200 IU/L) are considered to be resistant to IVIG therapy in acute stage [25]. Egami et al. developed the prediction model of IVIG resistance using age, illness days, platelet count, ALT, and CRP [34]. According to the Tremoulete et al. study, the poor performance of the Egami score in the ethnically diverse KD children suggested this score system based on the cohorts of Japanese children might be not suitable for other KD patients [26]. Kaya et al. also reported that the Egami score system had a low sensitivity for predicting the risk of IVIG resistance in Turkish children [37]. Fu et al. suggested a new scoring system in Chinese children, including polymorphous rash, perianal changes, fever duration (days) at initial IVIG treatment, neutrophil percentage, CRP and albumin levels, as well as total bilirubin [38]. Compared with the Kobayashi and Egami scoring systems, this new scoring system had a higher sensitivity and specificity for Chinese children, but was not good enough to be widely used because of its low sensitivity (54.1%) [38].

Japanese Egami score system had been demonstrated to be insufficiently useful in the ethnically diverse and different racial populations [26, 37, 38]. Addition of genetic markers into the scoring system may contribute to uncover the high risk group of IVIG-resistant patients [29]. Weng et al.'s study suggested that the IL-1B -511 TT genotype, IL-1B -31 CC genotype, or their TC/TC diplotype may be the potential genetic markers of IVIG resistance in Taiwanese KD children, and could be helpful in the scoring system for IVIG resistance [29]. Further study is warranted to develop a better predictive model of IVIG resistance, perhaps including specific biomarkers or genetic markers.

References

1. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, 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.
2. Newburger JW, Takahashi M, Burns JC, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. N Engl J Med. 1986;315:341–7.
3. Hsieh KS, Weng KP, Lin CC, Huang TC, Lee CL, Huang SM. Treatment of acute Kawasaki disease: aspirin's role in the febrile stage revisited. Pediatrics. 2004;114:e689–93.
4. McCrindle BW, Manlhiot C, Newburger JW, Harahsheh AS, Giglia TM, Dallaire F, et al. Medium-term complications associated with coronary artery aneurysms after Kawasaki disease: a study from the International Kawasaki Disease Registry. J Am Heart Assoc. 2020;9:e016440.
5. Miyamoto T, Ikeda K, Ishii Y, Kobayashi T. Rupture of a coronary artery aneurysm in Kawasaki disease: a rare case and review of the literature for the past 15 years. J Thorac Cardiovasc Surg. 2014;147:e67–9.
6. Orenstein JM, Shulman ST, Fox LM, Baker SC, Takahashi M, Bhatti TR, et al. Three linked vasculopathic processes characterize Kawasaki disease: a light and transmission electron microscopic study. PLoS One. 2012;7:e38998.

7. Hoshino S, Tsuda E, Yamada O. Characteristics and fate of systemic artery aneurysm after Kawasaki disease. J Pediatr. 2015;167:108–112.e2.
8. Harada K. Intravenous gamma-globulin treatment in Kawasaki disease. Pediatr Int. 1991;33:805–10.
9. Beiser AS, Takahashi M, Baker AL, Sundel RP, Newburger JW. A predictive instrument for coronary artery aneurysms in Kawasaki disease. Am J Cardiol. 1998;81:1116–20.
10. Muta H, Ishii M, Sakaue T, Egami K, Furui J, Sugahara Y, et al. Older age is a risk factor for the development of cardiovascular sequelae in Kawasaki disease. Pediatrics. 2004;114:751–4.
11. Kobayashi T, Inoue Y, Takeuchi K, Okada Y, Tamura K, Tomomasa T, et al. Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. Circulation. 2006;113:2606–12.
12. Asadi-Pooya AA, Borzoee M, Amoozgar H. The experience with 113 patients with Kawasaki disease in Fars Province, Iran. Turk J Pediatr. 2006;48:109–14.
13. Sabharwal T, Manlhiot C, Benseler SM, Tyrrell PN, Chahal N, Yeung RS, et al. Comparison of factors associated with coronary artery dilation only versus coronary artery aneurysms in patients with Kawasaki disease. Am J Cardiol. 2009;104:1743–7.
14. Weng KP, Hsieh KS, Huang SH, Ou SF, Ma CY, Ho TY, et al. Clinical relevance of the risk factors for coronary artery lesions in Kawasaki disease. Kaohsiung J Med Sci. 2012;28:23–9.
15. Popper SJ, Shimizu C, Shike H, Kanegaye JT, Newburger JW, Sundel RP, et al. Gene-expression patterns reveal underlying biological processes in Kawasaki disease. Genome Biol. 2007;8:R261.
16. Rowley AH, Shulman ST, Mask CA, Finn LS, Terai M, Baker SC, et al. IgA plasma cell infiltration of proximal respiratory tract, pancreas, kidney, and coronary artery in acute Kawasaki disease. J Infect Dis. 2000;182:1183–91.
17. Brown TJ, Crawford SE, Cornwall ML, Garcia F, Shulman ST, Rowley AH. CD8 T lymphocytes and macrophages infiltrate coronary artery aneurysms in acute Kawasaki disease. J Infect Dis. 2001;184:940–3.
18. Masuda H, Ae R, Koshimizu TA, Matsumura M, Kosami K, Hayashida K, et al. Epidemiology and risk factors for giant coronary artery aneurysms identified after acute Kawasaki disease. Pediatr Cardiol. 2021;42(4):969–77.
19. Alsaied T, Tremoulet AH, Burns JC, Saidi A, Dionne A, Lang SM, et al. Review of cardiac involvement in multisystem inflammatory syndrome in children. Circulation. 2021;143:78–88.
20. Belhadjer Z, Meot M, Bajolle F, Khraiche D, Legendre A, Abakka S, et al. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. Circulation. 2020;142:429–36.
21. Sundel RP, Burns JC, Baker A, Beiser AS, Newburger JW. Gamma globulin re-treatment in Kawasaki disease. J Pediatr. 1993;123:657–9.
22. Burns JC, Capparelli EV, Brown JA, Newburger JW, Glode MP. Intravenous gamma-globulin treatment and re-treatment in Kawasaki disease. Pediatr Infect Dis J. 1998;17:1144–8.
23. Fukunishi M, Kikkawa M, Hamana K, Onodera T, Matsuzaki K, Matsumoto Y, et al. Prediction of non-responsiveness to intravenous high-dose c-globulin therapy in patients with Kawasaki disease at onset. J Pediatr. 2000;137:172–6.
24. Durongpisitkul K, Soongswang J, Laohaprasitiporn D, Nana A, Prachuabmoh C, Kangkagate C. Immunoglobulin failure and retreatment in Kawasaki disease. Pediatr Cardiol. 2003;24:145–8.
25. Sano T, Kurotobi S, Matsuzaki K, Yamamoto T, Maki I, Miki K, et al. Prediction of non-responsiveness to standard high-dose gamma-globulin therapy in patients with acute Kawasaki disease before starting initial treatment. Eur J Pediatr. 2007;166:131–7.
26. Tremoulet AH, Best BM, Song S, Wang S, Corinaldesi E, Eichenfield JR, et al. Resistance to intravenous immunoglobulin in children with Kawasaki disease. J Pediatr. 2008;153:117–21.
27. Shulman ST. IVGG therapy in Kawasaki disease: mechanism(s) of action. Clin Immunol Immunopathol. 1989;53:S141–6.
28. Shendre A, Wiener HW, Zhi D, Vazquez AI, Portman MA, Shrestha S. High-density genotyping of immune loci in Kawasaki disease and IVIG treatment response in European-American case-parent trio study. Genes Immun. 2014;15:534–42.
29. Weng KP, Hsieh KS, Ho TY, Huang SH, Lai CR, Chiu YT, et al. IL-1B polymorphism in association with initial intravenous immunoglobulin treatment failure in Taiwanese children with Kawasaki disease. Circ J. 2010;74:544–51.
30. Schattner A. Lymphokines in autoimmunity—a critical review. Clin Immunol Immunopathol. 1994;70:177–89.
31. Lin C-Y, Lin C-C, Hwang B, Chiang B. Serial changes of serum interleukin-6, interleukin-8, and tumor necrosis factor among patients with Kawasaki disease. J Pediatr. 1992;121:924–6.
32. Leung DY, Cotran RS, Kurt-Jones E, Burns JC, Newburger JW, Pober JS. Endothelial cell activation and high interleukin-1 secretion in the pathogenesis of Kawasaki disease. Lancet. 1989;2:1298–302.
33. Gupta M, Noel GJ, Schaefer M, Friedman D, Bussel J, Johann-Liang R. Cytokine modulation with immune gamma-globulin in peripheral blood of normal children and its implications in Kawasaki disease treatment. J Clin Immunol. 2001;21:193–9.
34. Egami K, Muta H, Ishii M, Suda K, Sugahara Y, Iemura M, et al. Prediction of resistance to intravenous immunoglobulin treatment in patients with Kawasaki disease. J Pediatr. 2006;149:237–40.
35. Uehara R, Belay ED, Maddox RA, Holman RC, Nakamura Y, Yashiro M, et al. Analysis of potential risk factors associated with nonresponse to ini-

tial intravenous immunoglobulin treatment among Kawasaki disease patients in Japan. Pediatr Infect Dis J. 2008;27:155–60.
36. Faim D, Henriques C, Brett A, Francisco A, Rodrigues F, Pires A. Kawasaki disease: predictors of resistance to intravenous immunoglobulin and cardiac complications. Arq Bras Cardiol. 2021;116(3):485–91.
37. Kaya Akca U, Arslanoglu Aydin E, Aykan HH, Serin O, Sag E, Demir S, et al. Comparison of IVIG resistance predictive models in Kawasaki disease. Pediatr Res. 2022;91(3):621–6.
38. Fu PP, Du ZD, Pan YS. Novel predictors of intravenous immunoglobulin resistance in Chinese children with Kawasaki disease. Pediatr Infect Dis J. 2013;32:e319–23.

How to Prevent Complication of KD

Ho-Chang Kuo

Abstract

Kawasaki disease (KD) is a systemic vasculitis that mainly affects small and medium blood vessels, most commonly in children under 5 years of age. Although its cause is not yet known, KD has become the most common acquired heart disease in developing countries. In recent decades, the incidence has increased in many centuries including Japan, South Korea, and China. The most serious complications of KD are coronary artery lesions (CAL), including dilation, fistulas, aneurysms, arterial remodeling, stenosis, and occlusion. Aneurysm formation was observed in 20–25% of KD patients who did not receive intravenous immunoglobulin (IVIG) therapy, while 3–5% was observed in patients who received intravenous immunoglobulin (IVIG) therapy. Approximately 30% of KD patients may suffer from coronary artery dilation in the acute phase, although most are temporary. Reducing the occurrence and getting regression of CAL is very important for the treatment of KD. In this chapter, we will show the clinical methods to prevent the formation of CAL.

Keywords

Kawasaki disease · Prevention · Complication
CAL · Aneurysm · IVIG resistance

Introduction

Kawasaki disease (KD) is recognized as the most frequent acquired heart disease in children. Dr. Kawasaki et al. first described in Japan in 1967 [1]. As a form of systemic vasculitis, KD is reported to mainly affect small- and medium-sized blood vessels. The most serious complication or sequelae is the formation of coronary artery lesions (CAL), such as myocardial infarction, coronary artery fistula [2], coronary artery dilation, and coronary aneurysm, which may subsequently lead to long-term sequelae such as stenosis or obstruction and myocardial infarction [3]. The cause of KD is still unknown [4–6], but it has proven that its incidence is increasing worldwide, especially in Japan. This growth is, however, not significant in Taiwan [7–10].

KD may be caused by genetic background (*CD40*, *BLK*, *ITPKC*, *FCGR2A*, *CD40L*, *CASP3*, etc.) [11–14], source of infection (bacteria, virus, mycoplasma, etc.) [6, 15], and immune response [16, 17]. The standard treatment for KD is high-

H.-C. Kuo (✉)
Kawasaki Disease Center, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan

Department of Pediatrics, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan

Chang Gung University College of Medicine, Taoyuan, Taiwan
e-mail: sel7129@adm.cgmh.org.tw

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dose aspirin (80–100 mg/kg/day) and single high-dose intravenous immunoglobulin (IVIG, 2 g/kg), which have been shown to significantly reduce the incidence of coronary artery aneurysms (CAA) from 20–25% to 3–5% [18, 19]. Although it has been found that a single high dose of IVIG is more effective than four smaller daily doses or two daily doses with the same cumulative dosage [5], the effectiveness of IVIG in the treatment of KD is still under investigation. FCGR2A may be an answer from the results of genome-wide association studies (GWAS) and epigenetic methylation arrays [20, 21]. Hypomethylation of the CpG site in the FCGR2A promoter region is reported to be related to KD susceptibility and IVIG resistance; mRNA gene expression confirms this finding. *FCRG2A/2B* mRNA expression ratio was considerably higher in KD patients with CAL than in those without CAL. *FCGR2A* and *FCGR2B* both demonstrated increased methylation levels in KD patients that underwent IVIG treatment. *FCGR2A* expression influenced the IVIG treatment response of KD patients. The *FCGR2A/2B* mRNA expression ratio was greater in KD patients with CAL formation [22]. FCGR2A/2B is overexpressed in the acute phase and then subsided, which may indicate the therapeutic effect of IVIG on KD patients and the possible role of purified Fc partial products in the future KD treatment [20, 21].

Although IVIG treatment significantly reduces the incidence of coronary aneurysm formation, about one-third (~30%) of KD patients still have coronary artery dilation in the acute phase. In our previous report and database, using a series of analyses of coronary artery dilatation (CAL) [23], 15.3% (114/743) of KD patients experienced dilation in the acute phase, and 10.2% (35/341) still had dilation a few months after the onset, 5.9% (44/743) had CAL or aneurysm formation at least 1 year after the KD onset. It is very important to identify KD within 5–10 days of the onset of the disease so as to treat KD with a more precise regimen, especially for those children with IVIG resistance, in the high-risk group with CAL formation or IVIG resistance, or with CAL formation already. In this chapter, we show the clinical practice of preventing the formation of CAL adopted by the Taiwan Kawasaki Disease Center.

Precise Diagnosis (How to Identify Typical or Atypical Kawasaki Disease)

Clinical Diagnosis Criteria (Kuo Mnemonic: 1-2-3-4-5 for Rapid Memory)

The clinical features of KD include fever lasting more than 5 days and at least four of the following five symptoms: diffuse mucosal inflammation of strawberry tongue and cracked lips (1 mouth), bilateral nonsuppurative conjunctivitis (2 eyes), unilateral swollen cervical lymph node (3 fingers to check the lymph nodes), rigid angioedema of hands and feet (4 limbs = 2 hands +2 feet), abnormal skin rashes (5 means a lot of skin rashes) [5]. These five characteristic symptoms of KD may not be easy to remember for parents or first-line clinicians. Finding an easier way to remember the five characteristics of KD is important for both parents and clinicians so that KD can be identified earlier. To help solve this problem, we created "Kuo Mnemonic" to quickly recall KD diagnostic criteria (shown in Table 1), which has been modified from our previous review articles [17]. According to the Japanese Circulation Society Joint Working Group's standard (JCS 2008, Guidelines for the Diagnosis and

Table 1 Rapid memory method of "Kuo Mnemonic" for Kawasaki disease diagnostic criteria

Number	Mnemonic method	Clinical symptoms and signs
1	"One" mouth (1 mouth)	Diffuse mucosal inflammation with strawberry tongue and/or fissure lips
2	"Two" eyes (2 eyes)	Bilateral nonpurulent conjunctivitis
3	"Three"-finger check for neck lymph nodes (3 fingers to check neck lymph nodes)	Neck lymphadenopathy (unilateral, >1.5 cm)
4	"Four" limbs' changes (4 limbs = 2 hands and 2 feet)	Indurative over hands and feet (peeling in subacute stage)
5	"Five" = multiple skin rashes (5 means a lot)	Dysmorphic skin rashes

This table is modified from a previous report [17]

Management of Cardiovascular Sequelae of KD) [24], KD can be diagnosed even if the fever is less than 5 days. Nevertheless, according to the American Heart Association (AHA) criteria [3], a fever that lasts for 5 days or more is essential for diagnosing KD. The new AHA scientific statement shows that in the presence of ≥4 main clinical features, especially when redness or swelling of hands and feet occurs, fever for 4 days can be used to diagnose KD (fast memory is 4 days of fever–4 symptoms–4 induration of limbs (rule of 4–4–4) [25].

Bacillus Calmette–Guerin (BCG) Site Induration

In countries with routine BCG immunization policies (such as Taiwan, China Mainland, and Japan), one-third to one-half of KD patients will have erythema changes in BCG scars [4]. Tseng et al. reported that this bull's eye dermatoscopic sign is not only a useful diagnostic marker but also a biomarker of the severity of CAL formation in KD patients [26]. In addition, Uehara et al. [27] stated that redness or the formation of a crust on BCG vaccination site is a useful marker to distinguish KD from other childhood fever diseases. In Taiwan, the 2016 BCG vaccination schedule was changed to 5 months old. This sign of BCG induration cannot be used for children under 5 months old who are suspected of having KD in Taiwan.

If the patient has four or less clinical standard signs of KD, doctors should consider redness or crusting at the BCG vaccination site as a possible indicator of KD. In short, changes in BCG site induration can be used as an independent diagnostic criterion to help diagnose KD. If the patient is suspected of having KD but does not fully meet the diagnostic criteria, the doctor should further consider the induration of the BCG vaccination site and the six items of AHA supplemental criteria for KD, consult a KD expert, and arrange a cardiac ultrasound examination. Taking together, the five principle clinical features including BCG induration, AHA supplementary criteria, and cardioechography were the major three ways that can make the diagnosis of KD.

Consulting a Kawasaki Disease Expert

When fever lasts ≥7 days without a clear diagnosis, a KD specialist (such as a cardiologist, immunologist, infectious disease specialist or rheumatologist) should be consulted. The main diagnostic criteria of KD depend on five clinical symptoms, making the diagnosis subjective. There are currently no laboratory data (objective markers) that can be specifically used to diagnose KD. Some biomarkers including micro-RNA (identified by next-generation sequencing) [28] and CXCL10 (IFN-γ-inducible protein 10 [IP-10]) [29–31] were under development for clinical application.

Consulting an expert will improve the subjectivity of making diagnosis for KD. The *Expertscape* (objective rankings of medical expertise) provides a good way to find KD experts throughout the world and can be searched according to city, area, country, and continent (www.expertscape.com).

AHA Supplemental Criteria

The AHA and American Academy of Pediatrics (AAP) released the KD supplemental laboratory criteria in 2004 and revised in 2017 for patients suspected of having KD but with an incomplete diagnosis, which included the following six components: (1) urine ≥10 white blood cells/high-power field; (2) albumin ≤3.0 g/dL; (3) elevation of alanine aminotransferase; (4) platelet count ≥450,000/mm^3 after 7 days of fever; (5) total white blood cell count ≥15,000/mm^3; and (6) anemia by age [3, 32]. If a patient meets more than three of the supplementary criteria, incomplete KD can be diagnosed, and IVIG should be prescribed even before echocardiography arrangement [3].

COVID-19 and Kawasaki Disease

Coronavirus disease 2019 (COVID-19, Severe Acute Respiratory Syndrome Coronavirus 2 [SARS-CoV-2]) has emerged and evolved in China since the end of 2019 and has developed into a global pandemic. Cases of KD-like disease have been reported from New York City, certain regions of Italy, and the UK, increasing by nearly 6–10 times compared with the prevalence of Kawasaki disease in previous years, but such cases have not been detected to be increased in Japan and Taiwan. COVID-19 has also been reported to induce this Kawasaki-like disease called multisystem inflammatory syndrome in children (MIS-C), which is a new type of syndrome associated with SARS-CoV-2 in children [33–35].

Unlike COVID-19, KD's diagnostic criteria and medical methods are clear. In addition to the five main symptoms, some specific signs or symptoms of KD include induration at the site of Bacillus Calmette–Guerin (BCG) vaccination and coronary arteritis or aneurysm formation; conscious clinicians will also check echocardiograms of COVID-19 in children. Coronary artery dilation and aneurysms have also been found in rheumatism or infectious diseases, but they are mainly seen in patients with KD (more than 98%). It has been reported that BCG vaccination also has a certain protective effect in COVID-19 pandemic areas [36, 37]. The pattern of bull's eye dermatoscopy at the BCG vaccination site is associated with systemic inflammation in KD patients. BCG vaccination shows that there are some overlapping pathogenesis between KD, MIS-C and COVID-19 [26, 37].

The new type of coronavirus, reported as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), commonly referred to as COVID-19 [38], causes a kind of Kawasaki-like disease, which shares some symptoms with KD and has been mainly found in the USA and Europe. As of March 29, 2021, according to news reviews, more than 127,089,189 COVID-19 cases have been confirmed globally, and the death toll has exceeded 2,782,959 [38]. Children only accounted for less than 5% of the total number of confirmed COVID-19 cases. The common symptoms of COVID-19 include cough, erythema in the pharynx, headache, and fever [39]. The symptoms and clinical features of COVID-19 patients and KD patients overlap considerably. A new childhood disease caused by the novel COVID-19 virus, with inflammation of multiple systems, especially coronary artery lesions, is now called MIS-C. There are some overlapped and differences between COVID-19, MIS-C, macrophage activation syndrome (MAS), Kawasaki disease shock syndrome (KDSS) and KD [40]. Almost 50% MIS-C patients experienced shock, but only 7.2% of KD patients did [39]. There was not anyone case with MIS-C been reported in Taiwan till the end of year 2021. The overlap between COVID-19, KD, and MIS-C may provide a chance to figure out the etiology of KD.

Treating Kawasaki Disease and IVIG Resistance with Precision Medicine

IVIG (Intravenous Immunoglobulin or Intravenous Gamma-Globulin)

IVIG has been used as a treatment for KD since Furusho et al. [41] first prescribed it in 1983. That was more than 15 years after KD was first reported in 1967. Later, in 1986, Newburger et al. [19] found that high-dose IVIG (400 mg/kg/day for 4 days) was a safe and effective treatment, reducing the incidence of coronary aneurysm formation from 20–25% to 3–5%. In 1991, a single high-dose IVIG (2 g/kg) was reported to be more effective than the 4-day regimen [42]. A single high-dose IVIG (10–12 h infusion of 2 g/kg) and high-dose aspirin (80–100 mg/kg/day) are currently considered the gold standard for the treatment of KD. IVIG treatment should not be spread for more than 24 h, 2 days, or 4 days.

A single high dose (2 g/kg) of IVIG administered through a 10 to 12-h infusion course within 5–9 days of disease onset is the most effective treatment for KD now a day. Evaluation and treatment suggestions for patients suspected of having Kawasaki disease are listed in Table 2.

Table 2 Evaluation and treatment suggestions for patients suspected of having Kawasaki disease

Fever	Major symptoms		Treatment
4	4 (including limbs induration)		IVIG
<5	4	Follow daily	Not IVIG (when without CAL)
<5	5	Treatment according JCS and AHA 2017	Possible IVIG
≥5	5	2D + KS	IVIG
≥5	4	2D + KS	IVIG
≥5	3 + BCG	2D + KS	IVIG
≥7 (in 6-month-olds)	0	2D + SLC + consult KD expert	Possible IVIG (may consider steroid in high-risk group)
≥7	2–3	2D + SLC + consult KD expert	IVIG when positive (may consider steroid in high-risk group)
>10	2–3	2D + SLC + consult KD expert	IVIG when positive (may consider steroid in high-risk group)

This table is modified and adapted from Biomed J. 2017;40(3):141–6
2D cardiac echography, *SLC* supplemental laboratory criteria by AHA
Kobayashi score (KS): A seven-variable logistic model was constructed, including day of illness at initial treatment, age in months, percentage of white blood cells representing neutrophils, platelet count, and serum aspartate aminotransferase, sodium, and C-reactive protein [43]
KD Kawasaki disease, *CAL* coronary artery lesions
JCS Japanese Circulation Society Joint Working Groups [24]
AHA American Heart Association [3, 25]

Aspirin

Aspirin has been used to treat KD for more than 50 years, even before IVIG started in 1983. Although aspirin has important anti-inflammatory (high dose) and antiplatelet (low dose) functions, it does not seem to reduce the occurrence of CAL. During the acute phase of KD, the dose of aspirin is 80–100 mg/kg per day (30–50 mg/kg in Japan) [44] in four doses. Hsieh et al. [44] reported that when children also receive a single injection of high dose (2 g/kg) IVIG in the acute stage of KD, the high-dose aspirin does not affect the response rate of IVIG therapy, duration of fever, or incidence of CAL. In fact, it may not be necessary to treat children with acute KD with high-dose aspirin, because existing data show no substantial benefit in preventing IVIG treatment failure, CAL formation, or shortening the duration of fever. In our report, the use of high-dose aspirin in the acute phase of KD has no benefit to inflammation markers (C-reactive protein, hepcidin, and hemoglobin levels) [41]. The use of high-dose aspirin in the acute phase of KD still requires a multicenter randomized controlled trial to reach a conclusion. A multicenter randomized controlled trial for dosage of aspirin in acute stage of KD is undergoing in Taiwan (ClinicalTrials.gov Identifier: NCT02951234) [45]. Jia et al. reported that low-dose aspirin plus IVIG might be as effective as high-dose aspirin plus IVIG for the initial treatment of KD in a 12,176 cases meta-analysis [46].

Subsequently, 48–72 h after the fever subsides, the dosage can be reduced to 3–5 mg/kg/day, and it should continue for around 6 weeks after the onset or until CAL returns to normal.

IVIG Resistance (Nonresponsiveness or Failure)

Because IVIG-resistant patients have a higher risk of developing CAL, it is important to identify patients who may benefit from more aggressive treatment. A second dose of IVIG (2 g/kg) [3, 47], methylprednisolone pulse therapy [48], tumor necrosis factor-alpha blockade [49], cyclophosphamide, cyclosporin A, methotrexate [50], plasmapheresis [51], and plasma exchange [52] have

all been reported to be beneficial for KD patients who have failed initial IVIG therapy. Compared with IVIG treatment alone, the single-pulse intravenous methylprednisolone (IVMP, 30 mg/kg, maximum dose is 1000 mg) combined with IVIG as the main treatment for children with KD did not significantly improve the outcome of the disease [53]. Although IVMP does not seem to increase the therapeutic value when combined with IVIG for the initial treatment and the mechanism is still unknown (our preliminary results indicate that it may be related to the decreased expression of steroid receptors in the acute phase of KD, data not shown), IVMP therapy over a 3-day course of treatment seems to benefit the IVIG-resistant KD patients [47]. At the Chang Gung Memorial Hospital in Kaohsiung, Taiwan, we used a second course of high-dose IVIG (10–12 h, 2 g/kg) for initial IVIG-resistant KD patients; then we prescribed IVMP (30 mg/kg/day for continue 3 days) for continued IVIG resistance in the secondary dose; then we prescribed anti-TNF-alpha agent for continued resistance to IVMP.

Although the incidence of KD has increased in the past few decades, the recurrence rate of KD in Japan has remained basically unchanged during the past 30 years (3.89–6.51/1000 person-years). Risk factors for recurrence of KD include male sex, young age, and IVIG resistance [54].

Preventing Coronary Artery Lesion Formation

Treatment for KD patients with a proper dosage of IVIG (a single high dose of 2 g/kg of body weight, without limitation of maximal dosage) within the appropriate 10–12 h infusion duration [5], prescribed within the first 5–10 days of the illness [3] seems to be most likely to prevent CAL than treatment after the tenth day of the disease. However, if patients with KD are found to develop CAL even before the fifth day of the disease onset, IVIG should be given before the first AHA standard for KD fever for more than 5 days. If patients with KD have persistent systemic inflammation based on their elevated erythrocyte sedimentation rate (ESR) or CRP, and persistent fever without other explanations or aneurysm formation after 10 days of onset, IVIG should also be given to them (i.e., children whose diagnosis was missed earlier).

For patients with KD who are suspected of having peeling (or even no peeling) on admission but do not meet the diagnostic criteria after discharge, echocardiography should be considered. For severe KD or high-risk groups, Kobayashi et al. suggested that adding prednisolone to IVIG can significantly improve coronary outcome [55]. The Kobayashi score provides a useful tool for predicting the formation of CAL, so prednisolone may be effective for CAL regression in patients with KD who have already developed CAL [43]. Further investigation is needed before reaching a clear conclusion. Salgado et al. reported that despite treatment in the first 10 days, infants <6 months of age with acute KD are more likely to develop CAL. Therefore, adjuvant anti-inflammatory therapies to lower CAL should be targeted at this population [56].

Other Off-Label Treatments

No treatment difference was found between KD patients with CAL formation and patients without KD formation during the acute phase and after discharge from the hospital. After the fever subsides, only low-dose aspirin may be prescribed to KD patients, regardless of the formation of CAL. KD patients can be divided into different groups according to the severity of the disease, including KD shock syndrome, KD with giant aneurysm formation, KD with aneurysm formation, KD with coronary artery dilation, KD with transient coronary artery dilation, KD with IVIG resistance, and KD without CAL, nor IVIG resistance. In these KD populations, different treatment options may be needed under the spirit of precision medicine.

Dextromethorphan (DM) is a dextrorotatory morphinan that has been widely used as a nonopioid cough suppressant for decades, but its exact mechanism is unclear. Interestingly, previous studies using animal models of cerebral ischemia and hypoglycemia nerve damage have demon-

strated the neuroprotective activity of DM, which may be related to its effect on NADPH oxidase, because DM can effectively prevent the production of reactive oxygen species (ROS) induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. It has been reported that low-dose DM can reduce blood pressure and enhance vascular protection in experimental hypertensive patients [57]. TNF-α can enhance the generation of ROS and is an important factor in the formation and development of CAL in KD. It has been reported that vascular NADPH oxidase enzyme participates in endothelial damage triggered by TNF-α by increasing the production of ROS [58]. Finally, in addition to low-dose aspirin, DM may benefit patients with KD who develop CAL.

Potential Role of Molecular Hydrogen Gas (H_2) in KD [59]

The inflammatory process, oxidative stress and free radicals are all related to KD. In the literature review, many reports indicate that oxidative stress plays an important role in the inflammation and pathogenesis of KD [60]. It is reported that by reducing oxidative stress, H_2 is beneficial for many diseases including atopic dermatitis, hay fever, rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, COVID-19, depression, dementia, stroke, post-cardiac arrest syndrome, subarachnoid hemorrhage, myocardial infarction, chronic kidney disease, sepsis, hemorrhagic shock, and various cancers [61, 62]. Hydrogen inhalation may also play a role in the treatment of COVID-19, reducing disease progression by improving airway resistance [62]. Currently, at least four clinical trials of inhaled hydrogen for the treatment of COVID-19 have been registered on ClinicalTrials.gov. In addition, a preliminary investigation report stated that inhalation of hydrogen can significantly improve breathing difficulties in most COVID-19 patients [63]. The potential treatment role of hydrogen gas inhalation in patients with KD with or without CAL formation is still need further studies. A comparison between Kawasaki disease (KD) and multisystem inflammatory syndrome in children (MIS-C) is shown in Table 3. We reported the first case of KD with aneurysm formation and showed regression after hydrogen gas inhalation [64].

Table 3 Comparison between Kawasaki disease (KD) and multisystem inflammatory syndrome in children (MIS-C)

	Kawasaki disease (KD)	Multisystem inflammatory syndrome in children (MIS-C)
Etiology	Unknown	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
Principle symptoms	Five major symptoms (fissure lips and/or strawberry tongue, bilateral nonpurulent conjunctivitis, neck lymphadenopathy, limb induration, and polymorphic skin rash)	Nonspecific symptoms, including vomiting, abdominal pain, diarrhea, skin rash, and conjunctival injection, etc.
Fever (>38 °C)	100%	100%
Treatment	IVIG + aspirin (steroids for high-risk group)	IVIG, steroids, anti-IL6, hydrogen gas inhalation, etc.
Age distribution	85% <5 years old	9 years old (median)
Sex (gender)	Male > female, 1.5-fold	Male > female, twofold
Bacillus Calmette–Guerin (BCG) vaccine	Scar indurations (associated with systemic inflammation)	May have a protective role (no BCG scar induration)
Prevalence	Asia > America > Europe	Europe, America > Asia
Coronary aneurysm (%)	3–5	~14
Shock (%)	7.2	~50

This table was modified and adapted from Chen KD, Lin WC, Kuo HC. Chemical and biochemical aspects of molecular hydrogen in treating Kawasaki disease and COVID-19. Chem Res Toxicol. 2021;34(4):952–8 [59]

Promoting Kawasaki Disease Awareness

Long-term fever is accompanied by some respiratory or gastrointestinal symptoms, which can affect the heart. These are the characteristics of KD and make parents confused when going to the clinic or hospital. Cardiologists, infectious disease experts, rheumatologists, and even urologists may take care of KD patients in the acute phase of the disease. KD outpatient clinic (OPD) is a great way to reduce confusion among family members during visits and follow-ups.

Books targeting parents will help raise awareness of KD and make it easier for them to face this disease when necessary. We published four Chinese books on KD in Taiwan. The first is a more detailed book that describes immune mechanisms, images, genetic discoveries, infectious associations, treatment, follow-up, and parental questions/answers. The second book is a more approachable version, including quick memory method (1 mouth—2 eyes—3 finger-palpable neck lymph nodes—4 limb changes—5 skin rash) [17] for diagnostic criteria and many characteristic photos of KD to help parents more easily recognize this disease. The third book is especially aimed at parents who already have children with KD. The content includes pharmacology, rehabilitation, psychiatry, nursing, social work, nutrition, traditional Chinese medicine, and allergy. We also promoted awareness of KD through facebook (https://www.facebook.com/kawasakidisease), Line, newspapers, education lectures in mama class and kindergarten parents' meeting.

Conclusion

Raising KD awareness by the rapid memory method through Kuo Mnemonic, early diagnosis (through echocardiography, supplementary standards, and BCG induration), precise treatment (IVIG, second dose of IVIG, IVMP, anti-TNF-α, anti-IL6), and precision medicine (steroids or dextromethorphan, other anti-inflammatory drugs, or hydrogen gas inhalation) can all help reduce the coronary artery damage caused by KD.

References

1. Kawasaki T, Kosaki F, Okawa S, Shigematsu I, Yanagawa H. A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. Pediatrics. 1974;54(3):271–6.
2. Liang C-D, Kuo H-C, Yang KD, Wang C-L, Ko S-F. Coronary artery fistula associated with Kawasaki disease. Am Heart J. 2009;157(3):584–8.
3. Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, 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(17):2747–71.
4. Wang CL, Wu YT, Liu CA, Kuo HC, Yang KD. Kawasaki disease: infection, immunity and genetics. Pediatr Infect Dis J. 2005;24(11):998–1004.
5. Burns JC, Glode MP. Kawasaki syndrome. Lancet. 2004;364(9433):533–44.
6. Kuo HC, Yang KD, Chang WC, Ger LP, Hsieh KS. Kawasaki disease: an update on diagnosis and treatment. Pediatr Neonatol. 2012;53(1):4–11.
7. Chang LY, Chang IS, Lu CY, Chiang BL, Lee CY, Chen PJ, et al. Epidemiologic features of Kawasaki disease in Taiwan, 1996–2002. Pediatrics. 2004;114(6):e678–82.
8. Huang WC, Huang LM, Chang IS, Chang LY, Chiang BL, Chen PJ, et al. Epidemiologic features of Kawasaki disease in Taiwan, 2003–2006. Pediatrics. 2009;123(3):e401–5.
9. Nakamura Y, Yashiro M, Uehara R, Oki I, Watanabe M, Yanagawa H. Epidemiologic features of Kawasaki disease in Japan: results from the nationwide survey in 2005–2006. J Epidemiol. 2008;18(4):167–72.
10. Nakamura Y, Yashiro M, Uehara R, Sadakane A, Tsuboi S, Aoyama Y, et al. Epidemiologic features of Kawasaki disease in Japan: results of the 2009–2010 nationwide survey. J Epidemiol. 2012;22(3):216–21.
11. Kuo HC, Chang WC. Genetic polymorphisms in Kawasaki disease. Acta Pharmacol Sin. 2011;32(10):1193–8.
12. Onouchi Y, Gunji T, Burns JC, Shimizu C, Newburger JW, Yashiro M, et al. ITPKC functional polymorphism associated with Kawasaki disease susceptibility and formation of coronary artery aneurysms. Nat Genet. 2008;40(1):35–42.
13. Onouchi Y, Ozaki K, Buns JC, Shimizu C, Hamada H, Honda T, et al. Common variants in CASP3 confer susceptibility to Kawasaki disease. Hum Mol Genet. 2010;19(14):2898–906.
14. Lin MT, Wang JK, Yeh JI, Sun LC, Chen PL, Wu JF, et al. Clinical implication of the C allele of the ITPKC gene SNP rs28493229 in Kawasaki disease: association with disease susceptibility and BCG scar reactivation. Pediatr Infect Dis J. 2011;30(2):148–52.
15. Chang LY, Lu CY, Shao PL, Lee PI, Lin MT, Fan TY, et al. Viral infections associated with Kawasaki disease. J Formos Med Assoc. 2014;113(3):148–54.

16. Guo MM, Tseng WN, Ko CH, Pan HM, Hsieh KS, Kuo HC. Th17- and Treg-related cytokine and mRNA expression are associated with acute and resolving Kawasaki disease. Allergy. 2015;70(3):310–8.
17. Kuo HC, Hsu YW, Wu MS, Chien SC, Liu SF, Chang WC. Intravenous immunoglobulin, pharmacogenomics, and Kawasaki disease. J Microbiol Immunol Infect. 2016;49(1):1–7.
18. Wu MH, Chen HC, Yeh SJ, Lin MT, Huang SC, Huang SK. Prevalence and the long-term coronary risks of patients with Kawasaki disease in a general population <40 years: a national database study. Circ Cardiovasc Qual Outcomes. 2012;5(4):566–70.
19. Newburger JW, Takahashi M, Burns JC, Beiser AS, Chung KJ, Duffy CE, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. N Engl J Med. 1986;315(6):341–7.
20. Khor CC, Davila S, Breunis WB, Lee YC, Shimizu C, Wright VJ, et al. Genome-wide association study identifies FCGR2A as a susceptibility locus for Kawasaki disease. Nat Genet. 2011;43(12):1241–6.
21. Kuo HC, Chang JC, Kuo HC, Yu HR, Wang CL, Lee CP, et al. Identification of an association between genomic hypomethylation of FCGR2A and susceptibility to Kawasaki disease and intravenous immunoglobulin resistance by DNA methylation array. Arthritis Rheumatol. 2015;67(3):828–36.
22. Chang LS, Lo MH, Li SC, Yang MY, Hsieh KS, Kuo HC. The effect of FcgammaRIIA and FcgammaRIIB on coronary artery lesion formation and intravenous immunoglobulin treatment responses in children with Kawasaki disease. Oncotarget. 2017;8(2):2044–52.
23. Kuo HC, Yu HR, Juo SH, Yang KD, Wang YS, Liang CD, et al. CASP3 gene single-nucleotide polymorphism (rs72689236) and Kawasaki disease in Taiwanese children. J Hum Genet. 2011;56(2):161–5.
24. JCS Joint Working Group. Guidelines for diagnosis and management of cardiovascular sequelae in Kawasaki disease (JCS 2008)—digest version. Circ J. 2010;74(9):1989–2020.
25. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, 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(17):e927–e99.
26. Tseng HC, Ho JC, Guo MM, Lo MH, Hsieh KS, Tsai WC, et al. Bull's eye dermatoscopy pattern at bacillus Calmette–Guerin inoculation site correlates with systemic involvements in patients with Kawasaki disease. J Dermatol. 2016;43(9):1044–50.
27. Uehara R, Igarashi H, Yashiro M, Nakamura Y, Yanagawa H. Kawasaki disease patients with redness or crust formation at the Bacille Calmette–Guerin inoculation site. Pediatr Infect Dis J. 2010;29(5):430–3.
28. Kuo H-C, Hsieh K-S, Guo MM-H, Weng K-P, Ger L-P, Chan W-C, et al. Next-generation sequencing identifies micro-RNA-based biomarker panel for Kawasaki disease. J Allergy Clin Immunol. 2016;138(4):1227–30.
29. Chen MR, Kuo HC, Lee YJ, Chi H, Li SC, Lee HC, et al. Phenotype, susceptibility, autoimmunity, and immunotherapy between Kawasaki disease and coronavirus disease-19 associated multisystem inflammatory syndrome in children. Front Immunol. 2021;12:632890.
30. Ko TM, Kuo HC, Chang JS, Chen SP, Liu YM, Chen HW, et al. CXCL10/IP-10 is a biomarker and mediator for Kawasaki disease. Circ Res. 2015;116(5):876–83.
31. Hsu YW, Lu HF, Chou WH, Kuo HC, Chang WC. Functional correlations between CXCL10/IP10 gene polymorphisms and risk of Kawasaki disease. Pediatr Allergy Immunol. 2021;32(2):363–70.
32. McCrindle BW, Li JS, Minich LL, Colan SD, Atz AM, Takahashi M, et al. Coronary artery involvement in children with Kawasaki disease: risk factors from analysis of serial normalized measurements. Circulation. 2007;116(2):174–9.
33. Kuo HC. Kawasaki-like disease among Italian children in the COVID-19 era. J Pediatr. 2020;224:179–83.
34. Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al. Multisystem inflammatory syndrome in children in New York state. N Engl J Med. 2020;383(4):347–58.
35. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med. 2020;383(4):334–46.
36. Curtis N, Sparrow A, Ghebreyesus TA, Netea MG. Considering BCG vaccination to reduce the impact of COVID-19. Lancet. 2020;395(10236):1545–6.
37. Escobar LE, Molina-Cruz A, Barillas-Mury C. BCG vaccine protection from severe coronavirus disease 2019 (COVID-19). Proc Natl Acad Sci U S A. 2020;117(30):17720–6.
38. Li H, Burm SW, Hong SH, Ghayda RA, Kronbichler A, Smith L, et al. A comprehensive review of coronavirus disease 2019: epidemiology, transmission, risk factors, and international responses. Yonsei Med J. 2021;62(1):1–11.
39. Lin YJ, Lin IC, Yu HR, Kuo HC, Yang KD, Chang WC, et al. Tricuspid regurgitation in acute phase of Kawasaki disease associated with intensive care unit admission. Pediatr Cardiol. 2013;34(2):250–5.
40. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA. 2020;324(3):259–69.
41. Furusho K, Sato K, Soeda T, Matsumoto H, Okabe T, Hirota T, Kawada S. Lancet. High-dose intravenous gammaglobulin for Kawasaki disease. 1983;2(8363):1359.
42. Newburger JW, Takahashi M, Beiser AS, Burns JC, Bastian J, Chung KJ, et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. N Engl J Med. 1991;324(23):1633–9.

43. Kobayashi T, Inoue Y, Takeuchi K, Okada Y, Tamura K, Tomomasa T, et al. Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. Circulation. 2006;113(22):2606–12.
44. Hsieh KS, Weng KP, Lin CC, Huang TC, Lee CL, Huang SM. Treatment of acute Kawasaki disease: aspirin's role in the febrile stage revisited. Pediatrics. 2004;114(6):e689–93.
45. Kuo HC, Guo MM, Lo MH, Hsieh KS, Huang YH. Effectiveness of intravenous immunoglobulin alone and intravenous immunoglobulin combined with high-dose aspirin in the acute stage of Kawasaki disease: study protocol for a randomized controlled trial. BMC Pediatr. 2018;18(1):200.
46. Jia X, Du X, Bie S, Li X, Bao Y, Jiang M. What dose of aspirin should be used in the initial treatment of Kawasaki disease? A meta-analysis. Rheumatology (Oxford). 2020;59(8):1826–33.
47. Chen HH, Liu PM, Bong CN, Wu YT, Yang KD, Wang CL. Methylprednisolone pulse therapy for massive lymphadenopathy in a child with intravenous immunoglobulin-resistant Kawasaki disease. J Microbiol Immunol Infect. 2005;38(2):149–52.
48. Wright DA, Newburger JW, Baker A, Sundel RP. Treatment of immune globulin-resistant Kawasaki disease with pulsed doses of corticosteroids. J Pediatr. 1996;128(1):146–9.
49. Son MB, Gauvreau K, Burns JC, Corinaldesi E, Tremoulet AH, Watson VE, et al. Infliximab for intravenous immunoglobulin resistance in Kawasaki disease: a retrospective study. J Pediatr. 2011;158(4):644–9.e1.
50. Ahn SY, Kim DS. Treatment of intravenous immunoglobulin-resistant Kawasaki disease with methotrexate. Scand J Rheumatol. 2005;34(2):136–9.
51. Pinna GS, Kafetzis DA, Tselkas OI, Skevaki CL. Kawasaki disease: an overview. Curr Opin Infect Dis. 2008;21(3):263–70.
52. Mori M, Imagawa T, Katakura S, Miyamae T, Okuyama K, Ito S, et al. Efficacy of plasma exchange therapy for Kawasaki disease intractable to intravenous gamma-globulin. Mod Rheumatol. 2004;14(1):43–7.
53. Newburger JW, Sleeper LA, McCrindle BW, Minich LL, Gersony W, Vetter VL, et al. Randomized trial of pulsed corticosteroid therapy for primary treatment of Kawasaki disease. N Engl J Med. 2007;356(7):663–75.
54. Sudo D, Nakamura Y. Nationwide surveys show that the incidence of recurrent Kawasaki disease in Japan has hardly changed over the last 30 years. Acta Paediatr. 2017;106(5):796–800.
55. Kobayashi T, Saji T, Otani T, Takeuchi K, Nakamura T, Arakawa H, et al. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial. Lancet. 2012;379(9826):1613–20.
56. Salgado AP, Ashouri N, Berry EK, Sun X, Jain S, Burns JC, et al. High risk of coronary artery aneurysms in infants younger than 6 months of age with Kawasaki disease. J Pediatr. 2017;185:112–116.e1.
57. Wu TC, Chao CY, Lin SJ, Chen JW. Low-dose dextromethorphan, a NADPH oxidase inhibitor, reduces blood pressure and enhances vascular protection in experimental hypertension. PLoS One. 2012;7(9):e46067.
58. Yoshida LS, Tsunawaki S. Expression of NADPH oxidases and enhanced H(2)O(2)-generating activity in human coronary artery endothelial cells upon induction with tumor necrosis factor-alpha. Int Immunopharmacol. 2008;8(10):1377–85.
59. Chen KD, Lin WC, Kuo HC. Chemical and biochemical aspects of molecular hydrogen in treating Kawasaki disease and COVID-19. Chem Res Toxicol. 2021;34(4):952–8.
60. Yahata T, Hamaoka K. Oxidative stress and Kawasaki disease: how is oxidative stress involved from the acute stage to the chronic stage? Rheumatology (Oxford). 2017;56(1):6–13.
61. Sano M, Shirakawa K, Katsumata Y, Ichihara G, Kobayashi E. Low-flow nasal cannula hydrogen therapy. J Clin Med Res. 2020;12(10):674–80.
62. Guan WJ, Wei CH, Chen AL, Sun XC, Guo GY, Zou X, et al. Hydrogen/oxygen mixed gas inhalation improves disease severity and dyspnea in patients with coronavirus disease 2019 in a recent multicenter, open-label clinical trial. J Thorac Dis. 2020;12(6):3448–52.
63. Guan WJ, Chen RC, Zhong NS. Strategies for the prevention and management of coronavirus disease 2019. Eur Respir J. 2020;55(4):2000597.
64. Kuo H-C. Hydrogen gas inhalation regressed coronary artery aneurysm in kawasaki disease-case report and article review. Front Cardiovasc Med. 2022;9:895627. https://doi.org/10.3389/fcvm.2022.895627).

Imaging of Coronary Artery Abnormalities in Kawasaki Disease with Emphasis on Multimodalities

I-Hsin Tai and Kai-Sheng Hsieh

Abstract

This chapter describes multimodality imaging, which can survey coronary artery abnormalities (CAA) from the acute phase of Kawasaki disease (KD) through the convalescent to the long-term stage. With different risk stratification of CAA, we proposed complementary imaging modalities as single or combination applications. The appropriate application of multimodalities demonstrated and listed can aid clinicians in making the optimal choice for aneurysm status evaluation. At last, we design a nature course-matched multimodality utilization timing of KD-associated CAA, which should be helpful in the imaging management planning for KD experts.

Keywords

Multimodality imaging · Transthoracic echocardiography · Coronary CTA · CMRA Invasive coronary angiography · IVUS · OCT Aneurysm regression · Coronary stenosis

I.-H. Tai (✉) · K.-S. Hsieh
Department of Pediatric Cardiology, China Medical University Children's Hospital, Taichung City, Taiwan

Department of Medicine, College of Medicine, China Medical University, Taichung, Taiwan

Structural/Congenital Cardiovascular and Echocardiography Center, China Medical University Children's Hospital, Taichung, Taiwan

Introduction

The patients with KD may have severe cardiovascular sequela, variable-sized coronary aneurysms after the acute phase. Transthoracic echocardiography is the most common noninvasive tool to evaluate CAA in KD. After the acute phase, if indicated, other modalities like coronary computed tomography, magnetic resonance, or nuclear medicine all have roles in evaluating cardiovascular sequela from different points of view. Invasive imaging modalities for coronary arteries are not routinely used but should consider in symptomatic patients with high suspicions of coronary artery stenosis.

Noninvasive Evaluation of Coronary Artery Abnormalities in Kawasaki Disease

Transthoracic Echocardiography

Transthoracic echocardiography (TTE) is the primary imaging modality for assessing coronary aneurysms. It is noninvasive and has high sensitivity and specificity for detecting aneurysms in the proximal coronary artery segments. CAA can present various numbers, sizes, and characteristics during acute illness, usually occurring first in proximal segments and then distally (Figs. 1 and 2). It is sporadic to have distal

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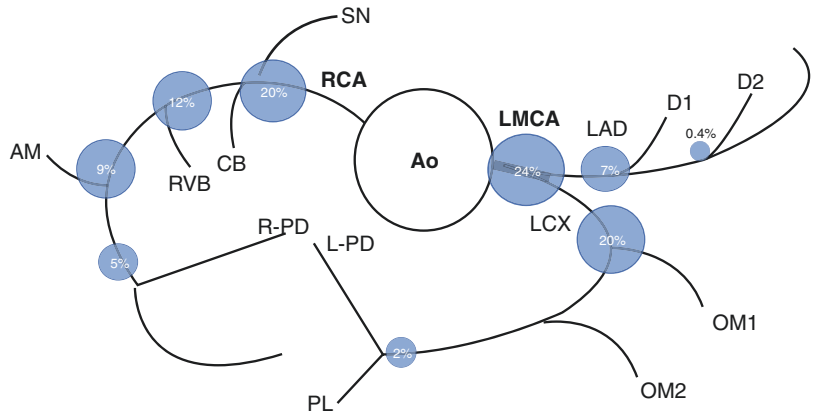

Fig. 1 Kawasaki disease (KD)-associated coronary aneurysm distribution and location [2]. *LMCA* left main coronary artery, *LAD* left anterior descending, *D1* diagonal first branch, *D2* diagonal second branch, *LCX* left circumflex, *OM1* obtuse marginal first branch, *OM2* obtuse marginal second branch, *L-PD* posterior descending branch from circumflex, *PL* posterolateral, *RCA* right coronary artery, *SN* sinus node branch, *CB* conus branch, *RVB* right ventricular branch, *AM* acute marginal branch, *R-PD* posterior descending branch from RCA

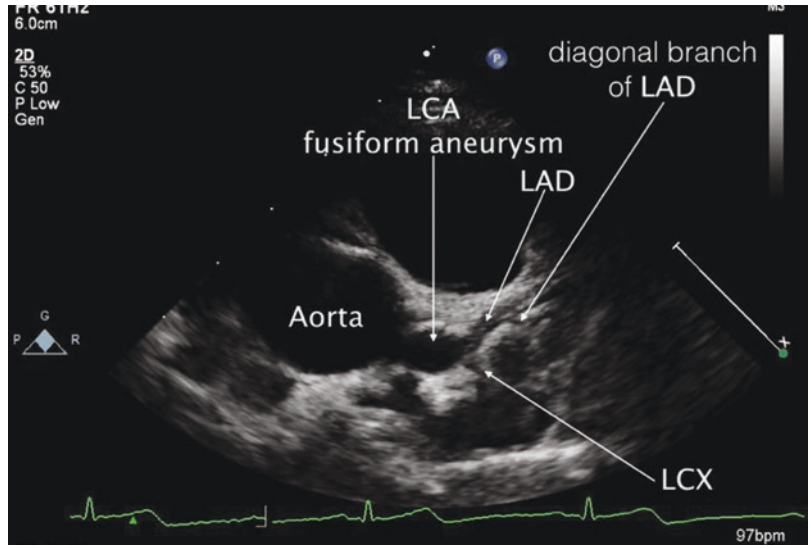

Fig. 2 Transthoracic echocardiography (TTE) can well delineate the proximal left main coronary artery, but the distal end is difficult to visualize. (Imaging from our institution)

involvement without some evidence of proximal segment abnormalities [1].

The latest American Heart Association (AHA) guideline [1] defines KD-associated coronary artery abnormalities solely based on the following *Z*-scores.

Z-Score Classification

1. No involvement: Always <2.
2. Dilation: 2 to <2.5; or if initially <2, a decrease in *Z* score during follow-up ≥1.
3. Small aneurysm: ≥2.5 to <5.
4. Medium aneurysm: ≥5 to <10, and absolute dimension <8 mm.
5. Large/giant aneurysm: ≥10, or absolute dimension ≥8 mm.

We emphasize the importance of utilizing high-frequency transducers to obtain detailed and high-resolution visualization of the coronary arteries (Fig. 3), even for older children, and low-frequency transducers for intracardiac structure

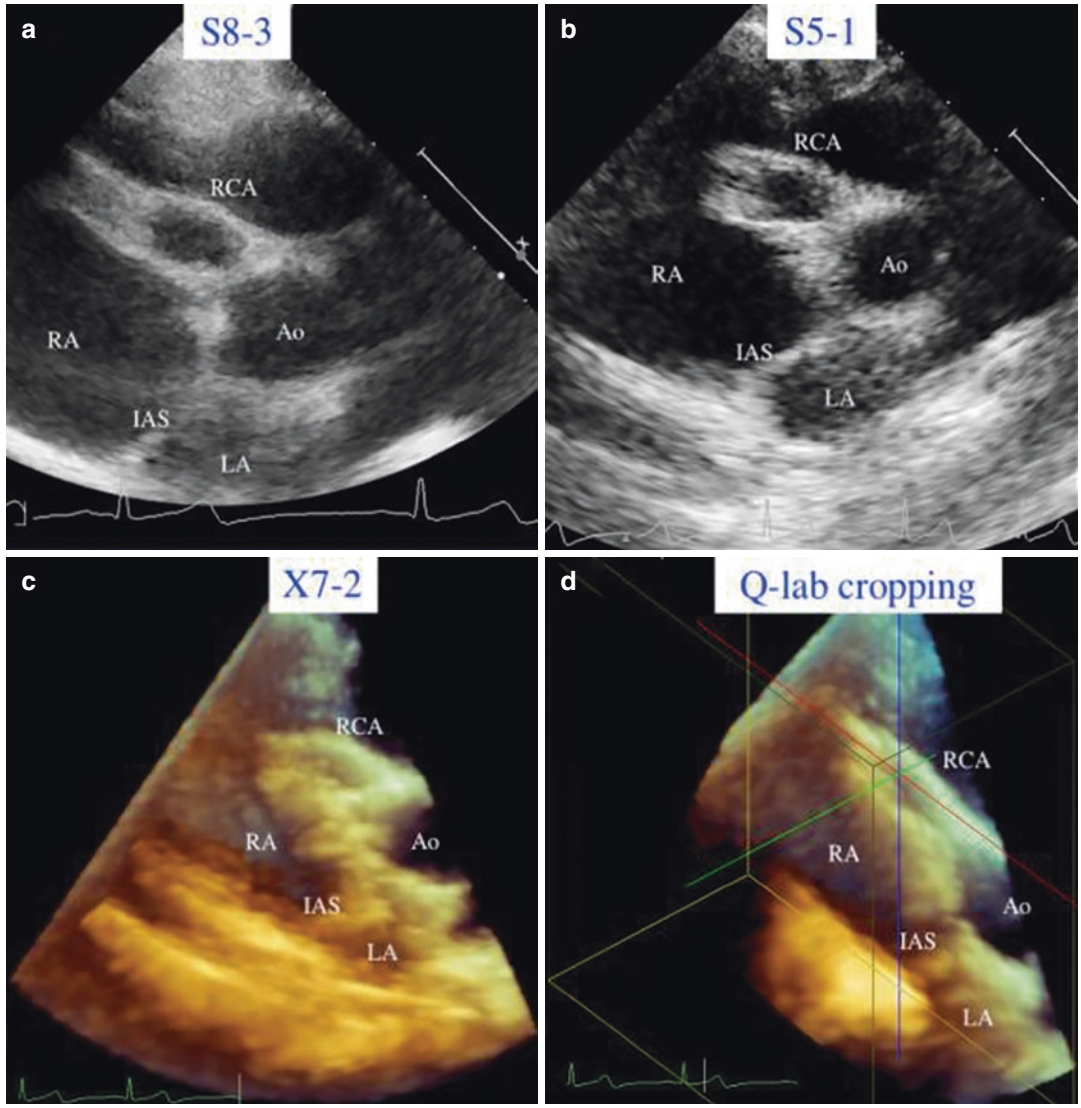

Fig. 3 Different frequency of transducers against the RCA aneurysm in a 6-year-old girl. The aneurysm can be best visualized with the transducer produced higher frequency. The frequency ranges from (**a**) 3–8 MHz, (**b**) 1–5 MHz, (**c**). three-dimensional probe—2–7 MHz, and (**d**) The still three-dimensional imaging provide visualization of the RCA aneurysm containing information including depth and neighboring structure. The dynamic display will show more detail. (Imaging from our institution)

evaluation. Studies should be recorded in dynamic video or digital cine format, which facilitates comparability for future reviews and studies [1, 3].

FOCUS Methodology

At present, there is no consensus regarding delineating the coronary artery by echocardiography. So far, the primary focus is on the measurement of luminal size, the quantitative on *Z* score, but the qualitative measure has not been well developed [1, 3]. Therefore, our team have proposed and adopted a comprehensive ultrasound evaluation methodology called focused optimal coronary ultrasound (FOCUS) (Fig. 4) [4, 5].

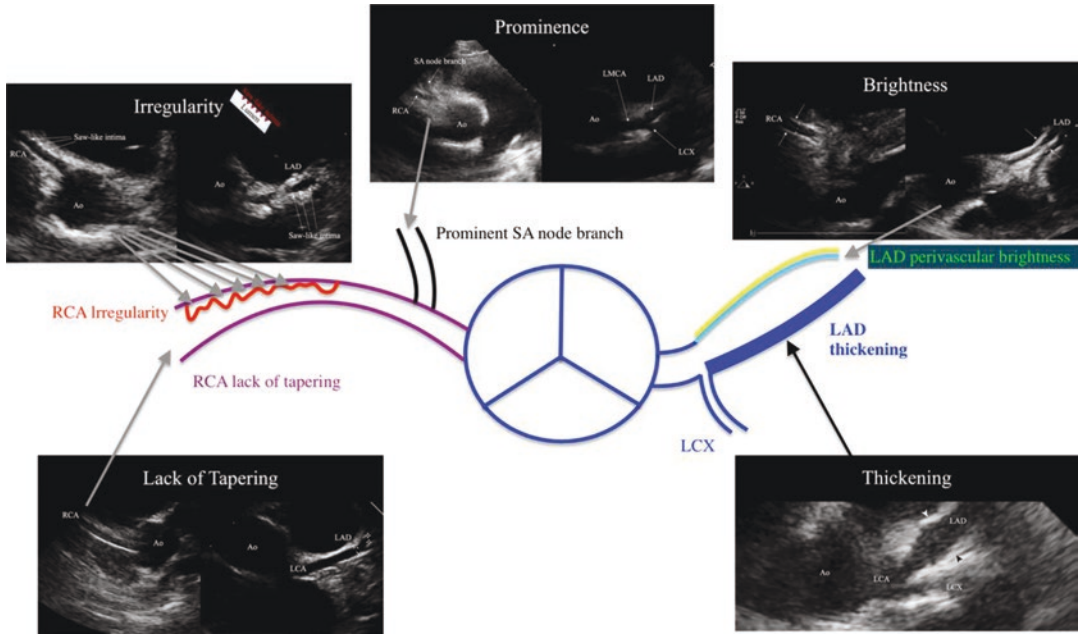

Fig. 4 Five components of the FOCUS imaging methodology. (Imaging from our institution)

Coronary artery abnormalities were scored as follows.

1. *Prominence* [4, 5]: The unusual clear margin of the coronary arteries due to hyperechogenicity over the perivascular region.
2. *Brightness of the arterial wall* [4–6]: Both sides of the vessel wall surrounding the coronary lumen brighten like a railway track without overt para-tissue, black-white gain.
3. *Irregularity of the arterial lumen* [4, 5]: Because of three-layer damage to the coronary arteries, there may be a saw-like appearance inside the coronary lumen.
4. *Lack of tapering* [3–5]: Because of the variability of coronary ectasia, there is a lack of average decrease in the caliber of the distal coronary arteries.
5. *Thickness of the arterial wall* [4–6]: In the ideal setting where a patient is cooperative with optimal ultrasound settings and the high-frequency transducer, the operator may appreciate the thickening of the coronary arterial wall.

Measurement of Coronary Lumen Size at Different Cardiac Cycles

From physiological aspects [7, 8], dynamic coronary artery blood flow and subsequent luminal diameter change within a cardiac cycle is an unpredictable factor causing variability of coronary dimensional measurement. A recent investigation conducted by Tai et al. [9] described that the cyclic variation of coronary luminal dimension throughout the cardiac cycle seems to alter the intra- and interobservers' variation, prompting the discussion of the utility of TTE with concomitant electrocardiogram use.

Coronary Computed Tomography Angiography

In 2003, Sato et al. detected occluded aneurysms with spiral coronary computed tomography angiography (CTA, 4-detector) in the era when invasive testing was still dominant in long-term follow-up of high-risk KD patients. In 2004, our research team first showed multislice coronary CTA (16-detector, Fig. 5) performed with retro-

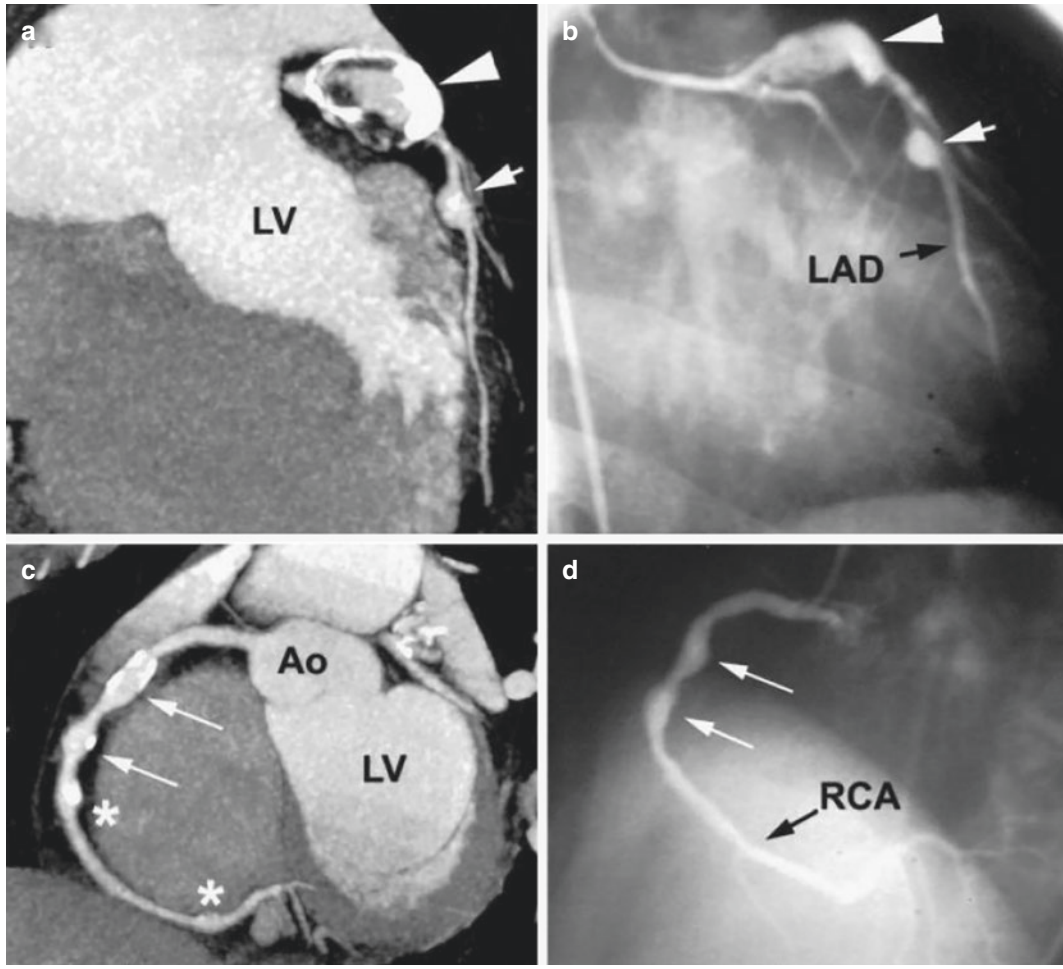

Fig. 5 (**a**) Multi-slice computed tomographic angiography of the left anterior descending artery reveals a giant aneurysm (large arrowhead) with calcified wall (high density area), thrombi (the low density area inside). A distal smaller aneurysm was also noted (small arrowhead). (**b**) Corresponding catheterized coronary angiography. Arrowheads correspond with those in a. (**c**) CT of the right coronary artery reveals two aneurysms (arrows). Two (asterisks) were more clearly visualized than with the catheterized coronary angiography (Panel d, arrows). (**d**) Corresponding catheterized coronary angiography of the panel c. Arrowheads correspond with those in c [22]

spective ECG-gated technique could delineate the distal coronary aneurysm even more precisely than invasive coronary angiography. With an advanced CTA machine, the imaging acquisition heartbeats in 64-slice and 320-slice were 7–8 and 1, respectively, thus accelerating the examination process, lower radiation exposure. Also, the faster the acquisition time, the less chance for errors such as respiratory motion artifact, heartbeats variability, and more extended temporal resolution to occur. Additionally, coronary CTA can disclose calcified coronary aneurysms represented by calcium score. Although the calcification burden carries the shortage to interfere with angiography accuracy, it can predict persistent or regressed aneurysms [10, 11].

Although TTE is convenient without radiation exposure, it faces limitations when approaching distal coronary segments. Coronary CTA has been proven superior to TTE for distal coronary artery visualization [12–15] concerning defining the number, position, shape, and size of each CAA and its thrombus association. As a result, it may be the most convenient noninvasive diagnostic modality to assess the whole coronary arterial tree in children with KD despite known

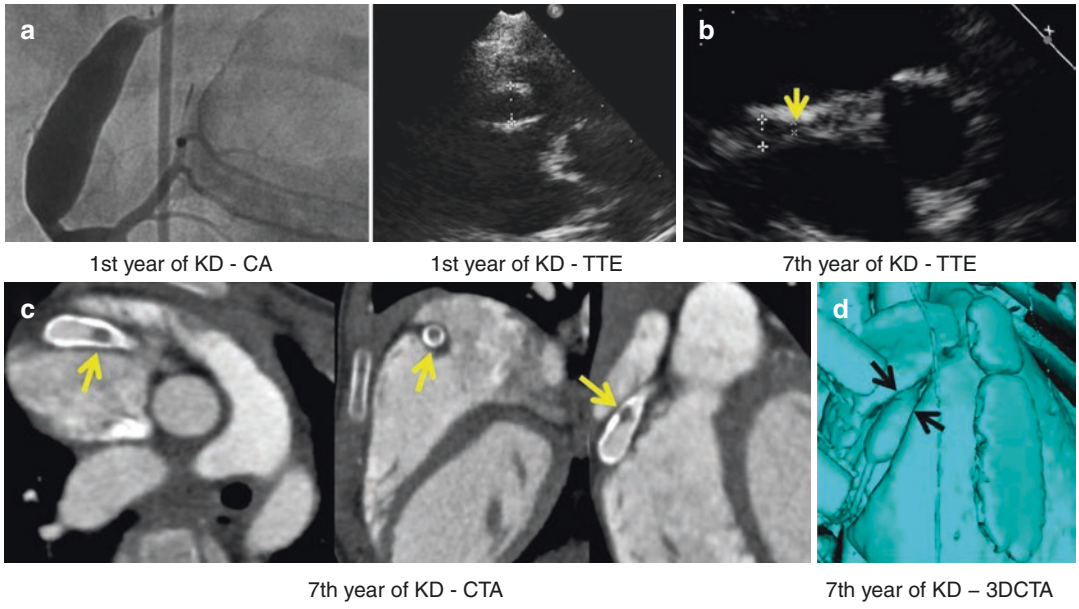

Fig. 6 A 7-year-old girl was admitted to our institution due to "ongoing stenosis" within a large fusiform RCA aneurysm revealed by coronary CTA after TTE showed a "regression" over proximal segment of RCA aneurysm (**a**). Left anterior oblique view of selective CA and corresponding TTE after first year of KD (**b**) TTE showed regression (yellow arrow) in luminal dimension after seventh year of KD. (**c**) Coronary CTA shows a contrast filling defect (yellow arrows) over proximal RCA (**d**). Three-dimensional reconstruction of coronary CTA showed aneurysmal shape (yellow arrow) of RCA. (Imaging from our institution)

disadvantages, such as radiation exposure, use of contrast media, and the need for β-blockers for heart rate regulation.

Furthermore, the introduction of dual-source CTA (DSCT) in 2005 improved temporal resolution of CTA from 135–175 to 75–80 (mini seconds) without heart rate regulation indicated (40–140 bpm was widely accepted). In summary, coronary CTA imaging nowadays has higher imaging quality, and faster acquisition without excess radiational risk.

Coronary CTA in the Patients with Possible Regression in a Chronic Phase of KD

In general, a regression can occur in small or medium-sized aneurysms but not in a giant aneurysm without significant luminal myofibroblastic proliferation (LMP). Coronary CTA provides extraluminal component information that echocardiography or catheterization cannot assess. The so-called regression obtained by echocardiography and catheterization angiography, could be falsely normal (Fig. 6) owing to vascular remodeling because both of them only review the diameter of the lumen. In such cases, coronary CTA should be used to demonstrate the aneurysmal shape of the coronary arteries with whole thickness despite the normal appearance of the luminal dimension. Coronary CTA can delineate the true margin of the coronary arterial wall because of the coronary arterial wall calcification or the radiation absorbance difference between coronary arteries and the overlying epicardial fat.

Coronary CTA yields excellent images of collateral circulation, a key characteristic of KD. A high-resolution CT scan eliminates partial volume effects, leading to false-positive results for culprit lesions with severe concentric calcification, which is another characteristic of KD. Although the previous document addressed the objection opinion [23], the latest investigation has clarified that the detection of occluded aneurysms by coronary CTA is feasible and effective [24, 25].

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (CMRI) plays a vital role in the evaluation of long-term follow-up of patients with KD and the assessment of cardiac function (Fig. 7) or compromised myocardial circulation [26] (Fig. 8). In addition, CMRI identifies abnormal perfusion reserve in KD-convalescent patients independent of coronary artery status [27].

CMRI can be used to detect myocardial edema with quantitative T2 mapping, scarring with delayed gadolinium enhancement (Fig. 9), and fibrosis with T1 mapping [28]. Despite the advantages of a radiation-free and waiver for heart rate control, the disadvantages, such as extended procedure time related to prolonged sedation of children, far outweigh the benefits, favoring the utility of CMRI. Conversely, as children age with persistent KD-associated CAA, their coronary arteries often cannot be adequately visualized by TTE. Therefore, CMRI may be a valuable alternative to noninvasively detect and monitor CAAs, reducing the need for coronary angiography in patients who might otherwise require serial catheterizations.

Greil et al. [29] compared results derived from coronary angiography with those from CMRI. Minor measurement discrepancies expected between these techniques, especially for tortuous vessels, and CMRI techniques to detect and measure distal CAA were limited. However,

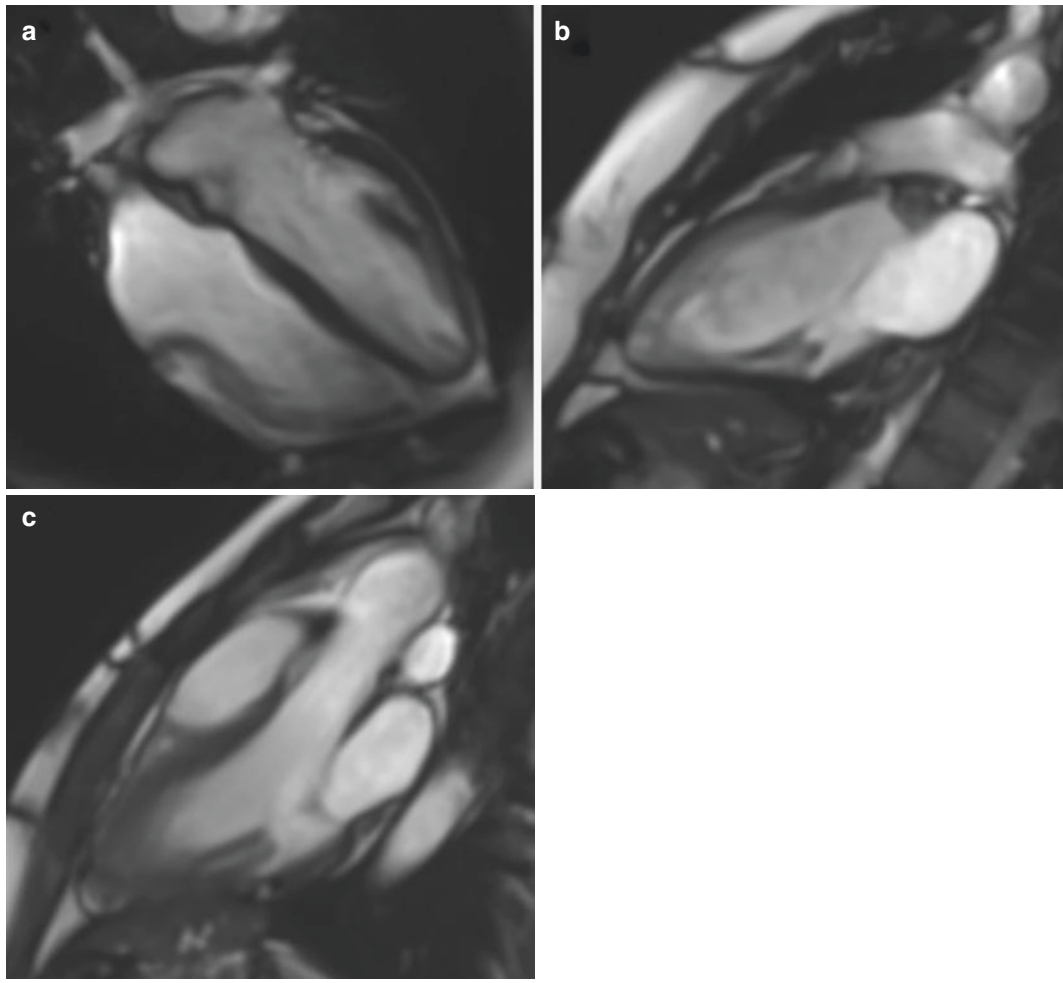

Fig. 7 The application of CMRI for measurement of left ventricular ejection fraction (**a**). Apical four chamber (**b**). Two-chamber view (**c**). Three-chamber view. (Imaging from our institution)

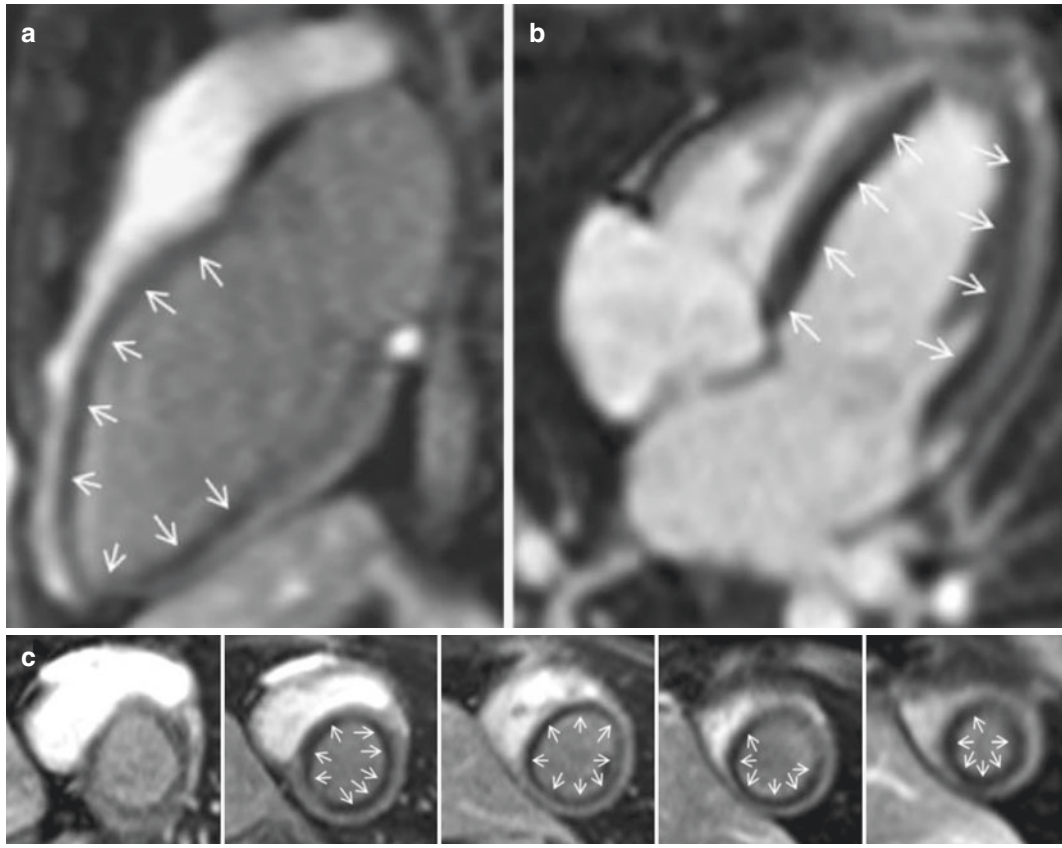

Fig. 8 The stress CMRI (0.84 mg/kg dipyridamole,0.1 mmol/kg gadolinium chelates) in the (**a**) two-chamber, (**b**) four-chamber, (**c**) short-axis view, disclosing perfusion defect in anterior, posterior, septal, and free wall. (Quoted from Garot et al. [30])

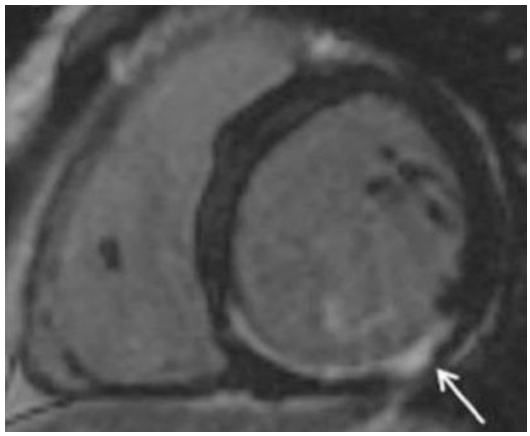

Fig. 9 The CMRI presents delayed hyperenhancement of gadolinium (arrow), which indicates myocardial scarring secondary to myocardial infarction. (Quoted from Tacke et al. [28])

CMRI seems superior to coronary CTA in evaluating CAA with calcification plaque (Fig. 10). Significant characteristics comparison between noninvasive imaging modalities was shown in Tables 1 and 2.

Invasive Evaluation of Coronary Artery Abnormalities in Kawasaki Disease

Invasive Selective Coronary Angiography

Invasive selective coronary angiography (CA, Fig. 11) can be valuable for some patients but not indicated for routine diagnosis, especially during

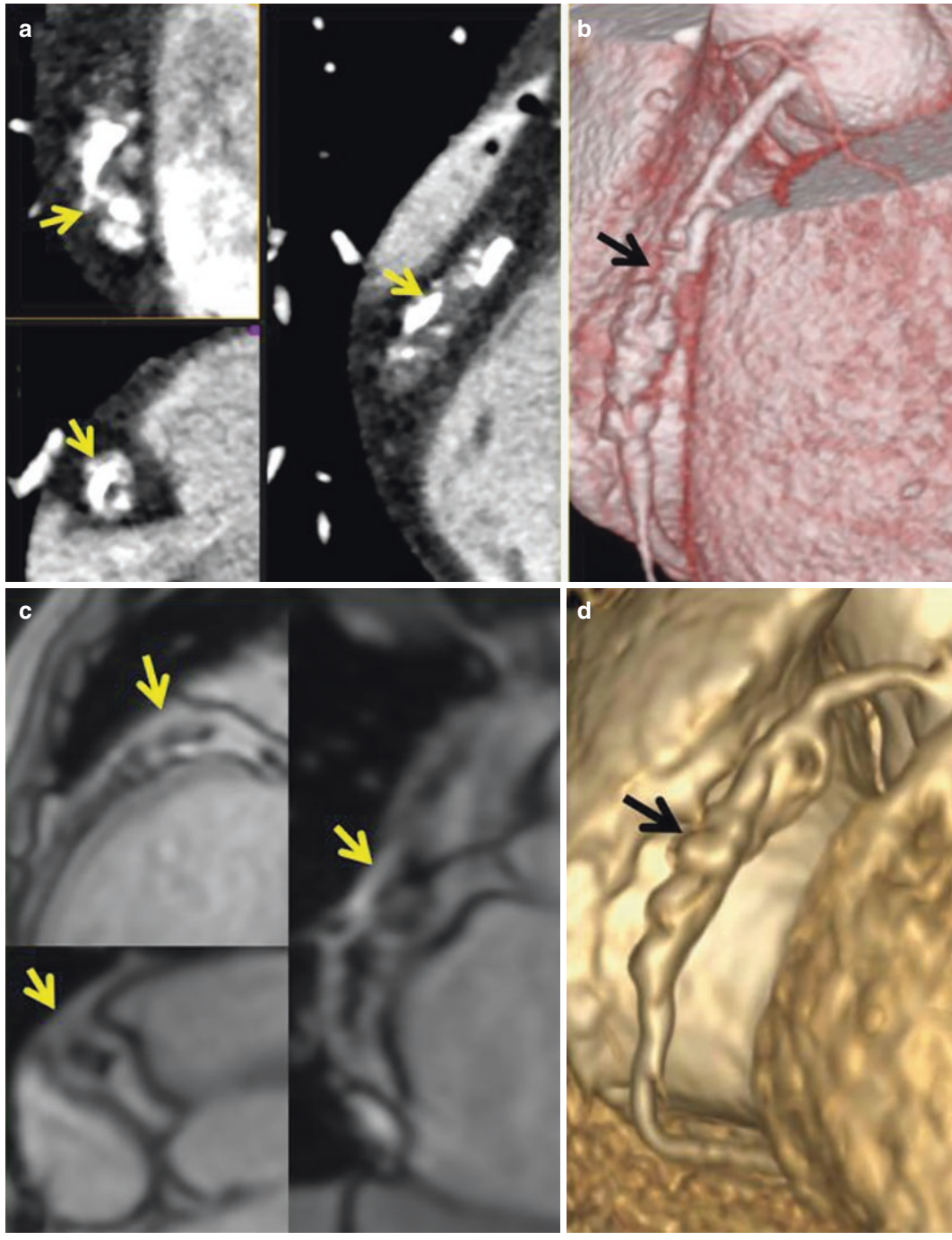

Fig. 10 Coronary CTA and CMRI yield a discrepant diagnosis in a 28-year-old female with RCA aneurysms secondary to KD. (**a**) Multiplane reformation with left upper panel, sagittal plane; left lower panel: axial plane; right panel: coronal plane, CTA showed blood flow enhanced, favor total occluded RCA aneurysm with hyperintense plaque, the calcification (yellow arrow), which may have blooming effect to interfere with the correct interpretation. (**b**) Three-dimensional coronary CTA of the RCA aneurysm. (**c**) Multiplane reformation with left upper panel, sagittal plane; left lower panel: axial plane; right panel: coronal plane, CMRI revealed partial blood flow with RCA thrombosis. The calcification appears as hypointense (yellow arrow) in CMRI. (**d**) Three-dimensional CMRI imaging of the RCA aneurysm. (Imaging from our institution)

Table 1 Comparison of noninvasive imaging modalities

	TTE	Coronary CTA	CMRI	SPECT
Coronary artery [16]				
Spatial resolution, mm	1–3	0.5–0.6	1–2	NA
Temporal resolution, ms	5–25	83–153	20–50	NA
Contrast/resolution	Moderate to low	Moderate	High	NA
Calcification interference	Intermediate	Major	Minor	NA
Whole vessel wall visualization	Moderate	High	High	NA
Myocardial structure				
Tissue characterization	1–2+	2–3+	4+	NA
Myocardial perfusion defect [17–19]	#Sensitivity 75.2% Specificity 52.4%	Sensitivity 95% Specificity 87%	Sensitivity 88% Specificity 90%	Sensitivity 49.1% Specificity 80.6%
LVEF evaluation [20, 21]	3+	0–2+	4+	3–4+

The comparison of four different modalities in evaluation of coronary and cardiac function. # means contrast echocardiography

TTE transthoracic echocardiography, *CTA* computed tomographic angiography, *MRI* magnetic resonance imaging, *SPECT* single-photon emission computed tomography, thallium-201 imaging, *CAD* coronary artery disease, *LVEF* left ventricular ejection fraction

Table 2 Modalities characteristic comparison between coronary CTA and CMRI

	Coronary CTA	CMRI
Spatial resolution	Higher	Lower
Myocardium perfusion status evaluation	Poor performance	Excellent performance
Imaging time (mean)	5-10 mins	60 mins
Radiation	Yes	No
Contrast	Yes	No
Breath hold	Required	No
Heart rate regulation	Required	No
Thrombus detection	First choice	Alternative
Distal coronary aneurysm	First choice	Alternative
Occluded aneurysm	First choice	Alternative

an acute illness. Since Coronary CTA or CMRI can now obtain nearly all structural and functional clinical information for KD-associated CAA, selective catheterization is now seldom performed except for the restoration of coronary blood flow via balloon dilatation or stent placement. Two imaging modalities still require catheterization to investigate coronary wall histology further: intravascular ultrasound and optical coherence tomography.

Intravascular Ultrasound

Intravascular ultrasound (IVUS, also named grayscale IVUS, Fig. 12) was first introduced in

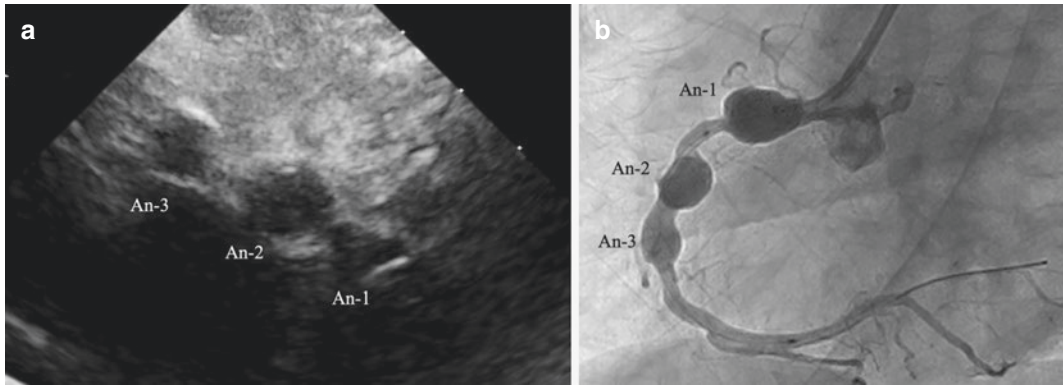

Fig. 11 The invasive selective coronary angiography of three aneurysm (An-1, An-2, An-3) over right coronary artery in the beading-arrangement. An dontes to aneurysm (Imaging from our institution)

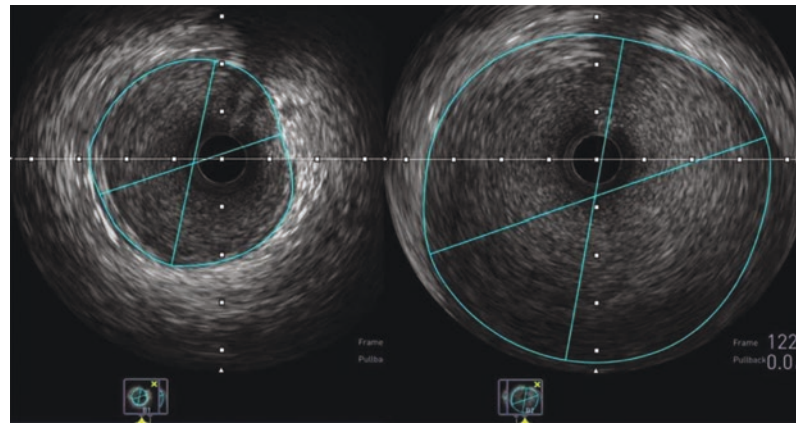

Fig. 12 Grayscale IVUS imaging of KD-associated CAA. (Imaging from our institution)

the 1980s to assist interventional cardiologists in evaluating coronary atherosclerotic disease. Then it was applied to comprehensively assess the coronary arterial wall structure and morphology in the chronic phase of KD. Based on the concept of LMP, which leads to ongoing luminal stenosis, we know that luminal regression does not equal coronary anatomy normal. Target on the injured coronary morphology, IVUS can differentiate regressed aneurysms from normal coronary arteries despite their comparable luminal dimensions.

Virtual Histology Intravascular Ultrasound

In the late 1990s, virtual histology IVUS (VH-IVUS) was invented for real-time in vivo plaque classification using the spectral analysis of a backscattered IVUS [31, 32] to elucidate the tissue characterization further and monitor atherosclerotic plaque stability. The literature shows that in vivo VH-IVUS has superior accuracy compared with histological evidence (Fig. 13) [33].

Optical Coherence Tomography (OCT)

Compared to IVUS, optical coherence tomography (OCT) provides the following.

- Nearly ten times the higher axial resolution.
- Providing a spatial definition of 10 μm.
- Unique information about the microstructure of the coronary wall.

As a result, it is an emerging tool in coronary pathology assessments and preplanning for coronary interventions. Figure 14 shows the relative

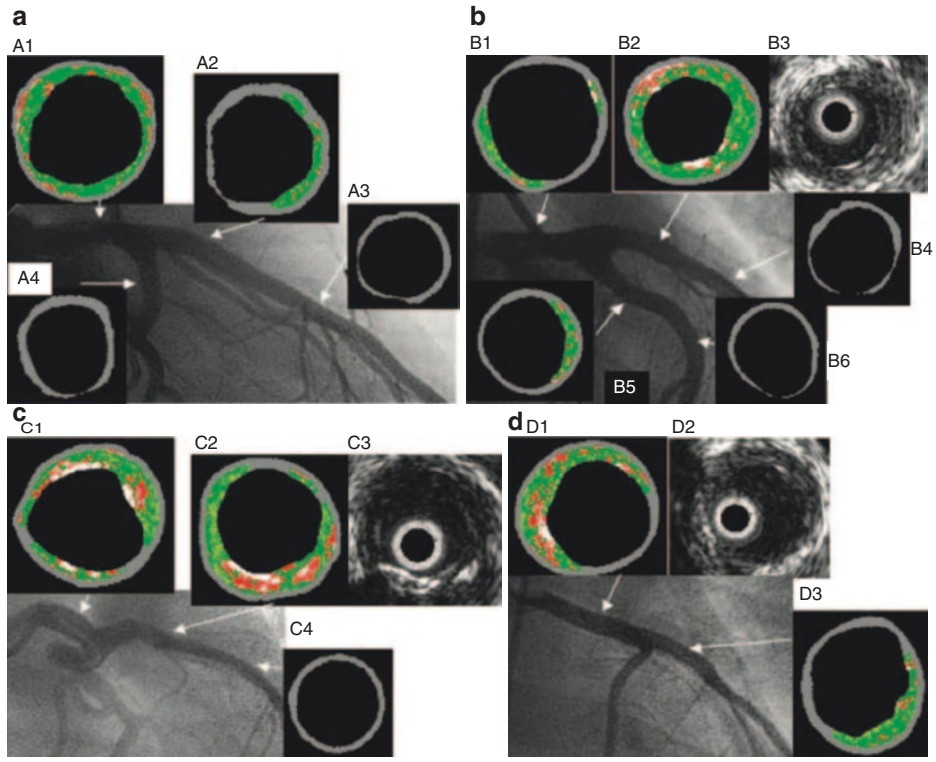

Fig. 13 VH-IVUS images with corresponding grayscale images in remodeling aneurysms (A1, A2, B1, B2, B5, C1, C2, D1, and D3) and relatively normal segments (A3, A4, B4, B6, and C4). Each of the four plaque components was assigned a respective color and defined as follows: fibrous area (green), the area of densely packed collagen; fibrofatty area (yellow), fibrous tissue with significant lipid interspersed in collagen; necrotic core area (red), a necrotic region consisting of cholesterol clefts, foam cell, and microcalcification; and dense calcium area (white). VH-IVUS imaging of regressed KD-associated left coronary aneurysms from (**a**) An 18-year-old male without the CV risk factor. (**b**) A 23-year-old female with a family history of ischemic heart disease. (**c**) A 26-year-old female with chronic exposure to cigarette smoking. (**d**) A 16-year-old female with chronic exposure to cigarette smoking. (Quoted from Mitani et al. [32])

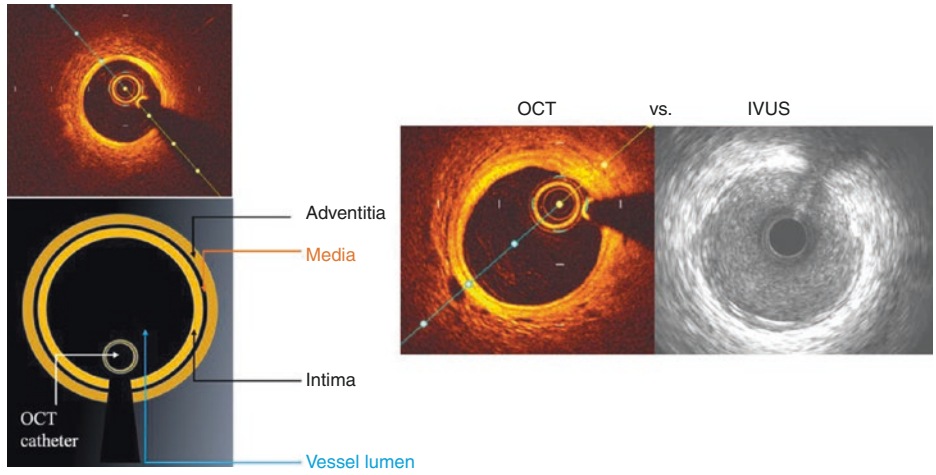

Fig. 14 Normal contour illustration of the intima, media, and adventitia layers in intracoronary OCT images. The OCT imaging has higher resolution against the three layers structure compared with IVUS in the patient with KD. (Imaging from our institution)

standard coronary segment from a patient with KD and scheme illustration of trilayer coronary arterial wall under OCT. We present the typical findings of OCT in coronary artery abnormalities from different patients with KD in our institution (Fig. 15).

Near-Infrared Spectroscopy Intravascular Ultrasound

Solely IVUS system has the shortage of foreshortening and underestimation of plaque burden. Near-infrared spectroscopy (NIRS) combined

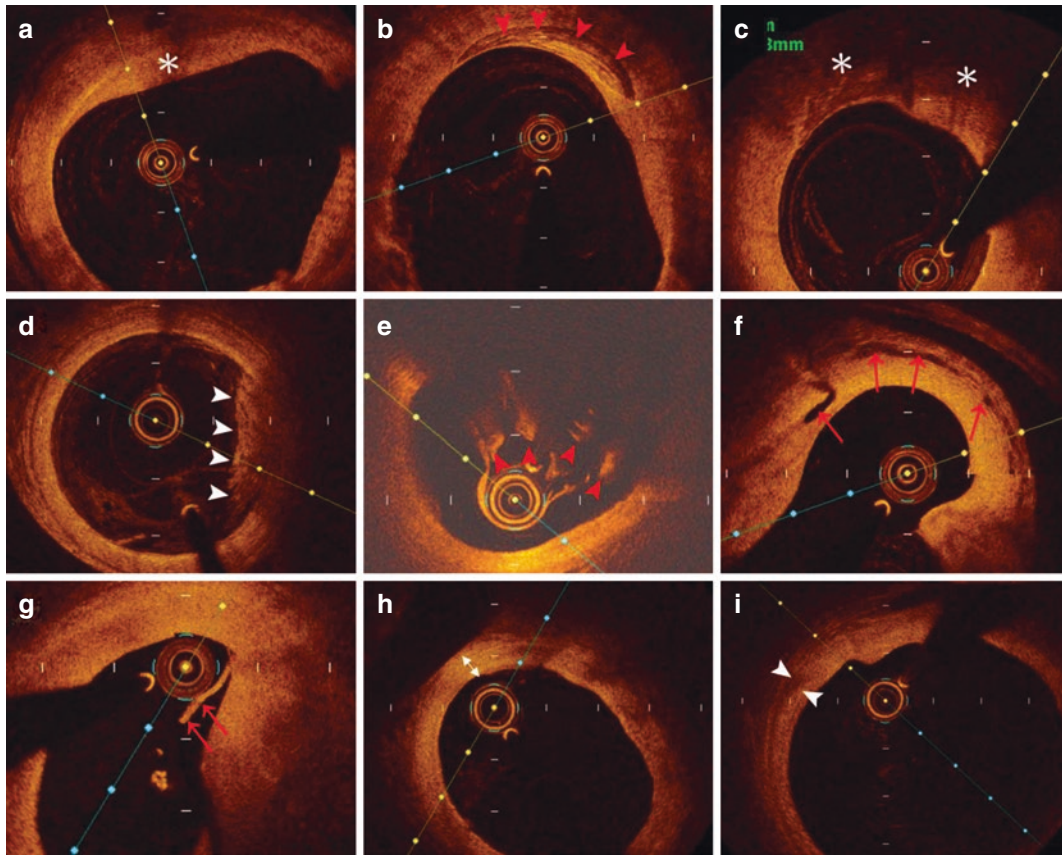

Fig. 15 Optical coherence tomography (OCT) data obtained from adult-aged patients with CAA secondary to KD. (**a**) Fibrous plaque (asterisk) is defined as homogeneous, signal-rich regions with low attenuation. (**b**) Calcified plaque (red arrowhead) is characterized by a well-demarcated border and with heterogeneous, low-signal composition. (**c**) Lipid plaque (asterisk) is defined as signal-poor regions with diffuse borders. (**d**) White thrombus (white arrow heads) presents with as a low-backscattering structure. (**e**) Red thrombus (red arrow heads) presenting with high attenuation because there is complete absorbance of the near-infrared light. (**f**) Intimal hyperplasia with sinusoid structures of varying size suggesting neovascularization (red arrow). (**g**) Intima dissection (red arrows). (**h**) Intima hyperplasia (white double arrow). (**i**) Destruction of media, presented by the disappearance of normal media (white arrow) and intima swelling. (Imaging from our institution)

with IVUS (NIRS-IVUS) is a novel emerging tool using catheter-based intravascular imaging modality. It provides a chemogram (Fig. 16) of the coronary artery wall, enabling the detection of the lipid core, precisely quantifying lipid accumulation (Fig. 17), and preventing distal embolization and periprocedural myocardial infarction in patients undergoing coronary angiography.

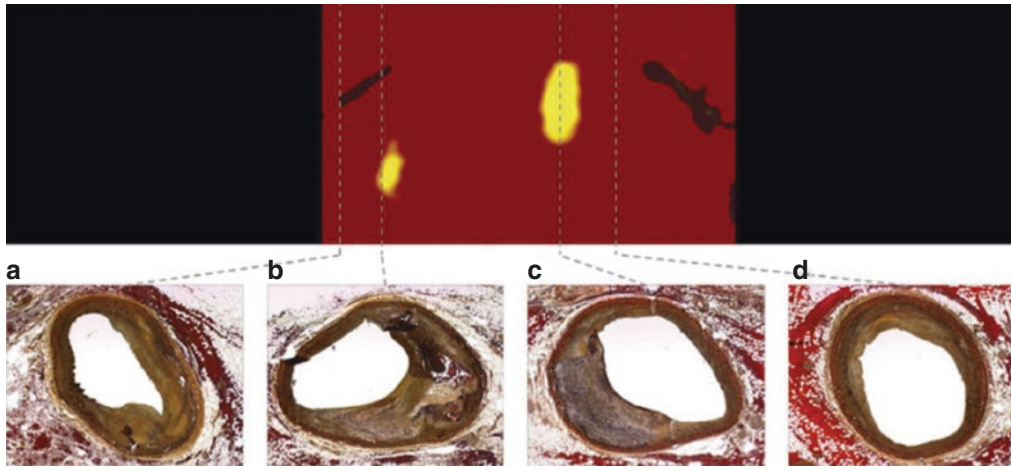

Fig. 16 Correlation between NIRS chemogram and pathology findings. The arterial wall lacking necrotic lipid core corresponds to "red" in chemogram (**a**, **d**), whereas necrotic lipid core plaques correspond to "yellow" (**b**, **c**). (Quoted from Kilic et al. [34])

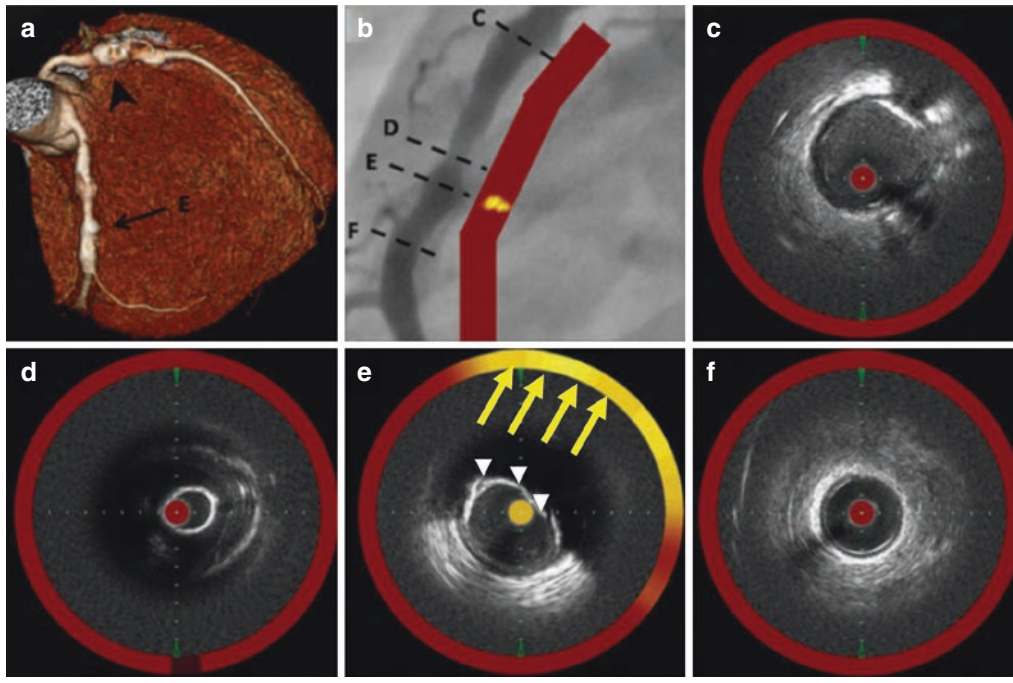

Fig. 17 Atherosclerotic changes in coronary aneurysms post-KD in vivo demonstration with NIRS. (**a**) A covered stent was placed in LAD aneurysm (arrow). (**b**) NIRS-IVUS in different coronary segments. (**c**) The segment with maximum diameter, calcification revealed by IVUS. (**d**) A napkin's rings of calcium in the middle RCA causing lumen narrowing. (**e**) NIRS showed large lipid position (yellow arrow) behind the superficial calcium (arrow head), indicating a lipid plaque in the arterial wall and cause lumen narrowing. (**f**) No calcification or lipid content identified in the segment

Giant Coronary Aneurysm Regression Validated by Transthoracic Echocardiography and Coronary CTA

A combination of TTE and coronary CTA can offer a detailed overview of CAA. Recently, Tai et al. showed incidental finding of significant coronary luminal regression of a giant coronary aneurysm (Fig. 18) after intravenous methylprednisolone pulse therapy (IVMP) for refractory KD validated by TTE in a 5-year-old patient with KD [35, 36]. The coronary CTA (Fig. 19) further confirmed the regression without the aneurysmal shape of coronary segments. Despite the promising initial outcome, the long-term result remains to be clarified. Therefore, we initiated a randomized, open-labeled, phase 1 clinical trial to elucidate the safety and efficacy of IVMP (ClinicalTrials.gov Identifier: NCT04509219).

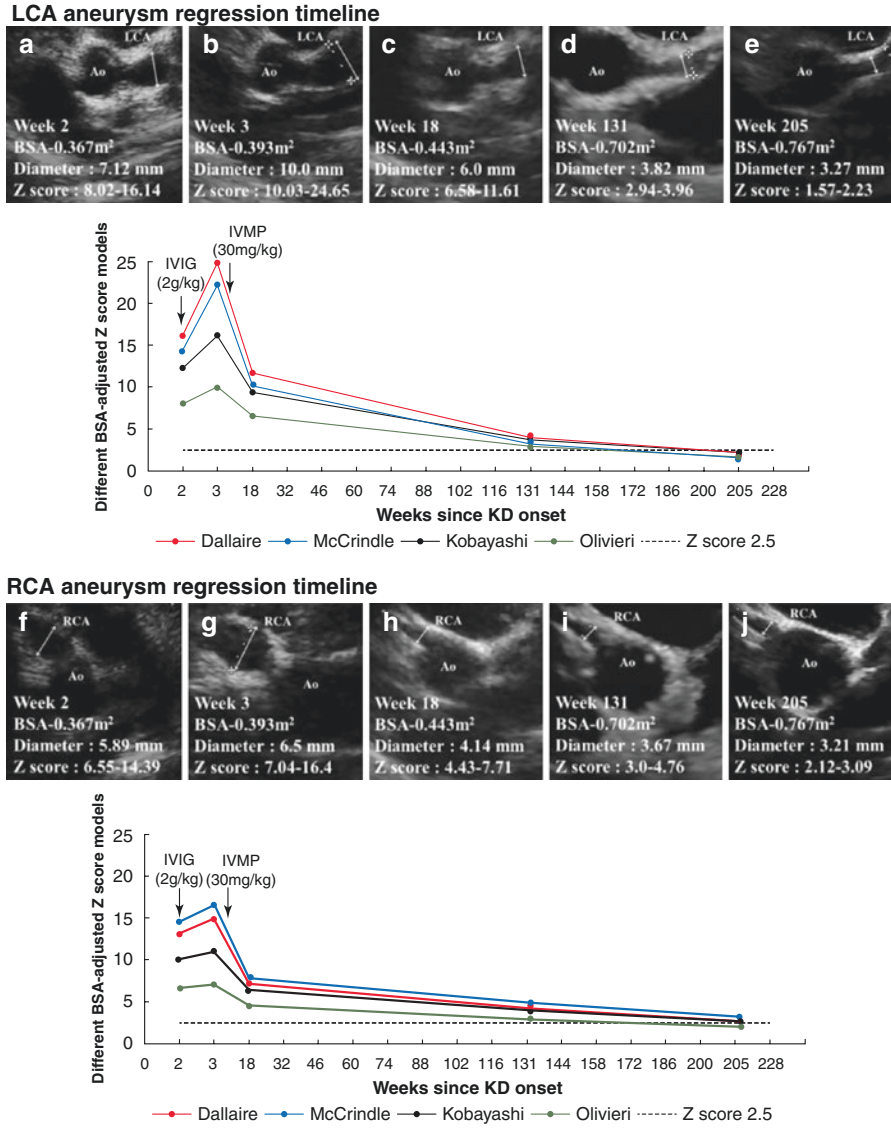

Fig. 18 A 5-year-old boy with KD-associated giant aneurysms underwent intravenous methylprednisolone pulse therapy just after acute phase (week 3–4 since KD onset). Serial echocardiography imaging revealed significant regression on both-side aneurysms during week 205 since KD onset. (**a**–**e**) The serial echocardiography showed full regression of the original giant LCA aneurysm from 10mm to 3.27mm. (**f**–**j**) The serial echocardiography showed near full regression of the original giant RCA aneurysm from 5.89mm to 3.21mm. (Quoted from Tai et al. [36])

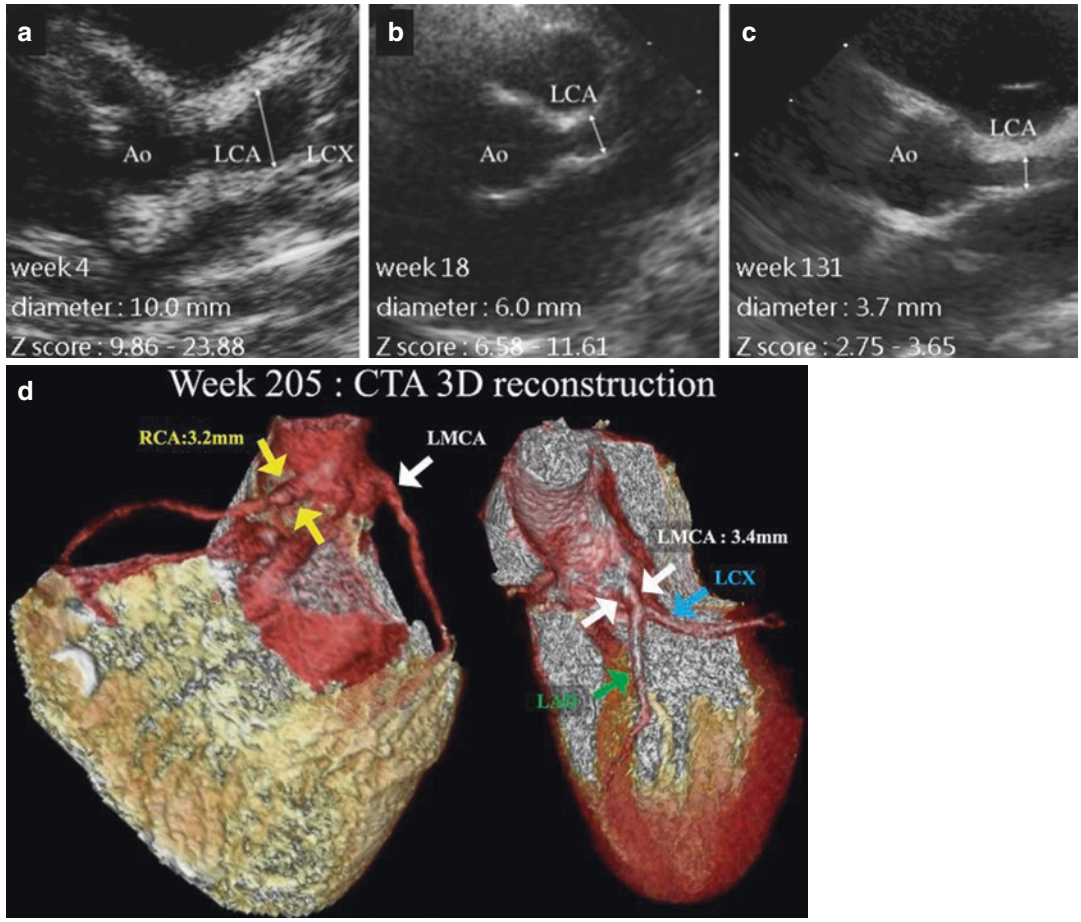

Fig. 19 Regression of the giant aneurysms validated by TTE and CTA. (**a**–**c**) TTE imaging showed coronary luminal dimension regression in week 131, (**d**) the 256-slice, three-dimensional reconstruction coronary CTA imaging also revealed true regression of the giant aneurysm without aneurysmal shape in the coronary vessel wall in week 205. (Imaging from our institution)

Summary (Take Home Message)

This chapter highlights the evidence-based clinical utilization of various imaging modalities in different risk stratification groups of Kawasaki disease-associated coronary aneurysms stages. The authors constructed an integrated application algorithm (Fig. 20) of imaging modalities from acute to chronic and non-invasive to invasive to aid KD experts.

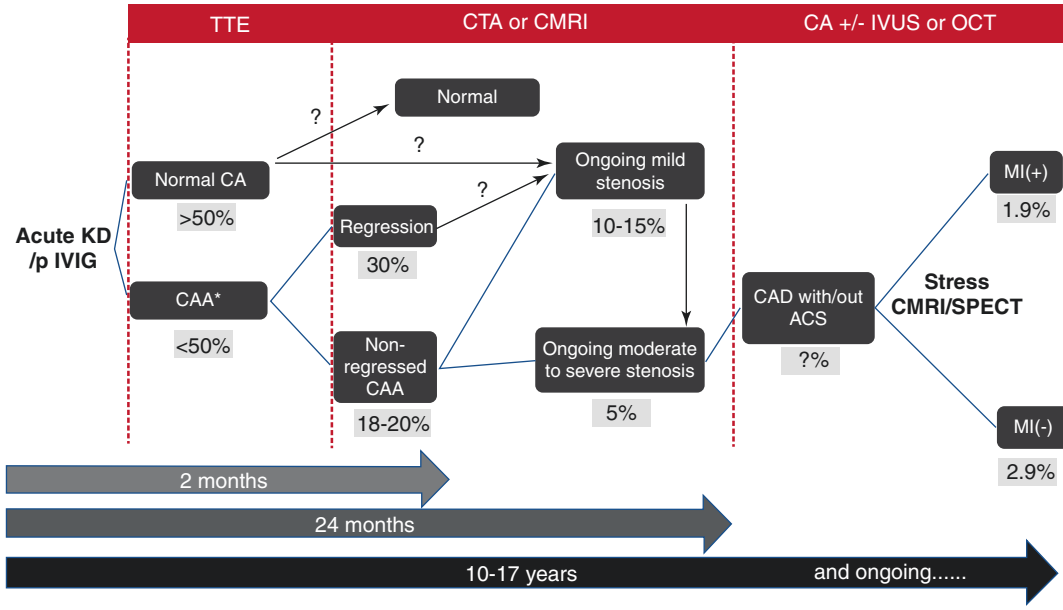

Fig. 20 The natural course [37, 38] of cardiovascular sequela in KD-associated CAA after initial IVIG infusion with corresponding proposed multimodality imaging. The blue box indicates coronary status, and the yellow box indicates the percentage of KD patients, the black box means proposed imaging modalities for follow-up, purple box denotes the long-term outcome for young adults. *Inclusive of transient dilatation; *MI* myocardial infarction, *ACS* acute coronary syndrome

References

1. 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(17):e927–99.
2. Fukazawa R, Kobayashi J, Ayusawa M, et al. JCS/JSCS 2020 guideline on diagnosis and management of cardiovascular sequelae in Kawasaki disease. Circ J. 2020;84(8):1348–407.
3. 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. Pediatrics. 2004;114(6):1708–33.
4. Tai I-H, I-CL, Kuo H-C, Lo M-H, Huang C-F, Lin Y-J, Kuo H-C, Hsieh K-S. Focused optimal coronary ultra sonography: a novel methodology for coronary image evaluation in acute Kawasaki disease. Ultrasound Med Biol. 2017;43.
5. Tai I-H, Hsieh K-S, Kuo H-C, Lo M-H, Huang C-F, Lin Y-J, Kuo H-C. One size doesn't fit all: a novel scoring method for detecting coronary arteritis in acute Kawasaki disease. In: EuroEcho imaging rapid fire abstract 2017, 21st annual meeting of the European Association of Cardiovascular Imaging (EACVI); 2017.
6. Newburger JW, Taubert KA, Shulman ST, et al. Summary and abstracts of the seventh international Kawasaki disease symposium: December 4–7, 2001, Hakone, Japan. Pediatr Res. 2003;53(1):153–7.
7. Tsuiki K, Watanabe M, Ikeda H, et al. Segmental diastolic narrowing of epicardial coronary arteries in aortic regurgitation. Phase analysis by quantitative angiography of coronary artery diameter change during cardiac cycles. Heart Vessel. 1990;6(1):48–54.
8. Di Mario C, Krams R, Gil R, Serruys PW. Slope of the instantaneous hyperemic diastolic coronary flow velocity-pressure relation. A new index for assessment of the physiological significance of coronary stenosis in humans. Circulation. 1994;90(3):1215–24.
9. I-H Tai, Kuo H-C, Hsieh K-S. Optimal coronary interpretation and correlation to acute Kawasaki disease using end-diastole image: the impact on inter-observer variation. In: 12th international Kawasaki disease symposium, 13 June 2018, Yokohama, Japan; 2018.
10. Kahn AM, Budoff MJ, Daniels LB, Oyamada J, Gordon JB, Burns JC. Usefulness of calcium scoring as a screening examination in patients with

a history of Kawasaki disease. Am J Cardiol. 2017;119(7):967–71.
11. Chen PT, Lin MT, Chen YS, Chen SJ, Wu MH. Computed tomography predict regression of coronary artery aneurysm in patients with Kawasaki disease. J Formos Med Assoc. 2017;116(10):806–14.
12. Yu Y, Sun K, Wang R, et al. Comparison study of echocardiography and dual-source CT in diagnosis of coronary artery aneurysm due to Kawasaki disease: coronary artery disease. Echocardiography. 2011;28(9):1025–34.
13. Chu WC, Mok GC, Lam WW, Yam MC, Sung RY. Assessment of coronary artery aneurysms in paediatric patients with Kawasaki disease by multidetector row CT angiography: feasibility and comparison with 2D echocardiography. Pediatr Radiol. 2006;36(11):1148–53.
14. Renzulli M, Piovaccari G, Fattori R. Potential of multislice CT in the follow-up of Kawasaki coronary disease. Eur Heart J. 2006;27(20):2384.
15. Aggarwala G, Iyengar N, Burke SJ, et al. Kawasaki disease: role of coronary CT angiography. Int J Cardiovasc Imaging. 2006;22(6):803–5.
16. Lin E, Alessio A. What are the basic concepts of temporal, contrast, and spatial resolution in cardiac CT? J Cardiovasc Comput Tomogr. 2009;3(6):403–8.
17. Senior R, Moreo A, Gaibazzi N, et al. Comparison of sulfur hexafluoride microbubble (SonoVue)-enhanced myocardial contrast echocardiography with gated single-photon emission computed tomography for detection of significant coronary artery disease: a large European multicenter study. J Am Coll Cardiol. 2013;62(15):1353–61.
18. Kajander S, Joutsiniemi E, Saraste M, et al. Cardiac positron emission tomography/computed tomography imaging accurately detects anatomically and functionally significant coronary artery disease. Circulation. 2010;122(6):603–13.
19. Nagel E, Klein C, Paetsch I, et al. Magnetic resonance perfusion measurements for the noninvasive detection of coronary artery disease. Circulation. 2003;108(4):432–7.
20. Arnese M, Cornel JH, Salustri A, et al. Prediction of improvement of regional left ventricular function after surgical revascularization. A comparison of low-dose dobutamine echocardiography with 201Tl single-photon emission computed tomography. Circulation. 1995;91(11):2748–52.
21. Sugeng L, Mor-Avi V, Weinert L, et al. Quantitative assessment of left ventricular size and function: side-by-side comparison of real-time three-dimensional echocardiography and computed tomography with magnetic resonance reference. Circulation. 2006;114(7):654–61.
22. Wu MT, Hsieh KS, Lin CC, Yang CF, Pan HB. Images in cardiovascular medicine. Evaluation of coronary artery aneurysms in Kawasaki disease by multislice computed tomographic coronary angiography. Circulation. 2004;110(14):e339.
23. Atsuko Suzuki YH, Iiyama T, Hara S, Ono H, Ichida H, Yamashita M. Use of magnetic resonance angiography for assessment of coronary artery lesions caused by Kawasaki disease. In: Saji BT, Newburger JW, Burns JC, Takahashi M, editors. Kawasaki disease: current understanding of the mechanism and evidence-based treatment. Japan: Springer; 2017. p. 279–84.
24. Sato Y, Kato M, Inoue F, et al. Detection of coronary artery aneurysms, stenoses and occlusions by multislice spiral computed tomography in adolescents with kawasaki disease. Circ J. 2003;67(5):427–30.
25. Peng Y, Zeng J, Du Z, Sun G, Guo H. Usefulness of 64-slice MDCT for follow-up of young children with coronary artery aneurysm due to Kawasaki disease: initial experience. Eur J Radiol. 2009;69(3):500–9.
26. Tacke CE, Romeih S, Kuipers IM, Spijkerboer AM, Groenink M, Kuijpers TW. Evaluation of cardiac function by magnetic resonance imaging during the follow-up of patients with Kawasaki disease. Circ Cardiovasc Imaging. 2013;6(1):67–73.
27. Bratis K, Chiribiri A, Hussain T, et al. Abnormal myocardial perfusion in Kawasaki disease convalescence. JACC Cardiovasc Imaging. 2015;8(1):106–8.
28. Tacke CE, Kuipers IM, Groenink M, Spijkerboer AM, Kuijpers TW. Cardiac magnetic resonance imaging for noninvasive assessment of cardiovascular disease during the follow-up of patients with Kawasaki disease. Circ Cardiovasc Imaging. 2011;4(6):712–20.
29. Greil GF, Stuber M, Botnar RM, et al. Coronary magnetic resonance angiography in adolescents and young adults with kawasaki disease. Circulation. 2002;105(8):908–11.
30. Garot J, h-Ici DO, Hovasse T, Piechaud JF. Images in cardiovascular medicine. Demonstration of extensive ischemia in a patient with Kawasaki disease. Circulation. 2010;121(20):e409–12.
31. Nair A, Kuban BD, Tuzcu EM, Schoenhagen P, Nissen SE, Vince DG. Coronary plaque classification with intravascular ultrasound radiofrequency data analysis. Circulation. 2002;106(17):2200–6.
32. Mitani Y, Ohashi H, Sawada H, et al. In vivo plaque composition and morphology in coronary artery lesions in adolescents and young adults long after Kawasaki disease: a virtual histology-intravascular ultrasound study. Circulation. 2009;119(21):2829–36.
33. Nasu K, Tsuchikane E, Katoh O, et al. Accuracy of in vivo coronary plaque morphology assessment: a validation study of in vivo virtual histology compared with in vitro histopathology. J Am Coll Cardiol. 2006;47(12):2405–12.
34. Kilic ID, Caiazzo G, Fabris E, et al. Near-infrared spectroscopy-intravascular ultrasound: scientific basis and clinical applications. Eur Heart J Cardiovasc Imaging. 2015;16(12):1299–306.
35. Tai I-H, Kuo H-C, Hsieh K-S. Significant regression of coronary aneurysm after methylprednisolone pulse therapy in Kawasaki disease. In: The 8th congress of the Asia-Pacific Pediatric Cardiac Society, Taipei; 2021.

36. Tai IH, Hsieh KS, Liao CC, Kuo HC. Regression of giant coronary aneurysm validated by echocardiography in Kawasaki disease. Circ Cardiovasc Imaging. 2021;14(6):e012153.
37. Lin MT, Sun LC, Wu ET, Wang JK, Lue HC, Wu MH. Acute and late coronary outcomes in 1073 patients with Kawasaki disease with and without intravenous gamma-immunoglobulin therapy. Arch Dis Child. 2015;100(6):542–7.
38. Kato H, Sugimura T, Akagi T, et al. Long-term consequences of Kawasaki disease. A 10- to 21-year follow-up study of 594 patients. Circulation. 1996;94(6):1379–85.

Clinical Research of Kawasaki Disease

Hsin Chi

Abstract

Kawasaki disease (KD) is an acute systemic inflammation illness. The diagnostic five clinical manifestations which notable in acute phase are bilateral nonexudative bulbar conjunctivitis which sparing the limbal area, dry fissured lips accompanied with hyperemia in oropharyngeal mucosa or strawberry tongue, unilateral anterior cervical lymphadenopathy, changes in the peripheral extremities, and polymorphous skin rash. Recognition of nonspecific clinical features observed in incomplete KD is key for prompt diagnosis. Kawasaki disease shock syndrome is a potentially life-threatening type of KD. Refractory KD patients are IVIG-resistant and at higher risk of developing coronary artery lesions (CALs). Infants under 1 year of age and adolescent with KD may have different manifestations and high risk of developing CALs.

Keywords

Age · Coronary artery lesions · Fever
Kawasaki disease · Incomplete

H. Chi (✉)
Mackay Children's Hospital, Taipei, Taiwan
e-mail: chi.4531@mmh.org.tw

Kawasaki disease (KD) is an acute systemic inflammation illness primarily affecting children [1, 2]. The diagnosis of KD is made up of fever of at least 5 days' duration in addition to four of five signs of mucocutaneous inflammation, which included bilateral conjunctival injection, erythema of the lips and oral cavity, cervical lymphadenopathy, changes in the distal extremities, and rash [3–5]. Coronary aneurysms generally appear during the convalescence phase. The absence of any laboratory tests for KD means that the diagnosis is made by the presence of a constellation of clinical features [6]. The study of clinical features of KD is important.

Fever

In the absence of other possible explanations, KD should be considered in any child with persistent fever. The diagnosis of classic KD is based on ≥5 days of fever (the first calendar day of fever is day 1 of onset) and ≥4 of the five major clinical features. Patients with KD always have fever and it reflects elevated levels of proinflammatory cytokines, particularly IL-1 and TNF, which mediate vascular inflammation [7]. To distinguish KD from a common viral exanthem, it is known that fever in KD typically remains above 38.5 °C (101.3 °F) and does not respond to or resolve with antibiotic therapy [8]. Fever usually lasts 5–17 days if untreated, with an average duration of 8 days [9]. Spontaneous resolution of

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fever after 7 days should not be considered evidence to exclude the diagnosis of KD. Fever usually resolves within 36 h after IVIG infusion is complete; if not, the patient is considered IVIG resistant. The fever will abate within 36 h after IVIG infusion is complete, but IVIG resistance is considered if fever persist. A small number of patients (15%) fail to respond to an initial single dose of IVIG (persistent or recurrent fever more than 36 h) and require further treatment [10]. In the absence of other clinical criteria for KD, infants ≤6 months of age are most likely to have prolonged fever; these infants are at particularly high risk for coronary artery lesions (CALs) [4]. KD could be diagnosed with only 4 days of fever in the presence of ≥4 major clinical criteria, especially when redness and swelling of the hands and feet are present. Likewise, an experienced clinician who has treated many patients with KD may make the diagnosis in the rare case of only 3 days of fever with the typical clinical presentation. However, Kobayashi et al. modified the fever definition for KD in 2020 [11]. While most physicians are aware that the traditional definition of KD requires a fever lasting more than 5 days, the 24th Nationwide Surveillance reports that approximately 9%, 25%, and 35% of KD patients received their first IVIG treatment on the third, fourth, and fifth day of fever onset, and the prevalence of CALs was lower than before. For this reason, the requirement for the duration of the fever was removed [12].

Conjunctivitis

On the part of ocular manifestation, previous studies have shown that bilateral nonexudative bulbar conjunctivitis and acute uveitis are happened in 80–90% and 20–80%, respectively [13–15]. In the present study in 2020, Shiari et al. reported that the incidence is 63.9% in nonexudative conjunctivitis which significantly higher in children with skin rashes; the incidence of uveitis is 36.1% [16]. This study also mentioned that uveitis has significant correlation with coronary artery dilatation, higher of neutrophil count and CRP levels. Choi et al. reported that uveitis is an important ocular sign in the diagnosis of incomplete KD and uveitis is correlated to older patient age and higher neutrophil count significantly [17]. After all, we know that child presented with nonexudative conjunctivitis and anterior uveitis in early course of the illness, ophthalmologic examinations is still crucial in differentiating KD from other diseases characterized by fever, rash, and bilateral conjunctivitis [18].

Although the most of ocular illness resolved spontaneously within 2–8 weeks [19]. Subconjunctival hemorrhage and punctate keratitis are observed and scleral or conjunctival scarring, posterior synechiae, and blindness have been noted in rare cases [4, 15, 20].

Oral Mucosa Manifestations

As we mentioned of hyperemia in oropharyngeal mucosa, hallmark of clinical presentation are redness of lips and vertical cracking. Virus such as adenovirus, enterovirus, and rhinovirus could be triggers for KD which had been reported before [21, 22]. This correlation indicated the increase in hyperemia in oropharyngeal mucosa caused not only by vasculitis of KD, but also viral pharyngitis related. When we make the diagnosis of KD, oral mucosal involvement is a common manifestation but severe lip changes are unusual [23]. Witness of such extensive lip changes could make the timely diagnosis much difficulty [24, 25]. We have known that 2017 AHA scientific statement said that oral ulcers and pharyngeal exudates are not consistent with KD [4]. But one present case report study had debate it. This case reported that herpes simplex virus as the inducer of KD had been reported in 2020. Such severe mucocutaneous manifestations presented with ulcerations and extensive lip cracking [26]. Those extensive and severe lip and oral mucosa manifestation could complicate with microstomia in some case report [24]. Strawberry tongue is described as exanthem of the tongue which presented by inflamed and hyperplastic papillae. Strawberry tongue can be a manifestation not only in KD but also other diseases such as toxic shock syndrome, scarlet fever, and group A streptococ-

cal pharyngitis [27]. Recently, a Mata-analysis of 4222 cases reported that clinical manifestation with hyperemia of oral mucosa and lip, cervical lymphadenopathy, swelling of the extremities, polymorphous rash are more likely to be IVIG resistant [28]. Isidori et al. said that oral and neck manifestations can be misdiagnosed as suppurative lymphadenitis or retropharyngeal infection at early stage in recent study of 2019 [29]. Not only ocular, lip, and tongue involvement but also other head and neck manifestations are crucial in timely diagnosis of KD.

Lymphadenopathy

The least common criterion found in patients with KD is cervical lymph node enlargement. It is usually unilateral, located in the anterior cervical triangle, nonfluctuant, nontender, and ≥1.5 cm in diameter. For up to 90% of children with incomplete disease, lymphadenopathy is absent, and for those who met criteria for KD, it is 40–50% [30]. Typical sonographic images of cervical lymph nodes feature a "cluster of grapes" appearance, but clinically it is often the case that only a single enlarged node is palpable. Ultrasonography is a valuable imaging modality to distinguish between nonsuppurative adenopathy and abscess formation brought about by suppurative lymphadenitis [31]. Occasionally KD patients present with only fever and cervical lymphadenopathy before other clinical features appear (node-first KD, NFKD). This presentation may be confused with bacterial or viral cervical lymphadenopathy or lymphadenitis and may delay the diagnosis of KD. Kanegaye et al. revealed that patients with NFKD have lower leukocyte, hemoglobin, and platelet counts and higher absolute band counts, C-reactive protein (CRP), alanine transaminase and γ-glutamyl transpeptidase levels, and erythrocyte sedimentation rates compare to bacterial cervical lymphadenitis [32]. Compared with patients with typical KD, patients with NFKD are older (mean age, 4 years vs. 1 year), admitted earlier (3 days vs. 4 days), have more severe inflammation (CRP levels: 7.6 mg/dL vs. 5.8 mg/dL), have more days of fever, but have similar rates of coronary artery lesions (CALs) and resistance to intravenous immune globulin [33].

Skin Manifestations

The skin manifestations of KD may not be simultaneous during a stage so must be carefully sought during medical history [34]. Nonspecific exanthema is observed in 50–90% of KD patients in acute and subacute stage. It appears most commonly as a nonspecific diffuse erythematous maculopapular eruption described as scarlatiniform, morbilliform, or urticarial within the first 5 days of fever [35]. Less commonly, other forms of exanthema-like psoriasiform, erythema multiforme-like, or pustular eruptions have been described [36–38]. Vesiculobullous lesions are rarely seen in KD patients and it should prompt consideration of an alternative diagnosis [4, 39, 40]. During the acute phase of KD, early desquamation with accentuation of the exanthema in the perineal and perianal region is highly suggestive of KD [41]. In a French series of 425 KD patients, erythema and desquamation over perineal region is 30% and 20%. In addition, KD patients in African/Afro-Caribbean and North African/Middle Eastern have significantly more perineal erythema (respectively 51%, 41%, and 27%) and desquamation (respectively 58%, 31%, and 13%) than European Caucasian [35]. The KD patients who underwent Bacillus Calmette–Guerin (BCG) vaccination, develop erythema, induration, crusting or rarely necrotic ulceration at the inoculation site during the acute phase [40]. Reactivation of BCG inoculation site is observed in more than 70% of the patients whose ages are from 6 to 20 months old [42]. However, reactivation of BCG inoculation site is reported only in a quarter of the cases in a Mexican retrospective series of 399 children with KD [43]. Younger children who received BCG vaccine within the 2 years of KD onset have more BCG inoculation site reactivation [43, 44].

Changes in the Extremities

During the acute phase, edema and/or erythema over hands and feet may occur with pain. During the subacute phase, desquamation of fingers and toes is noted in two-thirds of patients [4, 40]. The desquamation pattern of KD begins in a periungual distribution in contrast to the desquamation pattern associated with Coxsackie virus infection. So, diagnosis of periungual desquamation in a young child should look for others signs of KD if present [45]. The KD could occasionally complicate with distal ischemia and result in peripheral gangrene and amputation of toes and fingers in acute and subacute stage. Young infant (mean age 3 months) with incomplete KD are more reported with this complication [46–48]. During the early course of KD, changes in nail color of fingers and/or toes could be seen in acute or subacute stage. Orange/brown transverse chromonychia appear between 5 and 9 days after fever onset and begin to fade 10 days later and it is replaced by transverse leukonychia [49–51]. However, transverse grooves or furrows on nail plate which also known as Beau's lines are usually observed in convalescent stage about 1–2 months after fever onset due to defect in collagen cross-linking during the acute phase of KD. Beau's lines first appear at the cuticle and move forward about 1 mm per week along with the nail growth. Duration and time of the illness can be evaluated by its width and distance from the cuticle [52]. Proximal portion of the nail plate separates from the nail bed as known as onychomadesis sometimes could be found in KD patients and the nonspecific nail abnormalities often resolve spontaneously [53, 54].

Incomplete Kawasaki Disease

There are two main guidelines for diagnosis of incomplete KD, published by the American Heart Association (AHA) and the Japan Pediatric Society (JPS). The JPS defined incomplete KD in a different way from AHA. In the circumstance of excluding other illness, a patient may be diagnosed as incomplete KD if the patient: (1) has three principal clinical features with CALs by echocardiography, (2) fulfills three or four signs in the principal clinical features without CALs but with some features from other significant clinical features. If the patient presented with only one or two principal clinical features, incomplete KD may also be considered. Early in the disease course, elevation of hepatic transaminases may be observed. In the convalescent stage, thrombocytosis may be expected. Other laboratory features of KD such as elevation of BNP or NT-pro BNP, hypoalbuminemia or hyponatremia, and presence of sonographic findings including mitral valve regurgitation or pericardial effusion, and gallbladder hydrops should also raise suspicion for the diagnosis of incomplete KD [11]. According to the new algorithmic approach for evaluation of incomplete KD established by AHA on 2017, the patients who do not fulfill the principal clinical findings may be diagnosed with incomplete KD (sometimes referred to as atypical KD). The diagnosis of incomplete KD is made from the associated clinical findings, compatible laboratory and echocardiographic findings, if the patients had CRP ≥3.0 mg/dL and/or ESR ≥40 mm/h, and three or more than laboratory findings including anemia for age, platelet count of ≥450,000/mm^3 after the seventh day of fever, albumin ≤3.0 g/dL, elevated ALT level, WBC count of ≥15,000/mm^3, or positive echocardiogram [4].

Children diagnosed as incomplete KD are more likely to be at the extremes of the age spectrum, especially the young infant, as compared to those with complete presentation [55, 56]. The diagnostic clinical features which less frequently observed in incomplete KD are cervical lymphadenopathy (19–38.6%) and extremity changes (21–44.3%), and this pattern of finding is similar to the patient with complete presentation [57–61]. In two recent study conducted in 2012 and guideline from AHA in 2017, the patient's laboratory findings and coronary artery outcomes are comparable between the classic KD and incomplete KD [4, 60, 62]. During the Covid-19 pandemic in 2020, there is an association noted between Kawasaki-like multisystem inflammatory syn-

drome among children and SARS-CoV-2, incomplete KD is also recognized as a presentation among these infected children [63–65].

Kawasaki Disease Shock Syndrome

Kawasaki disease shock syndrome (KDSS) is a potentially life-threatening complication of KD. Kanegaye et al. reported KDSS in 13 (7%) of 187 KD patients in 2009, characterized by systolic hypotension for age, a sustained decrease in blood pressure greater than 20% from baseline, or clinical signs of poor perfusion [66]. Studies reported incidence rate 1.45–1.9% in Taiwan [67, 68]. A population-based study of Taiwan finds higher incidence of KDSS in KD patients aged 5 years and older and the age-specific distribution reveals the highest incidence occurred between the ages 8 and 9 years [68]. The mechanism of hypotension is unknown, but possibly including vasculitis with ongoing capillary leakage, myocardial dysfunction, and cytokine dysregulation [69]. Increased production of serum IL-6, IL-10, TNF-α, and IFN-γ are found, which may play a role in the pathogenesis of KDSS [70]. KDSS patients tend to have higher proportions of bandemia, neutrophilia, thrombocytopenia, lower hemoglobin level, higher CRP concentrations, hypoalbuminemia, hyponatremia [67, 70]. Patients who present with shock may be misdiagnosed as having bacterial sepsis or staphylococcal or streptococcal toxic shock syndrome, leading to a delay in treatment with intravenous immunoglobulin [4, 69]. Features that may help distinguish KDSS from toxic shock syndrome include younger age, thrombocytosis, and echocardiographic abnormalities such as valvulitis and coronary artery lesions [71]. Compared with patients with KD, the patients with KDSS have longer duration of fever and longer hospital stays [70]. KDSS patients have more severe inflammation and more intense systemic vasculitis. Multisystem involvement may be seen and presenting with cardiac, gastrointestinal, neurological, respiratory, and renal symptoms [72]. Higher risk of CALs, mitral regurgitation, and prolonged myocardial dysfunction are found [4]. Gamez-Gonzalez et al. report 72% of KDSS patients having CALs in a sample of 103 patients in 2018 [72]. IVIG resistance is more frequent in KDSS patients and it might be due to delayed treatment due to misdiagnosis initially and more severe inflammation [67].

Refractory Kawasaki Disease

Intravenous immunoglobulin (IVIG) although is the established treatment of acute KD, only around 80–90% of KD patients are sensitive to IVIG [73]. Moreover, IVIG-resistant patients are more prone to develop CALs. Therefore, it is important to develop a clinical tool to facilitate earlier intervention and reduce complications for the patients who will be resistant to IVIG. Previously, there were several risk-scoring systems to predict IVIG resistance in KD patients, namely, the Kobayashi, Egami and Sano risk scores [74–76]. Two randomized control trials examined the role of combination therapy with corticosteroids and IVIG as the first-line treatment for high-risk patients. The RAISE study assessed the efficacy of immunoglobulin plus oral prednisolone; another trial by Ogata et al. investigated IVIG and intravenous methylprednisolone-pulse combination therapy [77, 78]. Patients were less likely to need second-line treatment and had lower median z-scores in their coronary arteries in the steroid group. Patients with KD at high risk for nonresponse were identified by scoring system and then selected only these high-risk patients to receive intensified combination primary therapy.

Highest risk of IVIG unresponsiveness are considered in Taiwanese KD patients if the pre-IVIG levels of lymphadenopathy, percentage of neutrophils and albumin are identified [79]. Inflammation and infection result to neutrophil count increase. The severity of the clinical course in patients with shock and sepsis is correlated with marked neutrophilia and lymphocytopenia. The increased production of oxygen intermediate, neutrophil elastase and myeloperoxidase enhance the number and the function of circulating neutrophils. Therefore, it's believed that the pathogenesis of KD vasculitis involves the

activated neutrophil-mediated endothelial injury. Under conditions such as systemic infection and inflammation, the platelet count and the levels of proinflammatory cytokines stimulate megakaryocytic proliferation increase. A few hematological parameters such as the Neutrophil-to-Lymphocyte Ratios (NLR) and Platelet-to-Lymphocyte Ratios (PLR) are thought to be useful markers of the severity of the systemic inflammatory response [80]. As the Kobayashi, Egami and Sano scores consist of 7, 5 and 3 factors, the NLR and PLR can be calculated quickly, more conveniently to predict the possibility of IVIG resistance and help identify patients who might be expected to receive a benefit from anti-inflammatory processes. The risk of cardiac events and mortality in patients undergoing percutaneous coronary interventions could be independently predicted by the NLR (≥3.83) and PLR (≥150) alone but the NLR (≥3.83) and PLR (≥150) together had a much greater predictive ability than either NLR or PLR separately. Kawamura et al. revealed that the NLR is an independent predictor of IVIG resistance in patients with KD [81].

Infant Kawasaki Disease

Infant KD, especially for those patients who are under 6 months old, often presents as incomplete forms [4, 55, 82]. For the neonates who were under 28 days old, the incidence of KD is rare. There is a theory to explain this finding that maternal antibody could be passed from mother to neonate and reached protection effect [83]. A previous study reported that toxic shock syndrome toxin-1 might be involved in the pathogenesis of KD and maternal antibody against this toxin may protect young infants from developing KD [82, 84]. In the infant <6 months of age, prolonged fever and irritability are commonly found clinical manifestations of KD [4, 85].

Many evidences had showed infant KD presented with difficulty in diagnosis due to its atypical pattern, which often led to delay in recognition and IVIG treatment. Thus, the risk of CALs were higher compared to other age group [4, 55, 85–90]. Also, symptoms and signs of myocardial ischemia or infarction may be atypical and nonspecific, particularly in infants [4]. The least found clinical feature in infancy is lymphadenopathy, ranging from 13 to 47%. Lymphadenopathy is more frequent in the toddler and preschool age groups [88]. The other four clinical features shared similar frequency with subtle difference in majority among each study [55, 85–89].

Reactivation of the BCG site is a good predictor in KD and can help with early diagnosis in infant with atypical presentation [91–93]. A large analysis conducted in 15,524 KD patients in Japan reported that more than 70% of patients aged 3–20 months had redness or crust formation at the BCG. Notably, more than 80% patients aged 6–11 months had BCG site reactivation [42]. Chang et al. reported hydrops of gallbladder was more common in patients older than 6 months old than infants under 6 months old. (0% vs. 16%, $P < 0.001$) [55]. Other additional symptoms including cough and diarrhea were also recorded as common symptoms in the infant group [85, 88].

Kawasaki Disease in Adolescents

KD predominantly affects infants and young children but is increasingly recognized in older children. Studies reported the proportion of patients presenting with KD in adolescence to be 1% [94] to 6% [87]. A greater frequency of older children and adolescents with KD present with incomplete clinical features, making the diagnosis challenging and contribute to delay in diagnosis and treatment. Such delay may be associated with higher risk of coronary artery abnormalities [87, 94, 95]. Manlhiot et al. reported 25% of coronary artery abnormalities in adolescence (patients >9 years of age) [87]. A cross sectional study published from Indonesia comparing adolescents (aged >10 years) and children (aged ≤10 years) revealed more often incomplete KD in adolescents (59% vs. 29%). In KD subjects ≤10 years, manifestation of conjunctivitis, red lips/strawberry tongue, rash, and extremity changes is more characteristic, while patients in adolescence more often display features of cervical lymphadenopathy and coronary dilatation [96].

Laboratory Tests for KD

There were several laboratory parameters had been shown to be related to infant KD, including higher platelet counts [86–88, 97], lower hemoglobin levels, and lower albumin levels than group older than 1 year old [55, 86, 87]. In a recent Italian survey, AST was significantly higher in incomplete forms of infant KD, and this may helped with clinical diagnosis for atypical cases [89]. Higher level of Pro-BNP is also believed to be a good tool to diagnose incomplete KD in infants [97]. KD is diagnosed based on clinical criteria and no specific diagnostic laboratory test for KD is available to date. However, it is still challenging to diagnose KD due to ambiguously clinical pictures and shared laboratory similarities among a few bacterial disease and viral disease. The severity of systemic inflammation reflected in a variety of laboratory indices since KD is a systemic inflammatory process. Some parameters, therefore, including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell (WBC) count and differentials, albumin, hemoglobin, alanine transaminase(ALT), platelet count, and pyuria, have been used for the diagnosis of incomplete KD [5]. Furthermore, Laboratory parameters before and shortly after IVIG may reflect the severity of inflammation in KD patients and assist in informing further management [98]. Seo et al. classify patients into six groups and they find significant differences across the six groups [99]. WBCs, neutrophils differential and CRP values are the highest and albumin, hemoglobin and lymphocyte differential values are lowest in the sixth day group in the laboratory findings. The platelet count tends to increase after peak day along with increasing days of fever and shows highest value in the >eighth day group. Total protein level is the highest in the >eighth day group, and the ESR values do not fluctuate significantly. The AST and ALT values are highest in the <third day group. Negative correlations between the CRP and albumin and between the CRP and hemoglobin, and positive correlation between the CRP and neutrophil differential ($P < 0.01$ or $P < 0.05$) have been found. There is positive correlation between the albumin and hemoglobin ($P < 0.01$) and there is a negative correlation between albumin and neutrophil differential ($P < 0.05$).

References

1. Singh S, Vignesh P, Burgner D. The epidemiology of Kawasaki disease: a global update. Arch Dis Child. 2015;100(11):1084–8.
2. Lue HC, Chen LR, Lin MT, Chang LY, Wang JK, Lee CY, et al. Estimation of the incidence of Kawasaki disease in Taiwan. A comparison of two data sources: nationwide hospital survey and national health insurance claims. Pediatr Neonatol. 2014;55(2):97–100.
3. Alexoudi I, Kanakis M, Kapsimali V, Vaiopoulos G. Kawasaki disease: current aspects on aetiopathogenesis and therapeutic management. Autoimmun Rev. 2011;10(9):544–7.
4. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, 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(17):e927–e99.
5. Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, 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(17):2747–71.
6. Greco A, De Virgilio A, Rizzo MI, Tombolini M, Gallo A, Fusconi M, et al. Kawasaki disease: an evolving paradigm. Autoimmun Rev. 2015;14(8):703–9.
7. El-Radhi AS, Carroll J, Klein N. Fever in non-infectious diseases. In: Clinical manual of fever in children. Berlin: Springer; 2009. p. 137–73.
8. Golshevsky D, Cheung M, Burgner D. Kawasaki disease—the importance of prompt recognition and early referral. Aust Fam Physician. 2013;42:473–6.
9. Salo E, Pelkonen P, Pettay O. Outbreak of Kawasaki syndrome in Finland. Acta Paediatr Scand. 1986;75(1):75–80.
10. Jaggi P, Wang W, Dvorchik I, Printz B, Berry E, Kovalchin JP, et al. Patterns of fever in children after primary treatment for Kawasaki disease. Pediatr Infect Dis J. 2015;34(12):1315–8.
11. Kobayashi T, Ayusawa M, Suzuki H, Abe J, Ito S, Kato T, et al. Revision of diagnostic guidelines for Kawasaki disease (6th revised edition). Pediatr Int. 2020;62(10):1135–8.
12. Son MBF, Newburger JW. Kawasaki disease. Pediatr Rev. 2018;39(2):78–90.
13. Cunningham ET Jr. Uveitis in children. Ocul Immunol Inflamm. 2000;8(4):251–61.

14. Madhusudan S, Singh S, Suri D, Gupta A, Gupta A. Acute anterior uveitis as the presenting feature of Kawasaki disease. Indian J Pediatr. 2014;81(4):415.
15. Burke MJ, Rennebohm RM, Crowe W, Levinson JE. Follow-up ophthalmologic examinations in children with Kawasaki's disease. Am J Ophthalmol. 1981;91(4):537–9.
16. Shiari R, Jari M, Karimi S, Salehpour O, Rahmani K, Hassas Yeganeh M, et al. Relationship between ocular involvement and clinical manifestations, laboratory findings, and coronary artery dilatation in Kawasaki disease. Eye (Lond). 2020;34(10):1883–7.
17. Choi HS, Lee SB, Kwon JH, Kim HS, Sohn S, Hong YM. Uveitis as an important ocular sign to help early diagnosis in Kawasaki disease. Korean J Pediatr. 2015;58(10):374–9.
18. Smith LB, Newburger JW, Burns JC. Kawasaki syndrome and the eye. Pediatr Infect Dis J. 1989;8(2):116–8.
19. Burke MJ, Rennebohm RM. Eye involvement in Kawasaki disease. J Pediatr Ophthalmol Strabismus. 1981;18(5):7–11.
20. Burns JC, Joffe L, Sargent RA, Glode MP. Anterior uveitis associated with Kawasaki syndrome. Pediatr Infect Dis. 1985;4(3):258–61.
21. Chang LY, Lu CY, Shao PL, Lee PI, Lin MT, Fan TY, et al. Viral infections associated with Kawasaki disease. J Formos Med Assoc. 2014;113(3):148–54.
22. Cavallo F, Chiarelli F. An outbreak of Kawasaki-like disease in children during SARS-CoV-2 epidemic: no surprise? Acta Biomed. 2020;91(3):e2020015.
23. Singh A, Jindal AK, Pilania RK, Indla RT, Suri D, Singh S. Severe lip involvement in Kawasaki disease: a clinical oddity. J Clin Rheumatol. 2020;26(5):e149–e50.
24. Cakan M, Aktay Ayaz N, Keskindemirci G, Onan SH, Akoz Saydam F. A case of Kawasaki disease with severe lip and oral mucosa involvement complicated with microstomia and corrected with surgery. Arch Rheumatol. 2018;33(2):238–40.
25. Falcini F, Ricci L, Poggi GM, Simonini G, Calabri GB, de Martino M. Severe cutaneous manifestations in a child with refractory Kawasaki disease. Rheumatology (Oxford, England). 2006;45(11):1444–5.
26. Banday AZ, Neelam H, Singh MP, Sudhakar M, Jindal AK. Severe lip excoriation in Kawasaki disease: beware of herpes simplex virus. Rheumatology (Oxford, England). 2020; https://doi.org/10.1093/rheumatology/keaa081.
27. Shimizu A, Ebara Y, Nomura S, Yamada Y. Chronological changes in strawberry tongue in toxic shock syndrome toxin-1-mediated exanthematous disease. J Gen Fam Med. 2020;21(6):280–1.
28. Li X, Chen Y, Tang Y, Ding Y, Xu Q, Sun L, et al. Predictors of intravenous immunoglobulin-resistant Kawasaki disease in children: a meta-analysis of 4442 cases. Eur J Pediatr. 2018;177(8):1279–92.
29. Isidori C, Sebastiani L, Esposito S. A case of incomplete and atypical Kawasaki disease presenting with retropharyngeal involvement. Int J Environ Res Public Health. 2019;16(18):3262.
30. Fukushige J, Takahashi N, Ueda Y, Ueda K. Incidence and clinical features of incomplete Kawasaki disease. Acta Paediatr. 1994;83(10):1057–60.
31. Tashiro N, Matsubara T, Uchida M, Katayama K, Ichiyama T, Furukawa S. Ultrasonographic evaluation of cervical lymph nodes in Kawasaki disease. Pediatrics. 2002;109(5):E77.
32. Kanegaye JT, Van Cott E, Tremoulet AH, Salgado A, Shimizu C, Kruk P, et al. Lymph-node-first presentation of Kawasaki disease compared with bacterial cervical adenitis and typical Kawasaki disease. J Pediatr. 2013;162(6):1259–63, 63.e1–2.
33. Jun WY, Ann YK, Kim JY, Son JS, Kim SJ, Yang HS, et al. Kawasaki disease with fever and cervical lymphadenopathy as the sole initial presentation. Korean Circ J. 2017;47(1):107–14.
34. Piram M, Burns JC. Kawasaki disease for the pediatric dermatologist: skin manifestations and new insights into the pathophysiology. Clin Exp Dermatol. 2021;46(3):503–9.
35. Piram M, Darce Bello M, Tellier S, Di Filippo S, Boralevi F, Madhi F, et al. Defining the risk of first intravenous immunoglobulin unresponsiveness in non-Asian patients with Kawasaki disease. Sci Rep. 2020;10(1):3125.
36. Okada S, Hirano R, Okazaki-Emi S, Fukunaga S, Ishikawa Y. Erythema multiforme- and not erythema multiforme-like rashes in Kawasaki disease. Pediatr Int. 2019;61(12):1272–4.
37. Kamath S, Gurnee EA, Schenck OL, Chamlin SL, Mancini AJ. Pustular eruption in Kawasaki disease. J Pediatr. 2019;213:241–e1.
38. Haddock ES, Calame A, Shimizu C, Tremoulet AH, Burns JC, Tom WL. Psoriasiform eruptions during Kawasaki disease (KD): a distinct phenotype. J Am Acad Dermatol. 2016;75(1):69–76.e2.
39. Demir F, Abul MH, Dilber E, Orhan F, Kalyoncu M. A case of Kawasaki disease presenting with atypical cutaneous involvement and mimicking Stevens–Johnson syndrome. North Clin Istanb. 2020;7(1):67–70.
40. Bayers S, Shulman ST, Paller AS. Kawasaki disease: part I. Diagnosis, clinical features, and pathogenesis. J Am Acad Dermatol. 2013;69(4):501.e1–11; quiz 11–2.
41. Vignesh P, Singh S. Perianal skin peeling: an important clinical pointer toward Kawasaki disease. Eur J Rheumatol. 2018;5(1):81–2.
42. Uehara R, Igarashi H, Yashiro M, Nakamura Y, Yanagawa H. Kawasaki disease patients with redness or crust formation at the Bacille Calmette–Guerin inoculation site. Pediatr Infect Dis J. 2010;29(5):430–3.
43. Garrido-Garcia LM, Castillo-Moguel A, Vazquez-Rivera M, Cravioto P, Fernando G. Reaction of the BCG scar in the acute phase of Kawasaki disease in Mexican children. Pediatr Infect Dis J. 2017;36(10):e237–e41.

44. Araki T, Kodera A, Kitada K, Fujiwara M, Muraoka M, Abe Y, et al. Analysis of factors associated with development of Bacille Calmette–Guerin inoculation site change in patients with Kawasaki disease. J Int Med Res. 2018;46(4):1640–8.
45. Wang S, Best BM, Burns JC. Periungual desquamation in patients with Kawasaki disease. Pediatr Infect Dis J. 2009;28(6):538–9.
46. Mohsin M, Akhtar S. Kawasaki disease complicated by peripheral gangrene and a ventricular septal defect: an unusual association. Turk J Pediatr. 2019;61(2):301–4.
47. Malekzadeh I, Ziaee V, Sadrosadat T, Moardinejad MH, Sayadpour-Zanjani K. Kawasaki disease and peripheral gangrene in infancy. Iran J Pediatr. 2015;25(6):e3309.
48. Durall AL, Phillips JR, Weisse ME, Mullett CJ. Infantile Kawasaki disease and peripheral gangrene. J Pediatr. 2006;149(1):131–3.
49. Yamazaki-Nakashimada MA, Deguchi K, Gamez-Gonzalez B, Ulloa-Gutierrez R, Hamada H. Orange–brown chromonychia: a valid sign in Kawasaki disease in children of different ethnicities. Int J Rheum Dis. 2019;22(6):1160–1.
50. Thapa R, Pal P. Transverse orange–brown chromonychia in Kawasaki disease. Int J Dermatol. 2010;49(2):227–8.
51. Pal P, Giri PP. Orange–brown chromonychia, a novel finding in Kawasaki disease. Rheumatol Int. 2013;33(5):1207–9.
52. Parish LC. Hurwitz clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence. JAMA. 2012;307(15):1646.
53. Leung AKC, Leong KF, Lam JM. Onychomadesis in a 20-month-old child with Kawasaki disease. Case Rep Pediatr. 2019;2019:3156736.
54. Jindal AK, Bishnoi A, Dogra S, Singh S. A unique combination of nail changes in a boy with Kawasaki disease. J Clin Rheumatol. 2020;26(6):e210–e1.
55. Chang F-Y, Hwang B, Chen S-J, Lee P-C, Meng CCL, Lu J-H. Characteristics of Kawasaki disease in infants younger than six months of age. Pediatr Infect Dis J. 2006;25(3):241–4.
56. Chuang CH, Hsiao MH, Chiu CH, Huang YC, Lin TY. Kawasaki disease in infants three months of age or younger. J Microbiol Immunol Infect. 2006;39(5):387–91.
57. Sonobe T, Kiyosawa N, Tsuchiya K, Aso S, Imada Y, Imai Y, et al. Prevalence of coronary artery abnormality in incomplete Kawasaki disease. Pediatr Int. 2007;49(4):421–6.
58. Yu JJ. Diagnosis of incomplete Kawasaki disease. Korean J Pediatr. 2012;55(3):83.
59. Perrin L, Letierce A, Guitton C, Tran T-A, Lambert V, Koné-Paut I. Comparative study of complete versus incomplete Kawasaki disease in 59 pediatric patients. Joint Bone Spine. 2009;76(5):481–5.
60. Manlhiot C, Christie E, McCrindle BW, Rosenberg H, Chahal N, Yeung RS. Complete and incomplete Kawasaki disease: two sides of the same coin. Eur J Pediatr. 2012;171(4):657–62.
61. Yellen ES, Gauvreau K, Takahashi M, Burns JC, Shulman S, Baker AL, et al. Performance of 2004 American Heart Association recommendations for treatment of Kawasaki disease. Pediatrics. 2010;125(2):e234–e41.
62. Ghelani SJ, Sable C, Wiedermann BL, Spurney CF. Increased incidence of incomplete Kawasaki disease at a pediatric hospital after publication of the 2004 American Heart Association guidelines. Pediatr Cardiol. 2012;33(7):1097–103.
63. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet. 2020;395(10239):1771–8.
64. Toubiana J, Poirault C, Corsia A, Bajolle F, Fourgeaud J, Angoulvant F, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. BMJ. 2020;369:m2094.
65. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet. 2020;395(10237):1607–8.
66. Kanegaye JT, Wilder MS, Molkara D, Frazer JR, Pancheri J, Tremoulet AH, et al. Recognition of a Kawasaki disease shock syndrome. Pediatrics. 2009;123(5):e783–e9.
67. Chen PS, Chi H, Huang FY, Peng CC, Chen MR, Chiu NC. Clinical manifestations of Kawasaki disease shock syndrome: a case-control study. J Microbiol Immunol Infect. 2015;48(1):43–50.
68. Lin MT, Fu CM, Huang SK, Huang SC, Wu MH. Population-based study of Kawasaki disease shock syndrome in Taiwan. Pediatr Infect Dis J. 2013;32(12):1384–6.
69. Dominguez SR, Friedman K, Seewald R, Anderson MS, Willis L, Glodé MP. Kawasaki disease in a pediatric intensive care unit: a case-control study. Pediatrics. 2008;122(4):e786–e90.
70. Li Y, Zheng Q, Zou L, Wu J, Guo L, Teng L, et al. Kawasaki disease shock syndrome: clinical characteristics and possible use of IL-6, IL-10 and IFN-gamma as biomarkers for early recognition. Pediatr Rheumatol Online J. 2019;17(1):1.
71. Lin YJ, Cheng MC, Lo MH, Chien SJ. Early differentiation of Kawasaki disease shock syndrome and toxic shock syndrome in a pediatric intensive care unit. Pediatr Infect Dis J. 2015;34(11):1163–7.
72. Gamez-Gonzalez LB, Moribe-Quintero I, Cisneros-Castolo M, Varela-Ortiz J, Munoz-Ramirez M, Garrido-Garcia M, et al. Kawasaki disease shock syndrome: unique and severe subtype of Kawasaki disease. Pediatr Int. 2018;60(9):781–90.
73. Yilmazer MM, Ozdemir R, Mese T, Kucuk M, Oner T, Devrim I, et al. Kawasaki disease in Turkish children: a single center experience with emphasis on intrave-

nous immunoglobulin resistance and giant coronary aneurysms. Turk J Pediatr. 2019;61(5):648–56.
74. Kobayashi T, Inoue Y, Takeuchi K, Okada Y, Tamura K, Tomomasa T, et al. Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. Circulation. 2006;113(22):2606–12.
75. Egami K, Muta H, Ishii M, Suda K, Sugahara Y, Iemura M, et al. Prediction of resistance to intravenous immunoglobulin treatment in patients with Kawasaki disease. J Pediatr. 2006;149(2):237–40.
76. Sano T, Kurotobi S, Matsuzaki K, Yamamoto T, Maki I, Miki K, et al. Prediction of non-responsiveness to standard high-dose gamma-globulin therapy in patients with acute Kawasaki disease before starting initial treatment. Eur J Pediatr. 2007;166(2):131–7.
77. Kobayashi T, Saji T, Otani T, Takeuchi K, Nakamura T, Arakawa H, et al. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial. Lancet. 2012;379(9826):1613–20.
78. Ogata S, Ogihara Y, Honda T, Kon S, Akiyama K, Ishii M. Corticosteroid pulse combination therapy for refractory Kawasaki disease: a randomized trial. Pediatrics. 2012;129(1):e17–23.
79. Lin MT, Chang CH, Sun LC, Liu HM, Chang HW, Chen CA, et al. Risk factors and derived formosa score for intravenous immunoglobulin unresponsiveness in Taiwanese children with Kawasaki disease. J Formos Med Assoc. 2015;115(5):350–5.
80. Acet H, Ertas F, Akil MA, Ozyurtlu F, Polat N, Bilik MZ, et al. Relationship between hematologic indices and global registry of acute coronary events risk score in patients with ST-segment elevation myocardial infarction. Clin Appl Thromb Hemost. 2016;22(1):60–8.
81. Kawamura Y, Takeshita S, Kanai T, Yoshida Y, Nonoyama S. The combined usefulness of the neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in predicting intravenous immunoglobulin resistance with Kawasaki disease. J Pediatr. 2016;178:281–4.e1.
82. Hangai M, Kubota Y, Kagawa J, Yashiro M, Uehara R, Nakamura Y, et al. Neonatal Kawasaki disease: case report and data from nationwide survey in Japan. Eur J Pediatr. 2014;173(11):1533–6.
83. Rowley AH, Baker SC, Shulman ST, Garcia FL, Guzman-Cottrill JA, Chou P, et al. Detection of antigen in bronchial epithelium and macrophages in acute Kawasaki disease by use of synthetic antibody. J Infect Dis. 2004;190(4):856–65.
84. Nomura Y, Yoshinaga M, Masuda K, Takei S, Miyata K. Maternal antibody against toxic shock syndrome toxin-1 may protect infants younger than 6 months of age from developing Kawasaki syndrome. J Infect Dis. 2002;185(11):1677–80.
85. Singh S, Agarwal S, Bhattad S, Gupta A, Suri D, Rawat A, et al. Kawasaki disease in infants below 6 months: a clinical conundrum? Int J Rheum Dis. 2016;19(9):924–8.
86. Liu H-C, Lo C-W, Hwang B, Lee P-C. Clinical manifestations vary with different age spectrums in infants with Kawasaki disease. Sci World J. 2012;2012:210382.
87. Manlhiot C, Yeung RS, Clarizia NA, Chahal N, McCrindle BW. Kawasaki disease at the extremes of the age spectrum. Pediatrics. 2009;124(3):e410–e5.
88. Shi L, Li J, Qie D, Hua X, Pan J, Shi X, et al. Clinical manifestations of Kawasaki disease in different age groups: retrospective data from Southwest China. Clin Rheumatol. 2020;39(10):3027–32.
89. Mastrangelo G, Cimaz R, Calabri GB, Simonini G, Lasagni D, Resti M, et al. Kawasaki disease in infants less than one year of age: an Italian cohort from a single center. BMC Pediatr. 2019;19(1):1–7.
90. Yeo Y, Kim T, Ha K, Jang G, Lee J, Lee K, et al. Incomplete Kawasaki disease in patients younger than 1 year of age: a possible inherent risk factor. Eur J Pediatr. 2009;168(2):157–62.
91. Uehara R, Igarashi H, Yashiro M, Nakamura Y, Yanagawa H. Kawasaki disease patients with redness or crust formation at the Bacille Calmette–Guérin inoculation site. Pediatr Infect Dis J. 2010;29(5):430–3.
92. Kang JH, Hong SJ, Seo IA, Kwak MH, Cho SM, Kim DK, et al. Early detection of Kawasaki disease in infants. Korean Circ J. 2015;45(6):510.
93. Seo JH, Yu JJ, Ko HK, Choi HS, Kim Y-H, Ko J-K. Diagnosis of incomplete Kawasaki disease in infants based on an inflammation at the Bacille Calmette-Guérin inoculation site. Korean Circ J. 2012;42(12):823.
94. Zhao QM, Huang M, Huang MR, Chen S, Liu F, Huang GY, et al. Characteristics and trends in diagnosis of Kawasaki disease outside the usual age range. Clin Rheumatol. 2021;40(4):1515–23.
95. Cai Z, Zuo R, Liu Y. Characteristics of Kawasaki disease in older children. Clin Pediatr. 2011;50(10):952–6.
96. Advani N, Santoso LA, Sastroasmoro S. Profile of Kawasaki disease in adolescents: is it different. Acta Med Indones. 2019;51(1):42–6.
97. No SJ, Kim DO, Choi KM, Eun LY. Do predictors of incomplete Kawasaki disease exist for infants? Pediatr Cardiol. 2013;34(2):286–90.
98. Hwang JY, Lee KY, Rhim JW, Youn YS, Oh JH, Han JW, et al. Assessment of intravenous immunoglobulin non-responders in Kawasaki disease. Arch Dis Child. 2011;96(11):1088–90.
99. Seo YM, Kang HM, Lee SC, Yu JW, Kil HR, Rhim JW, et al. Clinical implications in laboratory parameter values in acute Kawasaki disease for early diagnosis and proper treatment. Korean J Pediatr. 2018;61(5):160–6.

Laboratory Research and Scoring System of Kawasaki Disease

Ho-Chang Kuo

Abstract

Laboratory data is very important for distinguish Kawasaki disease (KD) from children with fever. Laboratory data are variable including basic routine complete blood count, differential blood cell count, electrolyte, C-reactive protein, erythrocyte sedimentation rate, and liver enzyme, and some advanced examinations. This chapter will focus on the routine laboratory data in the role of distinguishing KD from fever illness in children and prediction score system for high-risk group of KD.

Keywords

Kawasaki disease · Laboratory data · Score system

H.-C. Kuo (✉)
Kawasaki Disease Center, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan

Department of Pediatrics, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan

Chang Gung University College of Medicine, Taoyuan, Taiwan

Laboratory Data for Distinguishing Kawasaki Disease from Fever in Children

Fever [1] is the most common reason that children see a doctor in a pediatric emergency department. In most cases, the main cause of fever is infection [2]. Among children with fever (FC), Kawasaki disease (KD) is the most worrying cause of acquired heart disease in children under 5 years of age [3]. KD is characterized by persistent fever for more than 5 days and five main clinical manifestations, including diffuse mucosal inflammation (1 mouth), bilateral nonsuppurative conjunctivitis (2 eyes), and nonsuppurative cervical lymphadenopathy (3 fingers to check the lymph nodes in the neck), rigid angioedema of the hands and feet (changes in 4 limbs), and polymorphic rash (5 means many skin rashes). According to the 2017 American Heart Association (AHA) statement, fever lasting more than 96 h with erythematous changes on the palm and three other major symptoms can also fit the diagnosis of KD (rule of 4: 4 days of fever with four major clinical presentations, including 4 limbs' induration) [4, 5]. However, all the major signs for diagnosing KD are subjective. To prevent the most common and severe sequelae and complications of coronary artery aneurysms (CAA) in KD patients [4, 6], intravenous immunoglobulin (IVIG) therapy needs to be administrated early. Randomized controlled studies and meta-analyses have all confirmed that IVIG

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treatment for KD patients is most effective within 10 days after fever onset and within 10–12 h of treatment; this can reduce the risk of CAA from 20–25% to 3–5% [5, 7–9]. Therefore, early recognition of KD is particularly important for both clinicians and parents. However, the challenge for clinicians is to distinguish KD from other febrile diseases as early as possible, because KD has many common clinical symptoms with other febrile diseases in childhood [10]. In addition, 20–30% of patients with KD do not fully meet the above diagnostic criteria and are therefore considered to have incomplete KD, which usually makes the diagnosis more challenging for inexperienced pediatricians [5, 11]. Patients with fever for ≥5 days (with 2 or 3 principal clinical features for KD) without other explanation should undergo laboratory testing, and if there is evidence of systemic inflammation, an echocardiogram should be obtained even if the patient does not fully meet the clinical criteria for KD. Infants ≤6 months old with fever for ≥7 days without other explanation should undergo laboratory testing, and if evidence of systemic inflammation is found, an echocardiogram should be obtained even if the infant has no clinical criteria for KD. The 2004 AHA supplemental laboratory criteria for KD included (1) albumin ≤3.0 g/dL; (2) anemia for age; (3) elevation of alanine aminotransferase; (4) platelets after 7 days ≥450,000/mm^3; (5) white blood cell count ≥15,000/mm^3; and (6) urine ≥10 white blood cells/high-power field. If a patient has more than 3 supplementary criteria, incomplete KD is diagnosed and IVIG should be prescribed before performing echocardiography.

Although there is no single laboratory test that can be used as the standard diagnostic tool for KD, many quick methods have been proposed to identify KD earlier [12–14]. However, these methods are far from being applied in clinical practice. Ling et al. described the KD scoring system that uses clinical manifestations, laboratory test results, or a combination of them to distinguish KD from FC [15] and further improved their two-step algorithm with another cohort in 2016 [10]. However, subjective clinical manifestations still play an important role in their predictive models.

Clinical Features Differentiating Children with Fever Suspected of Kawasaki Disease (Do Not Fit KD Diagnosis Upon Admission, But Fit Diagnosis During Follow-Up) [16]

When the initial clinical symptoms do not meet the traditional standards or the echocardiogram is normal, KD patients may miss the diagnosis or delay the diagnosis. Yan et al. conducted a study on a total of 50 febrile children who were initially suspected of having KD but did not meet the diagnostic criteria of the American Heart Association (AHA). However, some of these patients were diagnosed with KD when they visited the clinic for the second time at outpatient department. The patients' characteristics, clinical symptoms, and laboratory data (initial data at the first visit) were analyzed. Among them, 10 patients were diagnosed with KD at the second visit (group 1), while the other 40 patients still did not meet the requirements for KD diagnosis (group 2). Compared with group 2, a higher ratio of neutrophils to lymphocytes (NLR, $p = 0.037$) and a higher level of C-reactive protein (CRP, $p = 0.02$) were found in group 1. Patients with NLR >1.33 and CRP greater than 33 mg/L are more likely to suffer from KD (sensitivity 90%, specificity 69.2%, $p = 0.001$; odds ratio 20.25, 95% confidence interval 2.3–178.25). For patients with suspected KD who initially did not meet the criteria, clinicians should pay special attention to the initial laboratory data of elevated neutrophil to lymphocyte ratio and CRP levels and follow up such patients within 1 or 2 weeks after discharged from admission ward.

Nomogram Model for Predicting Kawasaki Disease

Liu et al. [17] published a report with a total of 420 children (227 KD and 193 sepsis). Logistic regression and a nomogram model were used to analyze the laboratory markers. For the study, 247 children were randomly selected

as the training modeling group and 173 as the validation group. After completing logistic regression analysis, white blood cell (WBC), anemia, procalcitonin (PCT), C-reactive protein (CRP), albumin, and alanine transaminase (ALT) demonstrated a significant difference with regard to predicting KD from sepsis. Patients were scored according to the nomogram, and patients with scores greater than 175 were placed in the high-risk group of KD. The area under the curve of the receiver operating characteristic (ROC) curve of the modeling group was 0.873, sensitivity was 0.893, and specificity was 0.746, while the ROC curve in the validation group was 0.831, sensitivity was 0.709, and specificity was 0.795. A novel nomogram prediction model may be help clinicians identify KD from sepsis with high accuracy (Fig. 1).

The Importance of Eosinophils in Kawasaki Disease

There is currently no single laboratory data that can distinguish KD from other febrile infectious diseases. Liu et al. [18] reported a study of 800 children (249 KD and 551 age- and gender-matched non-KD febrile infectious diseases), in which univariate and multivariate logistic regression and nomogram model were used to analyze the experimental results. The researchers randomly selected 562 children as the model group and 238 as the verification group. The prediction nomogram includes the percentage of high eosinophils (100 points), high C-reactive protein (93 points), high alanine aminotransferase (84 points), low albumin (79 points), and high white blood cells (64 points). This produced an area under the curve of 0.873 for the model group and

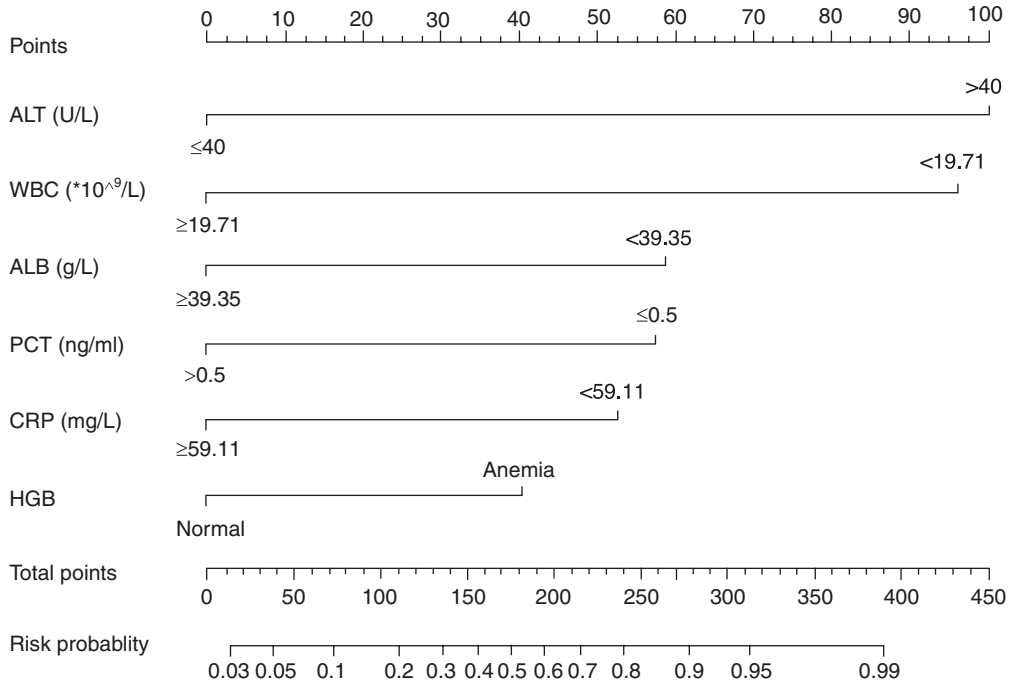

Fig. 1 Nomogram prediction score differentiating Kawasaki disease from sepsis. *WBC* white blood cell, *HGB* hemoglobin, *PCT* procalcitonin, *CRP* C-reactive protein, *ALB* albumin, *ALT* alanine transaminase. (Adapted from Sci Rep. 2020;10(1):13745)

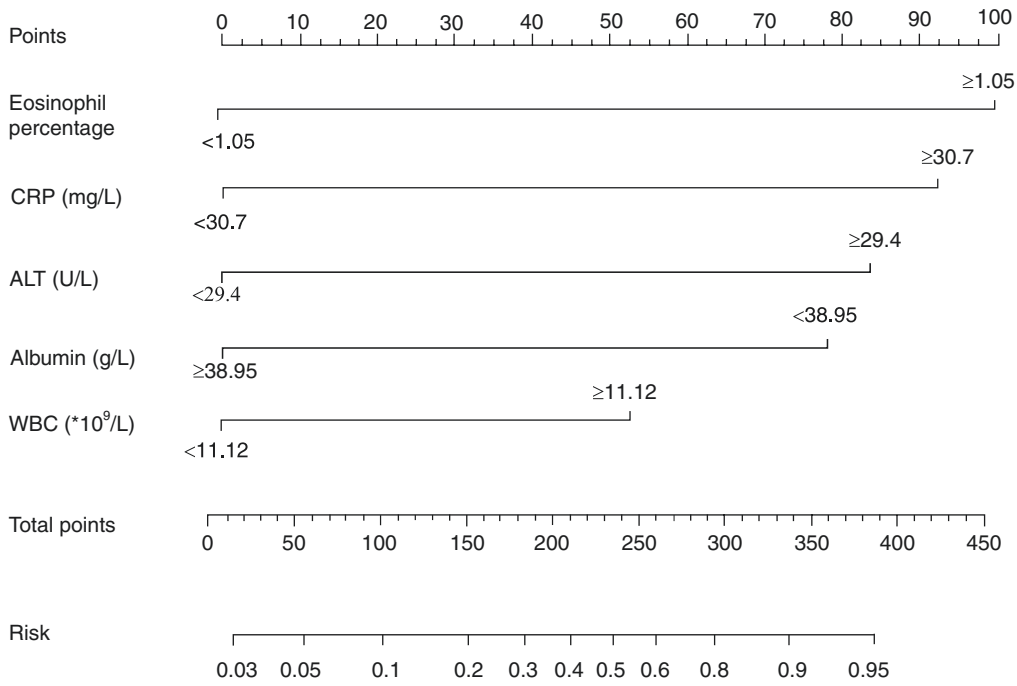

Fig. 2 The Kawasaki disease nomogram prediction score distinguishes KD from non-Kawasaki disease febrile infectious diseases (*WBC* white blood cell count, *CRP* C-reactive protein, *ALT* alanine aminotransferase). The results of multivariate regression analysis were used to construct a nomogram for predicting Kawasaki disease. A score proportional to the logarithm of the odds ratio is assigned to each independent predictor. The total score for each case is assigned by drawing a vertical line from the appropriate point of each predictor down to the rating scale and adding these scores. (Adapted from Front Pediatr. 2020;8:559389)

0.905 for the validation group. During the multiple logistic regression, eosinophilia showed the highest OR: 5.015 (95% CI: 3.068–8.197). The sensitivity and specificity of the validation group were 84.1% and 86%, respectively. Eosinophilia (percentage) plays a major role in the nomogram model and has high accuracy in predicting KD. This report demonstrates the importance of eosinophils in KD (Fig. 2).

We also found in previous studies that eosinophils in KD are elevated, suggesting that eosinophilia is related to IVIG responsiveness and can prevent the formation of CAL [19, 20]. Some data also indicate that the percentage of eosinophils and the absolute eosinophil count increase in acute KD, and the percentage of eosinophils continues to rise, reaching a peak during the recovery period [21]. Studies have shown that the incidence of peripheral blood eosinophil in patients with incomplete KD was significantly higher than that in the typical KD group. Therefore, unexplained eosinophilia may help diagnose incomplete KD [22]. Although the underlying mechanism of eosinophilia in KD is unclear, the accumulation of eosinophils in microvessels and the increase of eosinophils in peripheral blood may play a role in the pathogenesis of KD [23]. In conclusion, eosinophils may have protective or anti-inflammatory effects in KD through T-helper 2 cytokine (IL-4) [20, 24].

Tsai et al. [25] analyzed 6310 febrile children's and 485 KD subjects' biological parameters of a routine blood test, including complete blood count with differential, C-reactive protein, aspartate aminotransferase, and alanine aminotransferase. Receiver operating characteristic curve, logistic regression, and Youden's index were all used to develop a prediction model. Two other independent cohorts from different hospitals (one in Taiwan and one in China Mainland) were also used for verification. Eight independent predictors (platelets, eosinophils, alanine ami-

Table 1 Logistic regression analysis and scoring system for Kawasaki disease and fever controls demonstrate the important role of eosinophils

Variable	Univariate		Multivariate		Score
	Est. (95% CI)	*p*-Value	Est. (95% CI)	*p*-Value	
WBC (1000/μL)	2.993 (2.304–3.888)	<0.001	–	0.130	–
Platelets >280 (1000/μL)	3.506 (2.741–4.484)	<0.001	1.835 (1.363–2.470)	<0.001	2
Eosinophil >1.5%	6.673 (5.252–8.478)	<0.001	6.744 (5.040–9.023)	<0.001	7
ALT >30 (U/L)	7.299 (5.748–9.268)	<0.001	5.776 (4.325–7.712)	<0.001	6
CRP >25 (mg/L)	5.277 (4.048–6.881)	<0.001	5.878 (4.305–8.026)	<0.001	6
RBC <4.5 (million/μL)	1.905 (1.494–2.429)	<0.001	–	0.508	–
Hemoglobin <12 (g/dL)	3.138 (2.418–4.072)	<0.001	1.499 (1.090–2.060)	0.013	1
MCH <27 (pg/cell)	2.116 (1.663–2.692)	<0.001	1.794 (1.328–2.424)	<0.001	2
MCHC <33 (gHb/dL)	2.614 (2.028–3.368)	<0.001	1.547 (1.104–2.168)	0.011	2
Monocyte <7 (%)	4.569 (3.568–5.850)	<0.001	4.163 (3.125–5.545)	<0.001	4
				Total score	30

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notransferase, C-reactive protein, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and monocytes) were identified, and the top three scores were found to be eosinophil >1.5% (score: 7), alanine aminotransferase >30 U/L (score: 6), and C-reactive protein>25 mg/L (score: 6). A score of 14 (total score 30) represents the best sensitivity value plus specificity prediction rate for KD (as showed in Table 1). The sensitivity, specificity, and accuracy were 0.824, 0.839, and 0.838, respectively. The verification test of the two independent cohorts of KD patients (N = 103 and 170) from two different institutes had a sensitivity of 0.780 (213/273). This study only used the routine laboratory data of CBC/DC, CRP, and GOT/GPT (without using age, gender, clinical symptoms, or urine routine) to distinguish KD from fever illness. This study also demonstrated the importance of eosinophils in KD.

From other previous reports, increased eosinophils were found in KD prior to IVIG treatment, and the eosinophils were even higher following IVIG treatment [19, 20]. KD patients had higher eosinophil levels both before and after IVIG therapy than the enterovirus patients (treated with IVIG 1 g/kg), which indicated a T helper 2 immune response more predominant in KD [26]. According to previous reports, eosinophils are a heterogeneous cell population and have different characteristics based on the site in which they are located. Altogether, the role of anti-inflammatory eosinophils as protective cells may play a more important role in KD than inflammatory eosinophils. Eosinophils may play a very important role in KD, and a novel scoring system that includes eosinophils can help first-line physicians precisely identify and treat KD.

Neutrophil-to-Lymphocyte Ratio in Kawasaki Disease

Chang et al. [27] reported that male, IVIG resistance, anemia, hypoalbuminemia, elevated CRP levels, elevated neutrophil counts, elevated neutrophil/lymphocyte ratio (NLR), and elevated ALT levels are all risk factors for KD patients who developed CAL. After multivariate logistic regression analysis, male, IVIG resistance, NLR > 3.5, CRP > 103 mg/L and other characteristics are independent risk factors for predicting the formation of CAL. Then a scoring model was developed. At the cut-off point pf 2 points, the sensitivity was 60.8%, the specificity was 70.6%, and the AUC was 0.696.

CAL is the most serious complication of KD, but high-dose IVIG treatment can reduce the rate of coronary artery disease. However, 3–5% of patients still have coronary artery disease, which requires long-term follow-up and medication. Early classification of high-risk patients can remind clinicians to follow up frequently or try different anti-inflammatory treatment options, such as steroids [28].

Many scoring systems have been proposed for early detection of IVIG resistance in NLR [29–31], but few scoring systems are used to predict the formation of CAL in NLR. Nakano et al. revealed that age of onset, CRP, and platelet count can be used to predict patients at high risk of CAL [32]. Beiser et al. constructed a risk classification tool based on baseline hemoglobin level, neutrophil count, platelet count, and body temperature [33]. Kim et al. discovered that incomplete KD manifestations, IVIG resistance, longer duration of fever, and rs7604693 genetic variants in the PELI1 gene are all risk factors for the development of CAL [34]. Previous studies have shown that the body's immune system's response to systemic inflammation includes significant neutropenia and lymphopenia [35]. Neutrophils represent active nonspecific inflammation, while lymphocytes represent the regulatory pathway of the immune system. NLR stands for the balance between inflammation and immune regulation. Amano et al. demonstrated that the systemic inflammation that occurs in KD affects the formation of CAL [36]. Therefore, NLR may help indicate systemic inflammation and immune system responses in patients with KD. In addition, Ha et al. indicated that NLR can predict CAL formation and IVIG resistance in patients with KD [37]. Takeshita et al. revealed that the combination of NLR $\geq$ 3.83 and platelet/lymphocyte ratio (PLR) $\geq$ 150 is used to predict IVIG resistance in KD with high sensitivity (72%) and specificity (67%) [38]. NLR can be a reliable predictor of IVIG resistance, so this may be related to the increased risk of CAL formation in KD [39]. NLR is an independent risk factor for the formation of CAL. A higher level of NLR may indicate a higher level of inflammation and is related to coronary artery damage in KD.

Prognostic Nutrition Index (PNI) in Kawasaki Disease

Prognostic nutrition index (PNI) has been used to predict and evaluate post-operative status in patients with cancers for decades, ever since it was first announced in 1983 [40]. PNI has also been used to predict mortality in ST-segment elevation myocardial infarction (STEMI) patients [41]. Currently, PNI is determined by albumin (ALB) and total lymphocyte count (TLC), with albumin the consistent parameter in the PNI formula since various studies have shown its correlation with nutrition and immune status. By definition, higher albumin levels or lymphocyte counts contribute to higher PNI values, which indicate better self-healing ability due to a nutrition and immune capacity that is sufficient to prevent opportunistic infectious pathogen invasions.

In a study of 284 children with KD, Tai et al. [42] reported that 158 had CAL including transient dilatation and 126 did not during a 6-month follow-up period. Univariable analysis identified five laboratory variables (white blood cell, absolute neutrophil count, absolute monocyte count, platelet count, and PNI) as significant predictors of CAL formation ($p < 0.05$). Multivariate logistic regression model revealed that PNI and platelet count were significant predictors of CAL presence with their 95% confidence interval estimators 2.532 (1.394–4.599) and 1.004 (1.002–1.006), respectively. Using PNI to predict CAL presence gave an area under the receiver operating characteristic curve of 0.596 and the PNI cutoff point of 55.24, with 0.509 sensitivity and 0.678 specificity. Nutrition status resulting from the intake, absorption, and use of nutrients is particularly influenced by physiological and pathological status. PNI, a current long-term predictor of cancer, is a useful index for predicting CAL formation with high specificity prior to initial IVIG therapy and can thus alert clinicians in advance to adopt an aggressive therapeutic strategy.

C-Reactive Protein-to-Albumin Ratio (CRP/Alb) in Kawasaki Disease

The ratio of C-reactive protein (CRP) to albumin (CRP/Alb) is a new marker of inflammation. Recently, it has been recognized as a more useful sepsis indicator than CRP or albumin alone [43]. Studies have also shown that the CRP/Alb ratio can be used as a biomarker of disease

activity in patients with autoimmune diseases [44, 45] and Takayasu arteritis [46]. Since KD is also a systemic vasculitis involving small and medium blood vessels, especially coronary arteries, plasma CRP and/or albumin levels have been proposed as predictors of CAL formation or IVIG treatment response in children with KD [30, 47–49]. In a study of 410 patients with KD (143 KD with CAL and 267 KD without CAL), Tsai et al. [50] reported that KD children with CAL have a higher CRP/Alb ratio than children without CAL (3.14 ± 3.17 vs. 2.12 ± 2.04, $p < 0.001$). Multivariate logistic regression analysis showed that males (OR = 3.222, $p < 0.001$), incomplete KD (OR = 1.968, $p = 0.031$), more platelet counts (OR = 1.004, $p < 0.001$), higher CRP (OR = 0.982, $p = 0.048$) and higher CRP/Alb ratio (OR = 1.994, $p = 0.016$) are independent risk factors that predict the formation of CAL in KD. The incidence of CAL and IVIG resistance in KD children with a high CRP/Alb ratio (≧2.94) is higher than that of children with a low CRP/Alb ratio (<2.94) (49.6 vs. 28.7%, $p < 0.001$ and 11.6 vs. 3.5%, $p = 0.001$, respectively). Therefore, the CRP/Alb ratio can be used as a predictive marker of CAL formation and IVIG resistance in KD.

References

1. Massin MM, Montesanti J, Gerard P, Lepage P. Spectrum and frequency of illness presenting to a pediatric emergency department. Acta Clin Belg. 2006;61(4):161–5.
2. National Institute for Health and Care Excellence. Feverish illness in children: assessment and initial management in children younger than 5 years (clinical guideline CG160); 2013.
3. Kawasaki T, Kosaki F, Okawa S, Shigematsu I, Yanagawa H. A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. Pediatrics. 1974;54(3):271–6.
4. Wang CL, Wu YT, Liu CA, Kuo HC, Yang KD. Kawasaki disease: infection, immunity and genetics. Pediatr Infect Dis J. 2005;24(11):998–1004.
5. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, 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(17):e927–e99.
6. Liang CD, Kuo HC, Yang KD, Wang CL, Ko SF. Coronary artery fistula associated with Kawasaki disease. Am Heart J. 2009;157(3):584–8.
7. Newburger JW, Takahashi M, Beiser AS, Burns JC, Bastian J, Chung KJ, et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. N Engl J Med. 1991;324(23):1633–9.
8. Durongpisitkul K, Gururaj VJ, Park JM, Martin CF. The prevention of coronary artery aneurysm in Kawasaki disease: a meta-analysis on the efficacy of aspirin and immunoglobulin treatment. Pediatrics. 1995;96(6):1057–61.
9. Oates-Whitehead RM, Baumer JH, Haines L, Love S, Maconochie IK, Gupta A, et al. Intravenous immunoglobulin for the treatment of Kawasaki disease in children. Cochrane Database Syst Rev. 2003;(4):CD004000.
10. Hao S, Jin B, Tan Z, Li Z, Ji J, Hu G, et al. A classification tool for differentiation of Kawasaki disease from other febrile illnesses. J Pediatr. 2016;176:114–20.e8.
11. Liu YC, Lin MT, Wang JK, Wu MH. State-of-the-art acute phase management of Kawasaki disease after 2017 scientific statement from the American Heart Association. Pediatr Neonatol. 2018;59(6):543–52.
12. Kuo HC, Lo CC, Lin PX, Kao CC, Huang YH, Lin BS. Wireless optical monitoring system identifies limb induration characteristics in patients with Kawasaki disease. J Allergy Clin Immunol. 2018;142(2):710–1.
13. Huang YH, Kuo HC, Li SC, Cai XY, Liu SF, Kuo HC. HAMP promoter hypomethylation and increased hepcidin levels as biomarkers for Kawasaki disease. J Mol Cell Cardiol. 2018;117:82–7.
14. Kuo HC, Huang YH, Chung FH, Chen PC, Sung TC, Chen YW, et al. Antibody profiling of Kawasaki disease using Escherichia coli proteome microarrays. Mol Cell Proteomics. 2018;17(3):472–81.
15. Ling XB, Kanegaye JT, Ji J, Peng S, Sato Y, Tremoulet A, et al. Point-of-care differentiation of Kawasaki disease from other febrile illnesses. J Pediatr. 2013;162(1):183–8.e3.
16. Yan JH, Chang LS, Lin YJ, Guo MM, Huang YH, Kuo HC. Clinical characteristics for differentiating febrile children with suspected Kawasaki disease diagnosis. Front Pediatr. 2020;8:221.
17. Liu XP, Huang YS, Kuo HC, Xia HB, Yi S, Huang WD, et al. A novel nomogram model for differentiating Kawasaki disease from sepsis. Sci Rep. 2020;10(1):13745.
18. Liu X-P, Huang Y-S, Xia H-B, Sun Y, Lang X-L, Li Q-Z, et al. A nomogram model identifies eosinophilic frequencies to powerfully discriminate Kawasaki disease from febrile infections. Front Pediatr. 2020;8(856):559389.
19. Kuo HC, Yang KD, Liang CD, Bong CN, Yu HR, Wang L, et al. The relationship of eosinophilia to intrave-

nous immunoglobulin treatment failure in Kawasaki disease. Pediatr Allergy Immunol. 2007;18(4):354–9.
20. Kuo HC, Wang CL, Liang CD, Yu HR, Huang CF, Wang L, et al. Association of lower eosinophil-related T helper 2 (Th2) cytokines with coronary artery lesions in Kawasaki disease. Pediatr Allergy Immunol. 2009;20(3):266–72.
21. Tremoulet AH, Jain S, Chandrasekar D, Sun X, Sato Y, Burns JC. Evolution of laboratory values in patients with Kawasaki disease. Pediatr Infect Dis J. 2011;30(12):1022–6.
22. Oner T, Yilmazer MM, Guven B, Devrim I, Cilengiroglu OV, Demirpence S, et al. An observational study on peripheral blood eosinophilia in incomplete Kawasaki disease. Anadolu Kardiyol Derg. 2012;12(2):160–4.
23. Terai M, Yasukawa K, Honda T, Jibiki T, Hirano K, Sato J, et al. Peripheral blood eosinophilia and eosinophil accumulation in coronary microvessels in acute Kawasaki disease. Pediatr Infect Dis J. 2002;21(8):777–81.
24. Wojdasiewicz P, Poniatowski LA, Szukiewicz D. The role of inflammatory and anti-inflammatory cytokines in the pathogenesis of osteoarthritis. Mediat Inflamm. 2014;2014:561459.
25. Tsai CM, Chu CH, Liu X, Weng KP, Liu SF, Huang YH, et al. A novel score system of blood tests for differentiating Kawasaki disease from febrile children. PLoS One. 2021;16(1):e0244721.
26. Lin LY, Yang TH, Lin YJ, Yu HR, Yang KD, Huang YC, et al. Comparison of the laboratory data between Kawasaki disease and enterovirus after intravenous immunoglobulin treatment. Pediatr Cardiol. 2012;33(8):1269–74.
27. Chang LS, Lin YJ, Yan JH, 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(1):398.
28. Kobayashi T, Saji T, Otani T, Takeuchi K, Nakamura T, Arakawa H, et al. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial. Lancet. 2012;379(9826):1613–20.
29. Egami K, Muta H, Ishii M, Suda K, Sugahara Y, Iemura M, et al. Prediction of resistance to intravenous immunoglobulin treatment in patients with Kawasaki disease. J Pediatr. 2006;149(2):237–40.
30. Kobayashi T, Inoue Y, Takeuchi K, Okada Y, Tamura K, Tomomasa T, et al. Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. Circulation. 2006;113(22):2606–12.
31. Sano T, Kurotobi S, Matsuzaki K, Yamamoto T, Maki I, Miki K, et al. Prediction of non-responsiveness to standard high-dose gamma-globulin therapy in patients with acute Kawasaki disease before starting initial treatment. Eur J Pediatr. 2007;166(2):131–7.
32. Nakano H, Ueda K, Saito A, Tsuchitani Y, Kawamori J, Miyake T, et al. Scoring method for identifying patients with Kawasaki disease at high risk of coronary artery aneurysms. Am J Cardiol. 1986;58(9):739–42.
33. Beiser AS, Takahashi M, Baker AL, Sundel RP, Newburger JW. A predictive instrument for coronary artery aneurysms in Kawasaki disease. US Multicenter Kawasaki Disease Study Group. Am J Cardiol. 1998;81(9):1116–20.
34. Kim JJ, Hong YM, Yun SW, Han MK, Lee KY, Song MS, et al. Assessment of risk factors for Korean children with Kawasaki disease. Pediatr Cardiol. 2012;33(4):513–20.
35. Zahorec R. Ratio of neutrophil to lymphocyte counts—rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy. 2001;102(1):5–14.
36. Amano S, Hazama F, Kubagawa H, Tasaka K, Haebara H, Hamashima Y. General pathology of Kawasaki disease. On the morphological alterations corresponding to the clinical manifestations. Acta Pathol Jpn. 1980;30(5):681–94.
37. Ha KS, Lee J, Jang GY, Lee J, Lee KC, Son CS, et al. Value of neutrophil-lymphocyte ratio in predicting outcomes in Kawasaki disease. Am J Cardiol. 2015;116(2):301–6.
38. Takeshita S, Kanai T, Kawamura Y, Yoshida Y, Nonoyama S. A comparison of the predictive validity of the combination of the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio and other risk scoring systems for intravenous immunoglobulin (ivig)-resistance in Kawasaki disease. PLoS One. 2017;12(5):e0176957.
39. Deng YC, Wang X, Tang XC, Huang CZ, Yang J, Mo LY. Risk factors for coronary artery lesions secondary to Kawasaki disease in children. Zhongguo Dang Dai Er Ke Za Zhi. 2015;17(9):927–31.
40. Dempsey DT, Buzby GP, Mullen JL. Nutritional assessment in the seriously ill patient. J Am Coll Nutr. 1983;2(1):15–22.
41. Keskin M, Hayiroglu MI, Keskin T, Kaya A, Tatlisu MA, Altay S, et al. A novel and useful predictive indicator of prognosis in ST-segment elevation myocardial infarction, the prognostic nutritional index. Nutr Metab Cardiovasc Dis. 2017;27(5):438–46.
42. Tai IH, Wu PL, Guo MM, Lee J, Chu CH, Hsieh KS, et al. Prognostic nutrition index as a predictor of coronary artery aneurysm in Kawasaki disease. BMC Pediatr. 2020;20(1):203.
43. Ranzani OT, Zampieri FG, Forte DN, Azevedo LC, Park M. C-reactive protein/albumin ratio predicts 90-day mortality of septic patients. PLoS One. 2013;8(3):e59321.
44. Yang WM, Zhang WH, Ying HQ, Xu YM, Zhang J, Min QH, et al. Two new inflammatory markers associated with disease activity score-28 in patients with rheumatoid arthritis: albumin to fibrinogen ratio and C-reactive protein to albumin ratio. Int Immunopharmacol. 2018;62:293–8.
45. Qin G, Tu J, Liu L, Luo L, Wu J, Tao L, et al. Serum albumin and C-reactive protein/albumin ratio are use-

ful biomarkers of Crohn's disease activity. Med Sci Monit. 2016;22:4393–400.
46. Seringec Akkececi N, Yildirim Cetin G, Gogebakan H, Acipayam C. The C-reactive protein/albumin ratio and complete blood count parameters as indicators of disease activity in patients with Takayasu arteritis. Med Sci Monit. 2019;25:1401–9.
47. Mori M, Imagawa T, Yasui K, Kanaya A, Yokota S. Predictors of coronary artery lesions after intravenous gamma-globulin treatment in Kawasaki disease. J Pediatr. 2000;137(2):177–80.
48. Sabharwal T, Manlhiot C, Benseler SM, Tyrrell PN, Chahal N, Yeung RS, et al. Comparison of factors associated with coronary artery dilation only versus coronary artery aneurysms in patients with Kawasaki disease. Am J Cardiol. 2009;104(12):1743–7.
49. Xie T, Wang Y, Fu S, Wang W, Xie C, Zhang Y, et al. Predictors for intravenous immunoglobulin resistance and coronary artery lesions in Kawasaki disease. Pediatr Rheumatol Online J. 2017;15(1):17.
50. Tsai CM, Yu HR, Tang KS, Huang YH, Kuo HC. C-reactive protein to albumin ratio for predicting coronary artery lesions and intravenous immunoglobulin resistance in Kawasaki disease. Front Pediatr. 2020;8:607631.

Genetic Study of Kawasaki Disease

Imaniar Noor Faridah, Dyah Aryani Perwitasari, and Wei-Chiao Chang

Abstract

Kawasaki disease (KD) is a leading cause of acquired heart disease in children; however, the etiology of this disease is still unclear. Several genome-wide association studies (GWASs) indicated that genetic variations contribute to KD susceptibility and intravenous immunoglobulin (IVIG) responses. Application genetic risk score is another example of pharmacogenomics research for predicting IVIG unresponsiveness. High-throughput DNA sequencing technology has been developed on an unprecedented scale, and more and more genomic information will be available to understand the etiology and treatment of KD.

Keywords

Genetics · IVIG response · Kawasaki disease · Susceptibility

Introduction

Kawasaki disease (KD) is an acute disease that frequently affects children under five years of age, and the number of patients increases annually. Family history has been considered one of the important risk factors for KD [1]. KD incidence in northeastern Asian countries, including Japan, Korea, and Taiwan, is higher than in North America, Australia, and Europe. The etiology of this disease is still unclear. Genetic susceptibility has been proposed to interact with several environmental and immunological variables [2]. Infections such as bacterial [3] or viral infections, including enterovirus, adenovirus, human rhinovirus, and coronavirus [4], were reported to cause immune dysfunction and KD. For the treatment of KD, initial therapy with high-dose intravenous immunoglobulin (IVIG) and acetylsalicylic acid (ASA) is recommended as early as possible to reduce the risk of coronary artery abnormalities (CAAs). However, up to 20% of patients are

I. N. Faridah
Department of Clinical Pharmacy, School of Pharmacy, Taipei Medical University, Taipei, Taiwan

Faculty of Pharmacy, University of Ahmad Dahlan, Yogyakarta, Indonesia

D. A. Perwitasari
Faculty of Pharmacy, University of Ahmad Dahlan, Yogyakarta, Indonesia

W.-C. Chang (✉)
Department of Clinical Pharmacy, School of Pharmacy, Taipei Medical University, Taipei, Taiwan

Master Program in Clinical Pharmacogenomics and Pharmacoproteomics, School of Pharmacy, Taipei Medical University, Taipei, Taiwan

Integrative Research Center for Critical Care, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan

Department of Medical Research, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan
e-mail: wcc@tmu.edu.tw

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IVIG-unresponsive patients who show persistent fever 36~48 h after an initial IVIG infusion [5]. The mechanism of IVIG resistance is still unknown. Genetic polymorphisms play an important role in determining an inter-individual difference in the susceptibility of diseases and therapeutic outcomes. This chapter highlights the genetic factors that are becoming accepted as critical to KD susceptibility.

Genetics and KD

Recently, many studies reported functional roles of genetic polymorphisms in KD susceptibility and the responses to IVIG treatment using either family-based, candidate gene approaches, or genome-wide association studies (GWASs). KD susceptibility genes such as *ITPKC* [6–10], *FCGR2A* [8, 11–13], *BLK* [10, 11, 13–16], and *CD40* [10, 11, 13, 14, 17] have been widely reported in different populations. Moreover, genes such as *SAMD9L* [18], *IL16* [19], and *P2RY12* [20] were involved in pharmacological responses to IVIG treatment. This chapter proposes an overview of genes that have been identified to be related to KD susceptibility and IVIG responses, as summarized in Table 1.

B Lymphoid Tyrosine Kinase (BLK)

The *BLK* gene encodes an Src-family protein tyrosine kinase, which has important role in regulating of proinflammatory cytokine [34]. Previous genetic studies proved that rs2254546 (the G allele or GG genotype) [11, 13, 14, 21], rs2736340 [15], and rs6993775 [16] on the *BLK* gene were associated with the risk of KD. Furthermore, the single-nucleotide polymorphism (SNP), rs2254546, was validated for KD susceptibility in Taiwanese population. However, there was no evidence of any association with coronary arterial lesions (CALs) [14]. The rs2254546 SNP is located in an intergenic region between the family with sequence similarity 167 member A (*FAM167A*) and *BLK* on chromosome 8. However, the biological function of *FAM167A*, which is predominantly expressed in the human lungs, is still unclear [35]. Several SNPs on the *BLK* gene are known to be related to immune diseases, such as systemic lupus erythematosus (SLE) [36] and rheumatoid arthritis [37].

Caspase-3 (CASP3)

CASP3, located at 4q35.1, as one of effector caspases contributes to the cell apoptosis process. Activation of effector caspases (caspase-3, caspase-6, and caspase-7) cleaves certain targets leading to cell death [38]. Besides the apoptosis process, other cellular processes in which *CASP3* is involved include regulating B cell homeostasis [39]. Furthermore, the role of *CASP3* in KD follows the nuclear factor of activated T cells (NFAT) c2 pathway in response to signals from T cell receptor [40]. *CASP3* is known to cleave NFATc2 and influence transcriptional activity [41]. Not only *CASP3*, but also *ITPKC* acts as a regulator of the NFAT pathway in response to calcium signals. Decreasing activities of *CASP3* and *ITPKC* are related to hyperactivation of the immune system [9]. *CASP3* polymorphisms are genetic susceptibilities for cancer development, such as squamous cell carcinoma of the head and neck (SCCHN) [42] and endometrial cancer [43]. rs113420705 (G/A) of *CASP3* is related to KD susceptibility, CAL formation, and response to IVIG in Japanese and Han Chinese populations [9, 11]. However, a replication study in a Taiwanese population showed different results for IVIG response either with rs113420705 or a two-locus model (rs113420705 and rs28493229) [44]. In addition, rs72689236 was associated with aneurysm formation in Taiwanese KD children [45] and increased KD risk based on a meta-analysis study [22]. However, there was no significant association between rs72689236 and the IVIG response or CAL formation [45].

Cluster of Differentiation 40 (CD40) and CD40 Ligand (CD40L)

CD40, a costimulatory receptor, is a type-I transmembrane protein expressed by antigen-presenting cells, such as B cells. At the same time the CD40L is a type II transmembrane protein expressed by activated T cells. Interactions

between CD40 and the CD40L are essential for activation of the immune system, such as turning on signaling pathways including nuclear factor (NF)-κB-signaling pathways through tumor necrosis factor (TNF) receptor (TNFR)-associated factor (TRAF) proteins [46]. Moreover, ligation of CD40 and the CD40L enhances endothelial cell activation and mediates vascular remodeling and neovessel formation in KD. Expression of the CD40L is known

Table 1 Gene polymorphisms associated with Kawasaki disease (KD) susceptibility and the response to intravenous immunoglobulin (IVIG)

Gene	Chromosome location	Representative variants	Study design	Populations	Results	Reference
Genes related to susceptibility to Kawasaki disease						
BLK	8p23-22	rs2254546	Case-control study and meta-analysis	China	OR = 1.443, CI = 1.154 ~ 1.805	Yan et al. (2013) [11]
			GWAS and replication study	Japan	$p = 8.2 \times 10^{-21}$	Onouchi et al. (2012) [13]
			Case-control study and meta-analysis	China	OR = 1.55, CI = 1.42 ~ 1.70	Wang et al. (2014) [21]
			Case-control study	Taiwan	$p = 1.0 \times 10^{-5}$	Chen et al. (2020) [14]
		rs2736340	Replication and meta-analysis	Taiwan, Japan, Korea	Meta-$p = 4.74 \times 10^{-31}$	Chang et al. (2013) [15]
			Meta-analysis of GWASs	Japan, Korea, Taiwan	Meta-$p = 6.6 \times 10^{-33}$	Johnson et al. (2020) [10]
		rs6993775	Case-control study	Korea	$p = 4.63 \times 10^{-11}$	Sim et al. (2019) [16]
CASP3	4q34-35	rs113420705	Cohort study	Japan	$p = 0.022$	Onouchi et al. (2013) [9]
			Case-control study and meta-analysis	China	OR = 1.33, CI = 1.22 ~ 1.43	Yan et al. (2013) [11]
		rs2720378	Meta-analysis of GWASs	Japan, Korea, Taiwan	Meta-$p = 1.6 \times 10^{-8}$	Johnson et al. (2020) [10]
		rs72689236	Meta-analysis study	China, Japan	$p \leq 0.001$	Ferdosian et al. (2019) [22]

(continued)

Table 1 (continued)

Gene	Chromosome location	Representative variants	Study design	Populations	Results	Reference
CD40	20q12-13.2	rs1535045	Case-control study	Taiwan	$p = 0.0405$	Kuo et al. (2012) [17]
		rs4813003	GWAS and replication study	Japan	$p = 4.8 \times 10^{-8}$	Onouchi et al. (2012) [13]
			Case-control study and meta-analysis	China	OR = 1.37, CI = 1.27 ~ 1.47	Yan et al. (2013) [11]
			Case-control study	Taiwan	$p = 8.1 \times 10^{-4}$	Chen et al. (2020) [14]
		rs1883832	Meta-analysis of GWASs	Japan, Korea, Taiwan	Meta-$p = 1.5 \times 10^{-13}$	Johnson et al. (2020) [10]
FCGR2A	1q23	rs1801274	Case-control study and meta-analysis	China	OR = 1.331, CI = 1.094 ~ 1.619	Yan et al. (2013) [11]
			GWAS and replication study	Europe, the US, Taiwan, Korea, Hong Kong, and China	Meta-$p = 7.35 \times 10^{-11}$	Khor et al. (2011) [8]
			Family-based genetic study	Europe, Asia	$p = 0.001$	Shrestha et al. (2012) [12]
			GWAS and replication study	Japan	$p = 1.6 \times 10^{-6}$	Onouchi et al. (2012) [13]
			Meta-analysis study	China, Japan, Taiwan, Hong Kong, Korea, the Netherlands, Greece	$p \leq 0.001$	Ferdosian et al. (2019) [22]
HCP5	6	rs6938467	GWAS and replication study	Korea	$p = 5.24 \times 10^{-8}$	Kim et al. (2017) [23]

Table 1 (continued)

Gene	Chromosome location	Representative variants	Study design	Populations	Results	Reference
HLA-DQB2-HLA-DOB	6p21.3	rs2857151	Case-control study and meta-analysis	China	OR = 1.41, CI = 1.27 ~ 1.57	Yan et al. (2013) [11]
			GWAS and replication study	Japan	$p = 4.6 \times 10^{-11}$	Onouchi et al. (2012) [13]
HLA-E		rs2844724	Case-control study	Taiwan	$p < 10^{-7}$	Lin et al. (2009) [24]
IGHV3–66	14q33.32	rs4774175	Meta-analysis of GWASs	Japan, Korea, Taiwan	Meta-$p = 3.4 \times 10^{-6}$	Johnson et al. (2020) [10]
		rs6423677	Meta-analysis of GWASs	Japan, Korea, Taiwan	Meta-$p = 6.8 \times 10^{-10}$	Johnson et al. (2020) [10]
IL4	5q31.1	NS	Family-based genetic study		$p_{combined} = 0.002$	Burns et al. (2005) [25]
	−590	rs2243250	Case-control study	Iran	$p = 0.00$	Assari et al. (2018) [26]
	−33	rs2070874	Case-control study	Iran	$p = 0.00$	Assari et al. (2018) [26]
ITPKC	19q13.2	rs28493229	Case-control study	Japan	$p = 0.000081$	Onouchi et al. (2008) [6]
			Case-control study and meta-analysis	Taiwan	OR = 1.36, CI 1.12 ~ 1.66	Kuo et al. (2011) [7]
			GWAS and replication study	Europe, the US, Taiwan, Korea, Hong Kong, and China	Meta-$p = 1.68 \times 10^{-12}$	Khor et al. (2011) [8]
			Cohort study	Japan	$p = 7.1 \times 10^{-6}$	Onouchi et al. (2013) [9]
			Meta-analysis of GWASs	Japan, Korea, Taiwan	Meta-$p = 1.1 \times 10^{-14}$	Johnson et al. (2020) [10]

(continued)

Table 1 (continued)

Gene	Chromosome location	Representative variants	Study design	Populations	Results	Reference
MRP4	13q32.1	rs7320375 rs7329490	Family linkage and case-control study	Europe	$p = 8.8 \times 10^{-5}$ $p = 5.8 \times 10^{-4}$	Khor et al. (2011) [27]
		rs7986087	Case-control study	China	$p = 0.0197$	Che et al. (2018) [28]
			Family linkage and case-control study	Europe	$p = 3.0 \times 10^{-4}$	Khor et al. (2011) [27]
NMNAT2	1q25.3	rs2078087	GWAS and replication study	Korea	$p = 1.15 \times 10^{-6}$	Kim et al. (2017) [23]
SMAD3	15	rs4776338	Case-control study	Europe	$p = 0.00002$	Shimizu et al. (2011) [29]
		rs1438386	Case-control study	Taiwan	$p = 0.001$	Kuo et al. (2011) [30]
Genes related to the response of IVIG treatment						
CASP3	4q34-35	rs113420705	Cohort study	Japan	$p = 0.031$	Onouchi et al. (2013) [9]
HMGB1		rs1412125	Case-control study	Korea	$p = 0.027$	Ahn et al. (2019) [31]
IL4R	16p12.1	rs563535954	Case-control study	Japan	$p = 0.0337$	Amano et al. (2019) [32]
IL16	p.Asn1147Lys	rs11556218	GWAS and replication study	Korea	$p = 0.0078$	Kim et al. (2020) [19]
ITPKC	19q13.2	rs28493229	Cohort study	Japan	$p = 0.0099$	Onouchi et al. (2013) [9]
MRP4		rs1751034	Case-control study	China	$p = 0.023$	Wang et al. (2021) [33]
P2RY12	3q25.1	rs6809699	Case-control study	China	$p = 0.011$	Wang et al. (2020) [20]
SAMD9L	7	rs28662	Meta-analysis of GWASs	Korea, Japan	Meta-$p = 5.3 \times 10^{-6}$	Kim et al. (2020) [18]

GWAS genome-wide association study, *OR* odds ratio, *CI* confidence interval

to be higher in platelets of KD patients compared to febrile patients [47] and controls [48], and it then decreases 3 days after IVIG administration [47]. Results imply a potential role of CD40/CD40L in the immunopathogenesis of KD. Notably, a GWAS in a Japanese population reported that the CD40 region at 20q13, rs4813003 was associated with KD [13]. This finding was confirmed using meta-analysis data [11] and replication study in different population [14]. Furthermore, a significant correlation was also found between rs1535045 of CD40 and KD susceptibility within a dominant model in a Taiwanese population [17].

Fc Fragment of IgG Receptor IIa (FCGR2A)

The *FCGR2A* gene encodes a family member of immunoglobulin Fc receptors (FcγRIIA/CD32A). Polymorphisms of *FCGR2A* were associated with KD susceptibility [8, 12, 49] and other autoimmune diseases such as ulcerative collitis [50]. Results from a GWAS and meta-analysis study in various ethnic groups showed that *FCGR2A* on chromosome 1 (rs1801274, coding for His131) was associated with KD susceptibility [8, 22]. Consistent with GWAS results, studies in Asian and Caucasian populations demonstrated that an *FcγRIIA-131H* variant was associated with KD regardless in combination or subgroup populations [12]. The methylation status of the promoter regions of FCGR2A was also related to susceptibility to KD in CpG sites of G, H, and J as corresponding loci to NF-κB and Myc-Max [49]. Furthermore, specific findings related to gender (Korean and Japanese populations) showed that rs1801274 (p.His167Arg) in FCGR2A was correlated with KD susceptibility in males but not in females [51].

In addition, patients receiving IVIG, but not acute KD patients or controls, showed significant alterations in DNA methylation [52], while DNA methylation is important in regulating gene expressions. Furthermore, the methylation status of the promoter of *FCGR2A* is associated with IVIG treatment outcomes in the CpG sites of B, E, F, H, and J. The level of methylation was significantly higher in the group nonresponsive to IVIG [49]. Higher *FCGR2A* messenger (m)RNA expression was observed in IVIG-resistant KD patients than in IVIG-sensitive patients [53].

HLA Complex 5 (HCP5)

HCP5 is a gene mapped within the HLA class I region, between the *MICA* and *MICB* genes, and thought to play an essential role in immunity to retroviral infections [54]. Previous studies reported associations of *HCP5* in psoriatic disease [55] and Sjögren's syndrome [56]. A GWAS study in a Korean population showed that *HCP5* was associated with the pathogenesis of KD. *HCP5* (rs6938467) is linked to other genes (rs9380242, rs9378199, and rs9266669) within the HLA class I region. Due to the complex genetic structure of the HLA class I region, further research is necessary to confirm the true signals within this region [23].

Human Leukocyte Antigen (HLA)

HLA, which is located on chromosome 6, is one of the critical factors that is highly related to immunity and autoimmune diseases. The *HLA* is divided into three regions, which are class I (containing the classical *HLA-A*, *HLA-B*, *HLA-C*, *HLA-E*, *HLA-F*, and *HLA-G* genes), class II (containing the A and B genes, including *HLA-DPA1*, *HLA-DPB1*, *HLA-DQA1*, *HLA-DQA2*, *HLA-DQB1*, *HLA-DQB2*, *HLA-DRA*, *HLA-DRB1*, *HLA-DRB2*, *HLA-DRB3*, *HLA-DRB4*, and *HLA-DRB5*), and class III (containing non-*HLA* genes). HLA class I molecules can present peptides to $CD8^+$ T cells regardless of whether HLA class II binds to $CD4^+$ T cells. This binding is responsible for defense against pathogens [57]. Polymorphisms at HLA loci have widely been identified. Previous studies in Japanese and Han Chinese populations demonstrated that rs2857151 (in a genomic region between *HLA-DQB2* and *HLA-DOB*) has a significant association with KD [11, 13]. In contrast, different

results from a validation study in a Taiwanese population showed that rs2857151 exhibited no difference between KD patients and controls [14]. Other significant HLA loci were identified, including *HLA-B* (*HLA-B35* [58], *-B75* [58], and *-B54* [59]), *HLA-C* (*HLA-Cw09* [58]), and *HLA-E* (rs2844724 [24]). However, studies indicated no significant association between *HLA-DRB1* and KD in Korean [58] or Taiwanese [60] populations.

Immunoglobulin Heavy Chain (IGH) Variable (IGHV)

The *IGH* locus on chromosome 14 is a complex gene family that is important in providing primary components to the adaptive immune system. One group of *IGH* genes, *IGHV*, encodes components of immunoglobulin that are essential for recognizing and binding to particular antigens. IGHV has mostly been identified to be associated with chronic lymphocytic leukemia (CLL) [61], rheumatic heart disease [62], and other immune-related diseases [63]. A previous GWAS in Taiwan identified six SNPs (rs17113284, rs8005468, rs10129255, rs2007467, rs10150241, and rs12590667) in the *IGHV* region that are known as KD markers [64]. Furthermore, rs4774175 and rs6423677 in the *IGHV3–66* region were also related to KD pathogenesis [10].

Interleukin (IL)-4 and the IL-4 Receptor (IL-4R)

IL-4, which is mainly secreted by activated T cells, is a cytokine that plays a role in type 2 immune responses. Higher levels of IL-4 in plasma were found in acute KD patients than those in the convalescent phase or a control group [65]; however, levels showed no significant differences compared to KD shock syndrome [66]. The role of *IL-4* in the pathogenesis of KD was proven in several genetic association studies. A family-based study, which found 95 polymorphisms in 58 genes, showed that the C(−589)T variant in *IL-4* was correlated with susceptibility to KD, but not coronary artery aneurysms [25]. Strengthening previous findings, other positions of *IL-4* were also detected for KD. Frequencies of the major C allele and CC genotype at positions -590 (rs2243250) and -33 (rs2070874) of the *IL-4* gene were higher in Iranian KD patients than that in a control group [26].

In addition to the pathogenesis of KD, variants related to IVIG responses were also identified in the *IL4R* locus. For example, a study in a Japanese population indicated a significant association between the minor allele of rs563535954 and patients who were unresponsive to IVIG. In that study, IVIG-unresponsive patients presented with a fever (with an axial temperature of >37.5 °C) for more than 24 h after the first and second IVIG treatments [32].

Inositol-Triphosphate 3-Kinase C (ITPKC)

ITPKC, located on chromosome 19q13.2, is known as a negative regulator of T cells through Ca^{2+}-dependent NFAT signaling pathways [6]. The NFAT has important roles in the immune system, as it is associated with vascular stability, angiogenesis, and inflammation in endothelial cells [67–69]. Moreover, vascular endothelial cells (VECs) are involved in the pathogenesis of coronary artery injury in KD. One study showed that damage to endothelial cells increased levels of NFATc1, NFATc3, and inflammatory molecules [69]. *ITPKC* is able to regulate activation of the NLRP3 inflammasome through Ca^{2+} mobilization. The NLRP3 inflammasome is a sensor of the innate immune system responsive to harmful stimuli, such as pathogens, dead cells, and environmental irritants [70, 71]. Triggers required to activate the NLRP3 inflammasome include HMGB1/RAGE/cathepsin B signaling, K^+ efflux, and Ca^{2+} signaling [72, 73]. Activation of the NLRP3 inflammasome is associated with elevation of circulating protein levels of IL-1β and IL-18 in children with KD [73].

A variant of *ITPKC* with rs28493229 (C allele) was proven to have a significant association with KD susceptibility and CAL formation in Japanese and Taiwanese KD patients [6, 7, 9]. Although there was no association between rs28493229 and the response to IVIG treatment in a Taiwanese population [7, 44], the C allele of rs28493229 was found to be significantly higher in unresponsive IVIG patients compared to responsive patients in a Japanese population [9]. Furthermore, variants of rs7251246 exhibited significant correlations with CAL formation after multiple testing corrections [74].

Multidrug Resistance Protein 4 (MRP4)

MRP4, also known as ATP-binding cassette, sub-family C member 4 (ABCC4), is a member of the MRP family involved in multidrug resistance. As a molecular transporter, MRP4 can transport endogenous and exogenous components such as cGMP, bile acid, and urate, and is also involved in the distribution and excretion of some drugs such as antivirals (adefovir and tenofovir), antibiotics (cefazolin and cefotaxime), and others [75, 76]. Due to its role in pumping out endogenous and xenobiotic agents, overexpression of MRP4 could contribute to multidrug resistance. Doxorubicin in osteosarcomas [77], antiviral ganciclovir [78], and docetaxel in prostate cancer [79] are examples of drugs that it affects.

Associations of the *MRP4* gene with KD susceptibility were investigated in a European population based on family linkage studies. The genetic susceptibilities of three SNPs (rs7320375, rs7329490, and rs7986087) for KD were reported [27]. Furthermore, rs7986087 (T variant) was successfully replicated in a Chinese population [28]. In addition to KD susceptibility, the *MRP4* gene was reported to be involved in IVIG resistance in a Chinese population. Carriers of the C allele at rs1751034 of the *MRP4* gene were associated with a risk of IVIG resistance [33].

Nicotinamide Mononucleotide Adenylyl Transferase 2 (NMNAT2)

NMNAT is an enzyme that catalyzes an important step in the nicotinamide adenine dinucleotide (NAD^+) biosynthetic pathway. The NAD^+ pathway plays a critical role in immune modulation by affecting macrophage-driven inflammation [80]. Some studies related to the role of NAD^+ or NMNAT primarily focused on cancer or aging disorders, and not on KD [81, 82]. NMNAT2 is one of the isoforms of NMNAT enzymes that showed higher expression in colorectal cancer tissues [83]. However, a GWAS study in a Korean population identified rs2078087 in the *NMNAT2* locus to be associated with the pathogenesis of KD [23]. Further studies in other populations are needed to validate this gene.

SMAD3

SMAD3, a gene encodes SMAD family protein, plays a key role in the transforming growth factor (TGF)-β signaling pathway. As a multifunctional cytokine, activation of TGF-β can mediate growth control of cells of the immune system, regulate T-cell function, and induce cytostatic and apoptotic programs [84]. Functional roles of the TGF-β pathway in KD pathogenesis are related to immune responses and inflammatory processes [85]. Five genetic variations on the *SMAD3* gene for KD were found in people of European descent, including rs4776338 (A/G), rs7162912, rs12901071, rs1438386, and rs6494633 [29]. Moreover, a replication study in a Taiwanese population further confirmed the role of rs1438386 in KD [30].

High-Mobility Group Box 1 (HMGB1)

HMGB1 is a nonhistone DNA-binding protein that contributes to inflammatory processes. HMGB1 levels were higher in acute KD adolescent patients [86] and patients with autoimmune diseases [87]. However, its expression significantly decreased in the convalescent phase [88].

HMGB1 requires binding to the receptor for advanced glycation end products (RAGE) before activating various signaling pathways, such as NF-κB. Expressions of HMGB1, RAGE, and NF-κB were higher in acute KD patients and CAL patients. Findings indicated that HMGB1 might be associated with inflammatory processes during coronary artery injury in KD [89]. Indeed, the rs1412125 polymorphism of *HMGB1* in a Korean population was reported in CALs (in a recessive model) and IVIG resistance (in both recessive and allelic models). Still, it showed no association with KD susceptibility [31].

Interleukin (IL)-16

IL-16 is responsible for T cell activation and immune-mediated inflammatory disorders, such as SLE [90]. The relationship between *IL-16* and KD susceptibility is unclear; however, this gene was identified to be associated with response to IVIG treatment. A study in a Korean population indicated that a new coding variant, rs11556218 (p.Asn1147Lys), in the *IL-16* gene was associated with IVIG resistance. Further analysis indicated a strong effect from combining two risk variants (*SAMD9L* and *IL16*) for IVIG resistance [19].

Purinergic Receptor P2Y12 (P2RY12)

P2RY12 is one of eight subtypes of P2Y G-protein coupled receptors that have broad functions, including systemic immune responses [91]. P2Y12 is also known to be involved in platelet activation [92]. P2Y12 inhibitors, such as clopidogrel and prasugrel, were previously used as treatments for coronary artery disease [93]. No evidence clearly indicates an association between *P2RY12* variants and KD susceptibility. One study in China showed no significant association between variants of *P2RY12* and KD susceptibility; however, that study presented the relationship between a polymorphism of *P2RY12* (TT genotype of rs7637803) with CAA risk in KD patients [94]. Furthermore, one of five variants of the *P2RY12* gene (rs6809699 A > C) was also verified to be involved in IVIG resistance in ethnic Han Chinese individuals [20].

Sterile Alpha Motif Domain-Containing Protein 9-Like (SAMD9L)

SAMD9L, located on chromosome 7, is a gene that encodes a cytoplasmic protein. A mutation of *SAMD9L* was shown to contribute to cytopenia that may predispose persons to myelodysplastic syndrome (MDS) [95] and ataxia–pancytopenia (AP) syndrome [96]. Although evidence related to *SAMD9L* variants and susceptibility of KD has not yet been reported, there is evidence supporting the role of *SAMD9L* in response to IVIG treatment. A GWAS and replication study performed in a Korean population demonstrated that *SAMD9L* (rs28662) was involved in IVIG treatment responses. Those results were replicated in a Japanese cohort, and a stronger association was revealed in meta-analysis data [18].

Prediction of Intravenous Immunoglobulin Resistance Using a Genetic Risk Score (GSC)

A GSC was developed to estimate the contributions of genetic factors in specific individuals. The first study, which used a combination-weighted GSC (wGSC) algorithm of GWAS data for KD, was published by Chang's lab [97]. The lab integrated the additive effect of 11 SNPs to establish a predictive model for IVIG responsiveness in KD patients. The predictive model provided good performance with a specificity of 88.9% and sensitivity of 79.2% [97]. In light of the fact that genomic profiles are very important and have been linked to therapeutic outcomes of KD, data from the wGSC algorithm indicated the significance as a reasonable early detection method to reduce clinical risks in IVIG-resistant KD patients [97].

Conclusions

Nowadays, many genetic variations associated with KD pathogenesis or IVIG responses have been reported. Genomic approaches are able to provide excellent opportunities for personalized medicine and healthcare. Furthermore, they can help determine how to improve the specificity and sensitivity for predicting risks of KD and IVIG responses. Therefore, we wish to raise awareness about the value of genomic research and pharmacogenomics studies of KD.

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References

1. JCS Joint Working Group. Guidelines for diagnosis and management of cardiovascular sequelae in Kawasaki disease (JCS 2013). Digest version. Circ J. 2014;78(10):2521–62.
2. Elakabawi K, Lin J, Jiao F, Guo N, Yuan Z. Kawasaki disease: global burden and genetic background. Cardiol Res. 2020;11(1):9–14.
3. Tang Y, Yan W, Sun L, et al. Kawasaki disease associated with Mycoplasma pneumoniae. Ital J Pediatr. 2016;42(1):83.
4. Chang LY, Lu CY, Shao PL, et al. Viral infections associated with Kawasaki disease. J Formos Med Assoc. 2014;113(3):148–54.
5. 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. Circulation. 2017;135(17):e927–99.
6. Onouchi Y, Gunji T, Burns JC, et al. ITPKC functional polymorphism associated with Kawasaki disease susceptibility and formation of coronary artery aneurysms. Nat Genet. 2008;40(1):35–42.
7. Kuo H-C, Yang KD, Juo S-HH, et al. ITPKC single nucleotide polymorphism associated with the Kawasaki disease in a Taiwanese population. PLoS One. 2011;6(4):e17370.
8. Khor CC, Davila S, Breunis WB, et al. Genome-wide association study identifies FCGR2A as a susceptibility locus for Kawasaki disease. Nat Genet. 2011;43(12):1241–6.
9. Onouchi Y, Suzuki Y, Suzuki H, et al. ITPKC and CASP3 polymorphisms and risks for IVIG unresponsiveness and coronary artery lesion formation in Kawasaki disease. Pharmacogenomics J. 2013;13(1):52–9.
10. Johnson TA, Mashimo Y, Wu J-Y, et al. Association of an IGHV3-66 gene variant with Kawasaki disease. J Hum Genet. 2021;66(5):475–89.
11. Yan Y, Ma Y, Liu Y, et al. Combined analysis of genome-wide-linked susceptibility loci to Kawasaki disease in Han Chinese. Hum Genet. 2013;132(6):669–80.
12. Shrestha S, Wiener H, Shendre A, et al. Role of activating FcγR gene polymorphisms in Kawasaki disease susceptibility and intravenous immunoglobulin response. Circ Cardiovasc Genet. 2012;5(3):309–16.
13. Onouchi Y, Ozaki K, Burns JC, et al. A genome-wide association study identifies three new risk loci for Kawasaki disease. Nat Genet. 2012;44(5):517–21.
14. Chen M-R, Chang T-Y, Chiu N-C, et al. Validation of genome-wide associated variants for Kawasaki disease in a Taiwanese case–control sample. Sci Rep. 2020;10(1):11756.
15. Chang CJ, Kuo HC, Chang JS, et al. Replication and meta-analysis of GWAS identified susceptibility loci in Kawasaki disease confirm the importance of B lymphoid tyrosine kinase (BLK) in disease susceptibility. PLoS One. 2013;8(8):e72037.
16. Sim BK, Park H, Kim JJ, et al. Assessment of the clinical heterogeneity of Kawasaki disease using genetic variants of BLK and FCGR2A. Korean Circ J. 2019;49(1):99–108.
17. Kuo H-C, Chao M-C, Hsu Y-W, et al. CD40 Gene polymorphisms associated with susceptibility and coronary artery lesions of Kawasaki disease in the Taiwanese population. ScientificWorldJournal. 2012;2012:520865.
18. Kim J-J, Yun SW, Yu JJ, et al. Identification of SAMD9L as a susceptibility locus for intravenous immunoglobulin resistance in Kawasaki disease by genome-wide association analysis. Pharmacogenomics J. 2020;20(1):80–6.
19. Kim H-J, Kim J-J, Yun SW, et al. Association of the IL16 Asn1147Lys polymorphism with intravenous immunoglobulin resistance in Kawasaki disease. J Hum Genet. 2020;65(4):421–6.
20. Wang Z, Xu Y, Zhou H, et al. Association between P2RY12 gene polymorphisms and IVIG resistance in Kawasaki patients. Cardiovasc Ther. 2020;2020:3568608.
21. Wang W, Lou J, Lu X-Z, et al. 8p22–23-rs2254546 as a susceptibility locus for Kawasaki disease: a case–control study and a meta-analysis. Sci Rep. 2014;4(1):4247.
22. Ferdosian F, Dastgheib SA, Hosseini-Jangjou SH, et al. Association of TNF-α rs1800629, CASP3 rs72689236 and FCGR2A rs1801274 polymorphisms with susceptibility to Kawasaki disease: a

comprehensive meta-analysis. Fetal Pediatr Pathol. 2019;40:320–36.
23. Kim JJ, Yun SW, Yu JJ, et al. A genome-wide association analysis identifies NMNAT2 and HCP5 as susceptibility loci for Kawasaki disease. J Hum Genet. 2017;62(12):1023–9.
24. Lin YJ, Wan L, Wu JY, et al. HLA-E gene polymorphism associated with susceptibility to Kawasaki disease and formation of coronary artery aneurysms. Arthritis Rheum. 2009;60(2):604–10.
25. Burns JC, Shimizu C, Shike H, et al. Family-based association analysis implicates IL-4 in susceptibility to Kawasaki disease. Genes Immun. 2005;6(5):438–44.
26. Assari R, Aghighi Y, Ziaee V, et al. Interleukin-4 cytokine single nucleotide polymorphisms in kawasaki disease: a case-control study and a review of knowledge. Int J Rheum Dis. 2018;21(1):266–70.
27. Khor CC, Davila S, Shimizu C, et al. Genome-wide linkage and association mapping identify susceptibility alleles in *ABCC4* for Kawasaki disease. J Med Genet. 2011;48(7):467.
28. Che D, Pi L, Fang Z, et al. ABCC4 variants modify susceptibility to Kawasaki disease in a Southern Chinese population. Dis Markers. 2018;2018:8638096.
29. Shimizu C, Jain S, Davila S, et al. Transforming growth factor-beta signaling pathway in patients with Kawasaki disease. Circ Cardiovasc Genet. 2011;4(1):16–25.
30. Kuo H-C, Onouchi Y, Hsu Y-W, et al. Polymorphisms of transforming growth factor-β signaling pathway and Kawasaki disease in the Taiwanese population. J Hum Genet. 2011;56(12):840–5.
31. Ahn JG, Bae Y, Shin D, Nam J, Kim KY, Kim DS. HMGB1 gene polymorphism is associated with coronary artery lesions and intravenous immunoglobulin resistance in Kawasaki disease. Rheumatology. 2019;58(5):770–5.
32. Amano Y, Akazawa Y, Yasuda J, et al. A low-frequency IL4R locus variant in Japanese patients with intravenous immunoglobulin therapy-unresponsive Kawasaki disease. Pediatr Rheumatol. 2019;17(1):34.
33. Wang Y, Xu Y, Huang P, et al. Homozygous of MRP4 Gene rs1751034 C allele is related to increased risk of intravenous immunoglobulin resistance in Kawasaki disease. Front Genet. 2021;12:376.
34. Samuelson EM, Laird RM, Papillion AM, Tatum AH, Princiotta MF, Hayes SM. Reduced B lymphoid kinase (Blk) expression enhances proinflammatory cytokine production and induces nephrosis in C57BL/6-lpr/lpr mice. PLoS One. 2014;9(3):e92054.
35. Mentlein L, Thorlacius GE, Meneghel L, et al. The rheumatic disease-associated FAM167A-BLK locus encodes DIORA-1, a novel disordered protein expressed highly in bronchial epithelium and alveolar macrophages. Clin Exp Immunol. 2018;193(2):167–77.
36. Ramírez-Bello J, Jiménez-Morales S, Montufar-Robles I, et al. BLK and BANK1 polymorphisms and interactions are associated in Mexican patients with systemic lupus erythematosus. Inflamm Res. 2019;68(8):705–13.
37. Ramírez-Bello J, Fragoso JM, Alemán-Ávila I, et al. Association of BLK and BANK1 polymorphisms and interactions with rheumatoid arthritis in a Latin-American population. Front Genet. 2020;11:58.
38. Riedl SJ, Shi Y. Molecular mechanisms of caspase regulation during apoptosis. Nat Rev Mol Cell Biol. 2004;5(11):897–907.
39. Woo M, Hakem R, Furlonger C, et al. Caspase-3 regulates cell cycle in B cells: a consequence of substrate specificity. Nat Immunol. 2003;4(10):1016–22.
40. Onouchi Y, Ozaki K, Buns JC, et al. Common variants in CASP3 confer susceptibility to Kawasaki disease. Hum Mol Genet. 2010;19(14):2898–906.
41. Wu W, Misra RS, Russell JQ, Flavell RA, Rincón M, Budd RC. Proteolytic regulation of nuclear factor of activated T (NFAT) c2 cells and NFAT activity by caspase-3. J Biol Chem. 2006;281(16):10682–90.
42. Chen K, Zhao H, Hu Z, et al. CASP3 polymorphisms and risk of squamous cell carcinoma of the head and neck. Clin Cancer Res. 2008;14(19):6343–9.
43. Xu HL, Xu WH, Cai Q, et al. Polymorphisms and haplotypes in the caspase-3, caspase-7, and caspase-8 genes and risk for endometrial cancer: a population-based, case-control study in a Chinese population. Cancer Epidemiol Biomark Prev. 2009;18(7):2114–22.
44. Kuo H-C, Hsu Y-W, Wu C-M, et al. A replication study for association of ITPKC and CASP3 two-locus analysis in IVIG unresponsiveness and coronary artery lesion in Kawasaki disease. PLoS One. 2013;8(7):e69685.
45. Kuo H-C, Yu H-R, Juo S-HH, et al. CASP3 gene single-nucleotide polymorphism (rs72689236) and Kawasaki disease in Taiwanese children. J Hum Genet. 2011;56(2):161–5.
46. Elgueta R, Benson MJ, de Vries VC, Wasiuk A, Guo Y, Noelle RJ. Molecular mechanism and function of CD40/CD40L engagement in the immune system. Immunol Rev. 2009;229(1):152–72.
47. Wang C-L, Wu Y-T, Liu C-A, et al. Expression of CD40 ligand on CD4+ T-cells and platelets correlated to the coronary artery lesion and disease progress in Kawasaki disease. Pediatrics. 2003;111(2):e140.
48. Jindal AK, Rawat A, Goel S, et al. Expression of CD40 ligand on T cells and soluble CD40 ligand in children with Kawasaki disease: a single-center preliminary study from North India. J Clin Rheumatol. 2021;27(5):194–200.
49. Kuo H-C, Hsu Y-W, Wu M-S, et al. *FCGR2A* promoter methylation and risks for intravenous immunoglobulin treatment responses in Kawasaki disease. Mediat Inflamm. 2015;2015:564625.
50. Ce Z, Wang W, He Z, Wei L, Guo S. Association of FCGR2A rs1801274 polymorphism with susceptibility to autoimmune diseases: a meta-analysis. Oncotarget. 2016;7(26):39436–43.
51. Kwon Y-C, Kim J-J, Yun SW, et al. Male-specific association of the FCGR2A His167Arg poly-

morphism with Kawasaki disease. PLoS One. 2017;12(9):e0184248.
52. Li S-C, Chan W-C, Huang Y-H, et al. Major methylation alterations on the CpG markers of inflammatory immune associated genes after IVIG treatment in Kawasaki disease. BMC Med Genet. 2016;9(1):37.
53. Chang LS, Lo MH, Li SC, Yang MY, Hsieh KS, Kuo HC. The effect of FcγRIIA and FcγRIIB on coronary artery lesion formation and intravenous immunoglobulin treatment responses in children with Kawasaki disease. Oncotarget. 2017;8(2):2044–52.
54. Kulski JK, Dawkins RL. The P5 multicopy gene family in the MHC is related in sequence to human endogenous retroviruses HERV-L and HERV-16. Immunogenetics. 1999;49(5):404–12.
55. Rajesh D, Nagraj S, Kumar KSP, Kutty AVM, Balakrishna S. Evaluation of HCP5 and chemokine C receptor type 5 gene polymorphisms in Indian psoriatic patients. Indian J Dermatol. 2019;64(3):182–6.
56. Colafrancesco S, Ciccacci C, Priori R, et al. *STAT4, TRAF3IP2, IL10*, and *HCP5* polymorphisms in Sjögren's syndrome: association with disease susceptibility and clinical aspects. J Immunol Res. 2019;2019:7682827.
57. Dendrou CA, Petersen J, Rossjohn J, Fugger L. HLA variation and disease. Nat Rev Immunol. 2018;18(5):325–39.
58. Oh JH, Han JW, Lee SJ, et al. Polymorphisms of human leukocyte antigen genes in korean children with Kawasaki disease. Pediatr Cardiol. 2008;29(2):402–8.
59. Kwon Y-C, Sim Bo K, Yu Jeong J, et al. HLA-B*54:01 is associated with susceptibility to Kawasaki disease. Circ Genom Precis Med. 2019;12(1):e002365.
60. Huang FY, Chang TY, Chen MR, et al. Genetic variations of HLA-DRB1 and susceptibility to Kawasaki disease in Taiwanese children. Hum Immunol. 2007;68(1):69–74.
61. Ghiotto F, Marcatili P, Tenca C, et al. Mutation pattern of paired immunoglobulin heavy and light variable domains in chronic lymphocytic leukemia B cells. Mol Med. 2011;17(11–12):1188–95.
62. Parks T, Mirabel MM, Kado J, et al. Association between a common immunoglobulin heavy chain allele and rheumatic heart disease risk in Oceania. Nat Commun. 2017;8:14946.
63. Watson CT, Breden F. The immunoglobulin heavy chain locus: genetic variation, missing data, and implications for human disease. Genes Immun. 2012;13(5):363–73.
64. Tsai F-J, Lee Y-C, Chang J-S, et al. Identification of novel susceptibility loci for kawasaki disease in a Han chinese population by a genome-wide association study. PLoS One. 2011;6(2):e16853.
65. Hirao J, Hibi S, Andoh T, Ichimura T. High levels of circulating interleukin-4 and interleukin-10 in Kawasaki disease. Int Arch Allergy Immunol. 1997;112(2):152–6.
66. Li Y, Zheng Q, Zou L, et al. Kawasaki disease shock syndrome: clinical characteristics and possible use of IL-6, IL-10 and IFN-γ as biomarkers for early recognition. Pediatr Rheumatol Online J. 2019;17(1):1.
67. Scholz B, Korn C, Wojtarowicz J, et al. Endothelial RSPO3 controls vascular stability and pruning through non-canonical WNT/Ca(2+)/NFAT signaling. Dev Cell. 2016;36(1):79–93.
68. Rozen EJ, Roewenstrunk J, Barallobre MJ, et al. DYRK1A kinase positively regulates angiogenic responses in endothelial cells. Cell Rep. 2018;23(6):1867–78.
69. Wang Y, Hu J, Liu J, et al. The role of Ca(2+)/NFAT in Dysfunction and Inflammation of Human Coronary Endothelial Cells induced by Sera from patients with Kawasaki disease. Sci Rep. 2020;10(1):4706.
70. Alphonse MP, Duong TT, Shumitzu C, et al. Inositol-triphosphate 3-kinase C mediates inflammasome activation and treatment response in Kawasaki disease. J Immunol. 2016;197(9):3481–9.
71. Kelley N, Jeltema D, Duan Y, He Y. The NLRP3 inflammasome: an overview of mechanisms of activation and regulation. Int J Mol Sci. 2019;20(13):3328.
72. Murakami T, Ockinger J, Yu J, et al. Critical role for calcium mobilization in activation of the NLRP3 inflammasome. Proc Natl Acad Sci. 2012;109(28):11282.
73. Jia C, Zhang J, Chen H, et al. Endothelial cell pyroptosis plays an important role in Kawasaki disease via HMGB1/RAGE/cathespin B signaling pathway and NLRP3 inflammasome activation. Cell Death Dis. 2019;10(10):778.
74. Kuo H-C, Hsu Y-W, Lo M-H, Huang Y-H, Chien S-C, Chang W-C. Single-nucleotide polymorphism rs7251246 in ITPKC is associated with susceptibility and coronary artery lesions in Kawasaki disease. PLoS One. 2014;9(3):e91118.
75. Russel FGM, Koenderink JB, Masereeuw R. Multidrug resistance protein 4 (MRP4/ABCC4): a versatile efflux transporter for drugs and signalling molecules. Trends Pharmacol Sci. 2008;29(4):200–7.
76. Wen J, Luo J, Huang W, Tang J, Zhou H, Zhang W. The pharmacological and physiological role of multidrug-resistant protein 4. J Pharmacol Exp Ther. 2015;354(3):358.
77. He Z, Hu B, Tang L, et al. The overexpression of MRP4 is related to multidrug resistance in osteosarcoma cells. J Cancer Res Ther. 2015;11(1):18–23.
78. Adachi M, Sampath J, Lan L-B, et al. Expression of MRP4 confers resistance to ganciclovir and compromises bystander cell killing. J Biol Chem. 2002;277(41):38998–9004.
79. Huang H, Li J, Shen J, et al. Increased ABCC4 expression induced by ERRα leads to docetaxel resistance via efflux of docetaxel in prostate cancer. Front Oncol. 2020;10:1474.
80. Billingham LK, Chandel NS. NAD-biosynthetic pathways regulate innate immunity. Nat Immunol. 2019;20(4):380–2.

81. Minhas PS, Liu L, Moon PK, et al. Macrophage de novo NAD(+) synthesis specifies immune function in aging and inflammation. Nat Immunol. 2019;20(1):50–63.
82. Kiss A, Ráduly AP, Regdon Z, et al. Targeting nuclear NAD(+) synthesis inhibits DNA repair, impairs metabolic adaptation and increases chemosensitivity of U-2OS osteosarcoma cells. Cancers (Basel). 2020;12(5):1180.
83. Cui C, Qi J, Deng Q, Chen R, Zhai D, Yu J. Nicotinamide mononucleotide adenylyl transferase 2: a promising diagnostic and therapeutic target for colorectal cancer. Biomed Res Int. 2016;2016:1804137.
84. Siegel PM, Massagué J. Cytostatic and apoptotic actions of TGF-β in homeostasis and cancer. Nat Rev Cancer. 2003;3(11):807–20.
85. Travis MA, Sheppard D. TGF-β activation and function in immunity. Annu Rev Immunol. 2014;32:51–82.
86. Ng HY, Slomp S, Wilson-Gerwing T, Dietz J, Lodhi A, Holt T, Rosenberg A. High mobility group box 1 protein in children with Kawasaki disease and systemic juvenile idiopathic arthritis [abstract]. Arthritis Rheumatol. https://acrabstracts.org/abstract/high-mobility-group-box-1-protein-in-children-with-kawasaki-disease-and-systemic-juvenile-idiopathic-arthritis/. Published 2017. Accessed 22 March 2021.
87. Zhu B, Zhu Q, Li N, Wu T, Liu S, Liu S. Association of serum/plasma high mobility group box 1 with autoimmune diseases: a systematic review and meta-analysis. Medicine. 2018;97(29):e11531.
88. Hoshina T, Kusuhara K, Ikeda K, Mizuno Y, Saito M, Hara T. High mobility group box 1 (HMGB1) and macrophage migration inhibitory factor (MIF) in Kawasaki disease. Scand J Rheumatol. 2008;37(6):445–9.
89. Qian B, Huang H, Cheng M, Qin T, Chen T, Zhao J. Mechanism of HMGB1-RAGE in Kawasaki disease with coronary artery injury. Eur J Med Res. 2020;25(1):8–8.
90. Xue H, Gao L, Wu Y, et al. The IL-16 gene polymorphisms and the risk of the systemic lupus erythematosus. Clin Chim Acta. 2009;403(1):223–5.
91. Freeman TL, Swartz TH. Purinergic receptors: elucidating the role of these immune mediators in HIV-1 fusion. Viruses. 2020;12(3):290.
92. Andre P, Delaney SM, LaRocca T, et al. P2Y12 regulates platelet adhesion/activation, thrombus growth, and thrombus stability in injured arteries. J Clin Invest. 2003;112(3):398–406.
93. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2018;39(3):213–60.
94. Lu Z, Xu Y, Fu L, et al. P2RY12:rs7637803 TT variant genotype increases coronary artery aneurysm risk in Kawasaki disease in a southern Chinese population. J Gene Med. 2019;21(1):e3066.
95. Tesi B, Davidsson J, Voss M, et al. Gain-of-function SAMD9L mutations cause a syndrome of cytopenia, immunodeficiency, MDS, and neurological symptoms. Blood. 2017;129(16):2266–79.
96. Chen DH, Below JE, Shimamura A, et al. Ataxia-pancytopenia syndrome is caused by missense mutations in SAMD9L. Am J Hum Genet. 2016;98(6):1146–58.
97. Kuo H-C, Wong Henry S-C, Chang W-P, et al. Prediction for intravenous immunoglobulin resistance by using weighted genetic risk score identified from genome-wide association study in Kawasaki disease. Circ Cardiovasc Genet. 2017;10(5):e001625.

Epigenetics in Kawasaki Disease

Kuang-Den Chen

Abstract

Purpose of this chapter: The purpose of this review is to discuss recent evidence of epigenetic alterations and their contribution related to the complicated pathogenesis of Kawasaki disease.

There have been new observations of epigenetic alterations and their potential role in disease pathogenesis of Kawasaki disease. In recent years, there has been increasing evidence of epigenetic alterations and their potential role in disease pathogenesis of Kawasaki disease. Recent work has focused on clinical application of DNA methylation and miRNA biomarkers in progression of Kawasaki disease and how these epigenetic alterations play a key role in various aspects of the related gene expression. Changes in both DNA methylation and microRNA expression are fertile ground for investigation relating to clinical diagnosis and therapeutic targets in Kawasaki disease. However, current knowledge has relied on small cohorts that more large-scale studies are needed in the future for validation and to understand their target specificity and the efficacy in therapeutic applications of Kawasaki disease.

Keywords

Kawasaki disease · Global DNA hypomethylation · Pattern recognition receptors Intravenous immunoglobulin · microRNAs Endothelial microparticles

Kawasaki disease (KD) is an acute-onset systemic vasculitis, which largely affects young children before 5 years of age presenting as fever of unknown origin. While KD's etiology is largely unknown, a growing body of research suggests the fetal origin of KD pathogenesis is mediated by epigenetic changes. Even if epigenetic alterations can be inherited, which modulate the efficiency of gene transcription and can impact on health due to the presence of environmental stressors, some of those remarkably stable changes at least partially reversible. Some studies proposed that children with KD might be triggered by infectious agents that have a strong genetic susceptibility but does not confer actual predisposition to an infectious disease. Geographic Confounding in genome-wide association studies of Kawasaki disease contributes to abound conflicting results, whereas only loci within the CD40 and BLK genes reporting to be consistent between Japan and Taiwan [1, 2]. Genome-wide studies in recent years have indicated that epigenetic factors may

K.-D. Chen (✉)
Kawasaki Disease Center and Institute for Translational Research in Biomedicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan

Taiwan Association for the Promotion of Molecular Hydrogen, Kaohsiung, Taiwan
e-mail: dennis8857@cgmh.org.tw

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play a vital role in KD pathogenesis. Therefore, a deeper knowledge of the epigenetic modifications in the susceptibility and pathogenesis of KD may constitute promising new targets and therapeutics in acute KD.

Methylation in KD

For the first time, DNA methylation was examined in KD by Dr. Kuo HC's group and revealed a role of hypomethylation of FCGR2A in its susceptibility and poor response (resistance) to intravenous immunoglobulin (IVIG) treatment [3]. A significant association among methylation of FCGR2A promoter, susceptibility of KD and the responsiveness of IVIG treatment was also reported [4]. Another genome-wide study demonstrated that hypomethylation alterations in peripheral blood cells of KD patients were enriched in genes functionally associated with the immune inflammatory response including the primarily identified FCGR2A [5]. This study found the significant impact of IVIG administration on methylation patterns, and such impact was conducted mainly by hypermethylating CpG markers, suppressing expression levels of the corresponding genes including FCGR2A to represses excessive inflammatory responses. Furthermore, Dr. Kuo's team illustrated a series of Toll-like receptor (TLR) genes encoding TLR1, TLR2, TLR4, TLR6, TLR8, and TLR9 were hypomethylated in KD patients and their mRNA expression levels were remarkably increased compared with the controls [6]. The methylation levels and mRNA expression of these TLR genes can be reverted within 3-week IVIG treatment. TLRs are pattern recognition receptors (PRRs) that serve as the sensor of innate immune system. The results are among the first to prove an infectious immune response may be crucial in triggering KD. We further demonstrated site-specific hypomethylation of matrix metalloproteinase 9 (MMP9) and negative correlation of its increased transcript in KD patients who had diagnosed coronary arterial lesions [7]. A significant hypomethylation of hepcidin (HAMP) promoter, the negatively correlated HAMP expression and its reversibility after receiving IVIG therapy was reported [8]. This report also demonstrated the reliability and robustness of an in-house developed classification model that accurately serves as a KD predictor with high sensitivity and specificity. The epigenetic hypomethylation and upregulation of NLRC4 and NLRP12, which are members in the inflammasome sensors of NOD-like receptor (NLR) family, were observed in KD patients compared to the controls [9]. The negatively correlated upregulation of NLRC4, NLRP12, and IL-1β in KD patients were also demonstrated. Taken together, the cumulated evidence of hypomethylated alteration by Dr. Kuo's group suggested a global DNA hypomethylation was occurred in KD patients and may be critical in its pathogenesis as well as disease progression.

The global DNA hypomethylation in peripheral blood cells of KD patients was demonstrated for the first time that revealed a total of 97% hypomethylation in these epigenetic changes [10] (Fig. 1).

In this study, an enriched gene regulatory network in the corresponding genes of hypermethylated alteration in KD was examined, and the hypermethylated changes in the region of β-catenin (CTNNB1), its decreased mRNA levels and correlation with coronary artery lesions in KD were demonstrated. This study is the first that proved site-specific regulation in the few hypermethylated alteration may also be critical in KD pathogenesis.

MicroRNA Alteration in KD

The deficiency of regulatory T cells (Treg) with a reduction in Foxp3 expression has been implicated in association with skewed proinflammatory response of Th17 cells in acute KD patients [11]. The effects of microRNAs miR-31 and miR-155 were primarily investigated in children with KD, and the results showed that Foxp3 mRNA levels were affected by the miR-155/SOCS1 and the miR-31 in acute KD [12]. The decreased expression of miR-155, leading to aberrant SOCS1/STAT5 signaling and overexpression of miR-31 in acute KD were partially

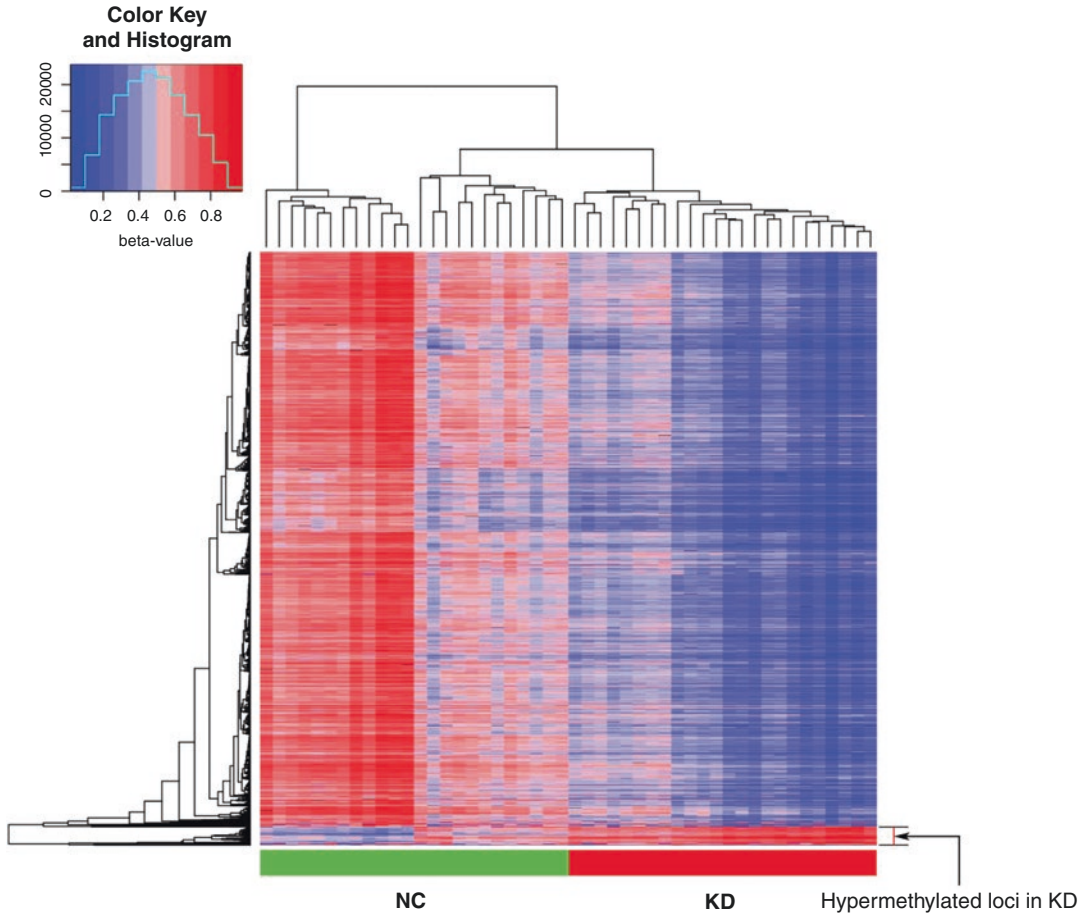

Fig. 1 Differential DNA methylation of individual CpG loci in peripheral blood cells. Unsupervised two-way hierarchical clustering and heat map of genomic regions that include CpG dinucleotides with a methylation difference of ≥20% found between Kawasaki disease patients (KD) and normal control subjects (NC) (reproduced with permission from [10])

reverted after IVIG treatment. Furthermore, proinflammatory microRNAs miR-200c and miR-371-5p, which potentially modulate TGF-β signaling, are involved in KD pathogenesis [13]. Both miR-200c and -371-5p were remarkably higher in serum of acute KD patients compared to the controls and shown to effectively distinguish between KD with IVIG-responsive and the nonresponsive patients indicating their ability as the useful diagnostic biomarkers and therapeutic targets [14]. Another proinflammatory microRNA miR-92a-3p, which has known to stimulate secretion of IL-6, was identified as a potential biomarker for diagnosis of KD and KD with coronary artery lesions [15]. Additionally, the role of blood-circulating microRNAs miR-223, miR-125a-5p, and miR-186 in KD and KD-induced injuries in vascular endothelial cells was illustrated [16–18].

Exosomes are cell-derived vesicles that interact with and are taken up by target cells and mediate cell–cell communication through transporting microRNAs [19, 20]. Endothelial microparticles (EMPs) are exosomes that are released from endothelial cells and can be found circulating in the blood. Recent studies have demonstrated that endothelial dysfunction is associated with later coronary damage events, where inflam-

mation occurs on the vascular endothelial cells, EMPs are released from the activated endothelial cells [21, 22]. It has been primarily demonstrated that exosome-shuttled microRNA miR-145 was increased in whole blood of acute KD children [23]. Several recent reports also demonstrated the contribution of microRNAs encapsulated in exosomes to the endothelial dysfunction progression in acute KD. Nakaoka et al. identified two microRNAsmiR-145-5p and miR-320a in KD patients with coronary artery lesions that were found to increase inflammatory cytokines in vitro and suggested to be involved in the pathogenesis of vasculitis in acute KD [24]. Zhang et al. screened serum exosomal microRNAs for the early diagnosis of KD by analyzing microarray data [25]. They identified miR-328, miR-575, miR-134, and miR-671-5p as potential biomarkers and their target genes that may be associated with inflammation and the prediction of outcomes of IVIG therapy.

In conclusion, growing evidence from in vivo and in vitro experiments have demonstrated promising diagnostic significance of circulating and exosomal microRNAs in KD, especially for distinguishing KD from other febrile diseases. However, these studies generally relied upon small phenotypically varied cohorts of patient and the controls. More studies are needed in the future for validation and to understand their target specificity and the efficacy in therapeutic applications.

References

1. Lee YC, Kuo HC, Chang JS, Chang LY, Huang LM, Chen MR, et al. Two new susceptibility loci for Kawasaki disease identified through genome-wide association analysis. Nat Genet. 2012;44(5):522–5.
2. Onouchi Y, Ozaki K, Burns JC, Shimizu C, Terai M, Hamada H, et al. A genome-wide association study identifies three new risk loci for Kawasaki disease. Nat Genet. 2012;44(5):517–21.
3. Kuo HC, Chang JC, Kuo HC, Yu HR, Wang CL, Lee CP, et al. Identification of an association between genomic hypomethylation of FCGR2A and susceptibility to Kawasaki disease and intravenous immunoglobulin resistance by DNA methylation array. Arthritis Rheumatol. 2015;67(3):828–36.
4. Kuo HC, Hsu YW, Wu MS, Woon PY, Wong HS, Tsai LJ, et al. FCGR2A promoter methylation and risks for intravenous immunoglobulin treatment responses in Kawasaki disease. Mediat Inflamm. 2015;2015:564625.
5. Li SC, Chan WC, Huang YH, Guo MM, Yu HR, Huang FC, et al. Major methylation alterations on the CpG markers of inflammatory immune associated genes after IVIG treatment in Kawasaki disease. BMC Med Genomics. 2016;9 Suppl 1:37.
6. Huang YH, Li SC, Huang LH, Chen PC, Lin YY, Lin CC, et al. Identifying genetic hypomethylation and upregulation of toll-like receptors in Kawasaki disease. Oncotarget. 2017;8(7):11249–58.
7. Kuo HC, Li SC, Huang LH, Huang YH. Epigenetic hypomethylation and upregulation of matrix metalloproteinase 9 in Kawasaki disease. Oncotarget. 2017;8(37):60875–91.
8. Huang YH, Kuo HC, Li SC, Cai XY, Liu SF, Kuo HC. HAMP promoter hypomethylation and increased hepcidin levels as biomarkers for Kawasaki disease. J Mol Cell Cardiol. 2018;117:82–7.
9. Huang YH, Lo MH, Cai XY, Kuo HC. Epigenetic hypomethylation and upregulation of NLRC4 and NLRP12 in Kawasaki disease. Oncotarget. 2018;9(27):18939–48.
10. Chen KD, Huang YH, Ming-Huey Guo M, Lin TY, Weng WT, Yang HJ, et al. The human blood DNA methylome identifies crucial role of beta-catenin in the pathogenesis of Kawasaki disease. Oncotarget. 2018;9(47):28337–50.
11. Jia S, Li C, Wang G, Yang J, Zu Y. The T helper type 17/regulatory T cell imbalance in patients with acute Kawasaki disease. Clin Exp Immunol. 2010;162(1):131–7.
12. Ni FF, Li CR, Li Q, Xia Y, Wang GB, Yang J. Regulatory T cell microRNA expression changes in children with acute Kawasaki disease. Clin Exp Immunol. 2014;178(2):384–93.
13. Yun KW, Lee JY, Yun SW, Lim IS, Choi ES. Elevated serum level of microRNA (miRNA)-200c and miRNA-371-5p in children with Kawasaki disease. Pediatr Cardiol. 2014;35(5):745–52.
14. Zhang W, Wang Y, Zeng Y, Hu L, Zou G. Serum miR-200c and miR-371-5p as the useful diagnostic biomarkers and therapeutic targets in Kawasaki disease. Biomed Res Int. 2017;2017:8257862.
15. Rong X, Jia L, Hong L, Pan L, Xue X, Zhang C, et al. Serum miR-92a-3p as a new potential biomarker for diagnosis of Kawasaki disease with coronary artery lesions. J Cardiovasc Transl Res. 2017;10(1):1–8.
16. Chu M, Wu R, Qin S, Hua W, Shan Z, Rong X, et al. Bone marrow-derived microRNA-223 works as an endocrine genetic signal in vascular endothelial cells and participates in vascular injury from Kawasaki disease. J Am Heart Assoc. 2017;6(2):e004878.
17. Li Z, Jiang J, Tian L, Li X, Chen J, Li S, et al. A plasma mir-125a-5p as a novel biomarker for Kawasaki disease and induces apoptosis in HUVECs. PLoS One. 2017;12(5):e0175407.

18. Wu R, Shen D, Sohun H, Ge D, Chen X, Wang X, et al. miR186, a serum microRNA, induces endothelial cell apoptosis by targeting SMAD6 in Kawasaki disease. Int J Mol Med. 2018 Apr;41(4):1899–908.
19. Turchinovich A, Samatov TR, Tonevitsky AG, Burwinkel B. Circulating miRNAs: cell-cell communication function? Front Genet. 2013;4:119.
20. Edgar JR. Q&A: what are exosomes, exactly? BMC Biol. 2016;14:46.
21. Davizon P, Lopez JA. Microparticles and thrombotic disease. Curr Opin Hematol. 2009;16(5):334–41.
22. Yamamoto S, Niida S, Azuma E, Yanagibashi T, Muramatsu M, Huang TT, et al. Inflammation-induced endothelial cell-derived extracellular vesicles modulate the cellular status of pericytes. Sci Rep. 2015;5:8505.
23. Shimizu C, Kim J, Stepanowsky P, Trinh C, Lau HD, Akers JC, et al. Differential expression of miR-145 in children with Kawasaki disease. PLoS One. 2013;8(3):e58159.
24. Nakaoka H, Hirono K, Yamamoto S, Takasaki I, Takahashi K, Kinoshita K, et al. MicroRNA-145-5p and microRNA-320a encapsulated in endothelial microparticles contribute to the progression of vasculitis in acute Kawasaki disease. Sci Rep. 2018;8(1):1016.
25. Zhang X, Xin G, Sun D. Serum exosomal miR-328, miR-575, miR-134 and miR-671-5p as potential biomarkers for the diagnosis of Kawasaki disease and the prediction of therapeutic outcomes of intravenous immunoglobulin therapy. Exp Ther Med. 2018;16(3):2420–32.

Transcriptomics in Kawasaki Disease

Tai-Ming Ko, Jan Vincent Beltran, and Jou-Yu Huang

Abstract

Transcriptomics is the high-throughput characterization of RNA. It has played an important role in defining the pathogenic characteristics of Kawasaki disease. It has aided in clarifying Kawasaki disease etiology and identifying its key mediators, which will further help to compensate for the limitations of existing intravenous immunoglobulin treatments. In addition, transcriptomics is being used for immune monitoring, diagnostic and prognostic biomarker identification. These features can be applied in stratifying patients, monitoring molecular changes related to disease severity, defining personalized treatment strategies, as well as providing clinical evidence. This chapter discusses the progress of transcriptomics in determining Kawasaki disease etiology and pathogenesis and developing diagnostic and predictive biomarkers. We also explore some analytical methods for extracting valuable information from high-dimensional datasets to improve our biological knowledge. Lastly, we discuss the emerging technology of transcriptomics in the study of the diversity of expression quantitative trait loci, B-cell and T-cell receptor repertoires, and assessment of Kawasaki disease heterogeneity using high-throughput single-cell sequencing.

Keywords

CD177 · Immune receptor repertoire · Intravenous immunoglobulin · Kawasaki disease · Next-generation sequencing · Neutrophil · RNA · Single-cell analysis · Transcriptomics

T.-M. Ko (✉)
Department of Biological Science and Technology, National Yang Ming Chiao Tung University, Hsinchu, Taiwan

Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan

Institute of Bioinformatics and Systems Biology, National Yang Ming Chiao Tung University, Hsinchu, Taiwan

Center for Intelligent Drug Systems and Smart Bio-devices (IDS2B), National Yang Ming Chiao Tung University, Hsinchu, Taiwan

Taiwan International Graduate Program in Molecular Medicine, National Yang Ming Chiao Tung University and Academia Sinica, Taipei, Taiwan
e-mail: tmko@nycu.edu.tw

J. V. Beltran
Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan

Taiwan International Graduate Program in Molecular Medicine, National Yang Ming Chiao Tung University and Academia Sinica, Taipei, Taiwan

J.-Y. Huang
Department of Biological Science and Technology, National Yang Ming Chiao Tung University, Hsinchu, Taiwan

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Introduction

Kawasaki disease (KD) is a systemic vasculitis affecting children aged ≤5 years. It is the most common cause of childhood acquired heart disease, causing inflammation primarily in the coronary arteries. If left untreated, as many as 25% of children develop coronary artery aneurysms (CAAs) [1, 2]. Incomplete recovery may also lead to death from myocardial infarction; hence, long-term health monitoring may be required in some cases [3].

One of the most serious complications of KD is coronary aneurysm, a swelling in the wall of the coronary artery. The standard treatment for KD is aspirin and intravenous immunoglobulin (IVIG) administration. IVIG can prevent the development of CAAs. Treatment is administered within 10 days of disease onset. As mentioned before, approximately 25% of untreated cases develop CAA; IVIG treatment can reduce this risk to 5–10%, restricting the occurrence to IVIG-resistant KD cases [3].

A large-scale transcriptomic analysis has been performed to determine the etiology and pathogenesis of KD. However, more similar studies are needed to verify these findings. Similarly, highly specific and sensitive biomarkers for KD have not yet been established, and further research on their molecular basis is required.

In the last two decades, transcriptomics has enabled the use of high-throughput technologies (such as whole-genome DNA microarrays) for the simultaneous measurement of thousands of RNA transcripts in blood, urine, saliva, and biopsy specimens, replacing techniques such as PCR. Previous studies on leukocytes and tissues have demonstrated that microarrays can be used to characterize molecular networks related to cancer, autoimmunity, infection, and vaccination [4–6]. The recently developed next-generation sequencing (NGS) technology can comprehensively characterize noncoding RNAs, including micro and long noncoding RNAs, and perform qualitative and quantitative measurement and sequencing of isoforms through long-read sequencing. Currently, the transcriptome is routinely evaluated in combination with whole-genome or whole-exome sequencing for expression quantitative trait loci (eQTL) analysis; chromatin accessibility has been used in combination to further define genetic and epigenetic transcriptional regulators. Targeted sequencing can characterize T and B cell receptor repertoires. High-throughput single-cell sequencing is advancing the analysis of heterogeneous cell compartments and identifying new cell subpopulations.

In the following section, we discuss how transcriptomics has helped in the understanding of KD pathogenesis. We mention emerging applications of this technology in conducting research such as immune receptor repertoire diversity, and single-cell analysis. We also discuss the potential application of transcriptomics to solve the clinical problems surrounding KD and summarize some lessons learned from the transcriptomics of KD monitoring.

Transcriptomics to Unravel Mechanisms of KD

Following cancer research, the analysis of the transcription profile of pediatric patients began in the early twenty-first century. Thus far, these studies have provided important clues that may aid in the identification and characterization of new targets in different pediatric diseases and expansion of the new field of interferon-associated diseases. Gene expression profiling has identified therapeutic targets for KD that is susceptible to innate immune activation and IL-1 blockade. Although NGS has taken gene expression profiling to a new level, the research summarized in this section has mainly used hybridization-based platforms.

mRNA Transcripts in Patients' Blood

In terms of transcripts, IVIG treatment has a greater impact on which cell populations in the peripheral circulation becomes dysregulated. For this reason, when the acute symptoms of most patients have been relieved, many research groups checked the gene expression in PBMC or whole blood obtained from KD patients before and after IVIG treatment.

Using cDNA microarray (Affymetrix Human Genome U133A array), monocyte-derived transcripts, such as secreted peptides (adrenomedullin, S100A8, S100A9, S100A12, and TNF superfamily) have been determined in Japanese patients; results suggested that IVIG inhibits activated monocytes and macrophages in patients with KD [7]. Another study using human FL GeneChip probe arrays also confirmed that adrenomedullin transcript levels are significantly higher in the acute phase than in the recovery phase of KD [8]. By analyzing the whole transcriptome (approximately 18,000 unique human genes) of peripheral whole blood obtained from patients during the acute, subacute, and convalescent phases of illness, the dynamic and variable nature of the acute phase of the disease as well as the involvement of neutrophils in KD have been determined [6]. Additionally, higher *CEACAM1* transcript levels have been found to be associated with subsequent nonresponse to IVIG treatment [6]. Compared with the control group, higher expression levels of B cell activation-related genes have been observed in patients with KD [9]. Using cDNA microarray (Affymetrix Human Genome U133 Plus 2.0 array), a set of transcripts related to late-differentiated granulocytes has been found to be significantly increased in Japanese patients. The neutrophil PRV-1 protein (CD177) and G-CSF levels of nonresponding patients were significantly higher than those of responding patients. These findings indicate that G-CSF stimulation of granulocytes may be an important risk factor for KD onset [10]. cDNA microarray (Agilent G4112F Human Whole Genome Oligo Arrays) analysis in US patients demonstrated that high transcript levels of *MMP-8*, *S100 family*, and *CEACAM1* to be associated with IVIG resistance [5]. Moreover, it has been revealed that the IL-1 signaling pathway is important in KD development [5, 11]. KD-associated long noncoding RNAs (lncRNAs) transcripts have been identified in Taiwanese patients by employing a new version of the Agilent array [4]. Based on mRNA profiling, CD177 transcripts were found to be more abundant in the acute KD stage and IVIG-resistant individuals than in IVIG-susceptible individuals [4]. The following studies also support the role of CD177 in KD by combining data from epigenetic (Illumina HumanMethylation450 BeadChip) and mRNA profiling [Affymetrix GeneChip(R) Human Transcriptome Array 2.0] [12]. These two studies validate the roles of CD177 in two independent Taiwanese cohort studies [10]. Regarding lncRNA profiling, interestingly, *XLOC_006277* was found to be significantly associated with CAA. When *XLOC_006277* is knocked down, the expression of matrix metalloproteins MMP-8 and MMP-9, related to tissue remodeling and coronary artery disease, is also suppressed [4].

mRNA Transcripts in KD Patients' Heart Tissues

The findings on activated immune pathways in coronary artery target tissues are valuable for investigating the pathogenesis of KD, especially the molecular insights of coronary arteritis. Blood transcriptome studies have limitations on investigating the molecular events on the heart tissue from patients with KD. Therefore, using transcriptomics profiling to investigate the coronary artery tissues of KD can provide previously unknown information and may have therapeutic implications. A previous study of deep sequencing of heart tissues obtained from patients with KD has revealed that T lymphocyte activation, production of immunoglobulin, and responses of type I interferon were the major upregulated molecular pathways in KD arteritis [13]. These findings are compatible with genetic polymorphisms that lead to a reduction in the negative regulation of T lymphocyte responses, in turn associated with the abnormal development of KD and CAAs. Of note, there are several type I interferon-induced proteins (i.e., CXCL9 or CXCL10) that have been indicated as potential KD biomarkers [14, 15].

mRNA Transcripts in KD-Like Mouse Models

The lack of identification of disease-causing factors and detailed molecular mechanisms involved in Kawasaki disease has become a challenge for

the development of targeted and effective treatment options. The etiology of KD remains unclear, and the pathogenesis of KD requires studies that are conducted in a KD-symptom-like mouse model. Pathological features that are similar to that of KD vasculitis can be induced in mice by injecting the cell wall components of *Lactobacillus casei* [16–18] and *Candida albicans* [19–21]. Gene expression profiling has been performed in *the Lactobacillus casei* cell wall extract (LCWE)-induced Kawasaki disease mouse model [22, 23] to investigate the detailed pathogenic mechanism of KD. The study identified that the activation of caspase 1, IL-1α, and IL-1β was crucial for the development of coronary arteritis, aneurysm, myocarditis, and abdominal aortic aneurysm. IL-1 has the ability to promote the differentiation of activated $CD8^+$ T cells, and increases the frequency of $CD4^+$ and $CD8^+$ T cells in blood from patients with KD [24]. Infiltration of antigen-stimulated cytotoxic $CD8^+$ T cells and activated dendritic cells in the arterial layer of coronary aneurysms has also been reported [25]. Recent studies have also pointed out that KD might be caused by a variety of pathogenic sources [26] therefore, it is imperative to understand the changes in the shared downstream mechanism following antigen stimulation. Recent animal experiments have also successively explored the relevant mechanisms of LCWE-induced T-cell activation [27].

Noncoding Transcripts Biosignatures in KD

In addition to mRNA, other types of transcriptomic signatures such as miRNA (a class of small noncoding RNAs that regulate mRNA expression) have also been reported in patients with KD. A variety of miRNAs are differentially expressed in the blood of patients with KD, indicating abnormal changes in the regulatory network. In addition, miRNAs are stable molecules and can be noninvasively accessed from peripheral blood, therefore, they possess the potential to be used as a biomarker for diagnosis. Several miRNAs were found to be related to acute Kawasaki disease from serum exosomes or coronary artery tissues. These miRNAs include miR-19a-3p, miR-23a, miR-27b, miR-143, miR-145, miR-184, miR-210-3p, and miR-223 [28–33]. These miRNAs may provide clues to the molecular mechanisms underlying the development of cardiovascular disease related to Kawasaki disease.

Emerging Applications of Transcriptomics in Kawasaki Disease

Immune Receptor Repertoire

The adaptive immune system is composed of a large number of lymphocytes, including B and T cells. These cells have unique antigen specificity and can provide long-term protection against a variety of pathogens. Through these mechanisms, lymphocytes maintain a very high number of unique receptors to deal with multiple pathogens in the environment. In KD, the characterization of this enormous immune receptor repertoire is critical in the investigation of the pathogenesis of the disease. Targeted high-throughput sequencing of the variable regions of B-cell and T-cell receptors can be performed to precisely investigate clonal expansion in various immune states.

B cells have been hypothesized to play a role in KD. The identification of the association between SNPs clustered in IGHV (encoding immunoglobulin heavy chain variable region) and KD risk indicates the possibility of the involvement of B cells in KD [34]. In addition, large-scale genetics studies (genome-wide association studies) of two races uncovered potential pathogenic roles of B cells in KD as the BLK (encoding B lymphatic tyrosine kinase) that is selectively expressed in B cells is most closely related to the KD genetic locus [35, 36]. A comprehensive full-length immunoglobulin sequencing analysis of the transcripts in KD has revealed that the immune system of patients with KD exhibits an infection-like pattern [37]. The supporting evidence indicated that the diversity index of acute IgM clonotypes was extremely low and possessed certain dominant IgM clonotypes. In addition, most dominant IgM clonotypes completely disappeared from the peripheral

blood. Another independent cohort study also confirmed the infection patterns through multiplex-PCR-based B-cell receptor (BCR) analysis. Therefore, functional validation of these dominant immunoglobulin clonotypes and their potential clinical applications need to be investigated in future studies.

Neutrophil-Associated Genes as Potential Targets in Kawasaki Disease

It is worth noting that distinguishing KD from other high fever and pediatric infectious diseases with similar symptoms, such as staphylococcal and streptococcal toxic shock syndrome, measles, and other viral and inflammatory diseases, is difficult. Therefore, establishing reliable markers for the differential diagnosis of KD is important for the accurate diagnosis and early therapeutic intervention. Previously, many potential targets such as IL-1, CD177, and CXCL10 demonstrated key roles of neutrophils in KD [4, 6, 10, 12, 14]. Neutrophils have been shown to play a crucial role in aneurysm formation by migrating to coronary artery endothelium. The roles of neutrophils in KD were supported by CD177 findings in KD [4, 10, 12] and a hypothesized working mechanism can be generated. In KD, neutrophil migration is possibly mediated by binding of CD177 to β2 integrin (CD11b/CD18) receptor [38]; neutrophils then adhere to endothelial cells through ICAM-1 surface ligands, thereby driving transport. During this process, CXCL10 (IP-10) secreted by endothelial cells might be strongly upregulated and released to patients' plasma [14], leading to the downregulation of CXCR3 in T cells of patients with acute KD; thus, it has been recently identified as a diagnostic marker for KD [14]. Concurrently, IL-6 derived from B cells induces macrophages to produce CXCL10, mediated by STAT3 phosphorylation [39]. Additionally, B cells also undergo autocrine production of IL-6 that is amplified by CXCL10 and maintain STAT3 signal, a necessary condition for driving B cells to differentiate into IgA-secreting plasma cells and penetrate the site of inflamed tissues to produce plasma cells. Simultaneously, macrophages exhibit active toll-like receptor (TLR) signaling, which can be used as an early chemotactic signal to trigger the release of chemokines that attract neutrophils, including CXCL8, the most effective neutrophil attractant. CXCR3 receptors are highly expressed on activated T cells in plasma. CXCL10 and CXCL9, endogenous ligands of CXCR3, are involved in cardiovascular problems and aneurysms (Fig. 1) [4, 5, 10, 12, 14, 38, 40, 41].

Perspective of Transcriptomics in Kawasaki Disease

While children lose loses the antibodies transferred from their mothers, the exposure to new infections and antigens can stimulate generation of new antibodies. In addition, the microbiota changes over time, which may cause significant changes in immune homeostasis [42]. However, the assessment of the altered immune status of children and the heterogeneity of immune cells have become research challenges. This is especially true for KD. In vitro and in vivo research platforms lack ideal disease simulation tools, and several mechanisms of cell heterogeneity cannot be further explored and remain obscure owing to insufficient analysis.

In the past decade, many RNA-sequencing (RNA-seq) technologies and microarrays have been widely used to study gene expression patterns at the population level. The emergence of single-cell RNA sequencing (scRNA-seq) provides an unprecedented opportunity to explore the gene expression profiles at the single-cell level. At present, scRNA-seq has become an ideal choice for studying the key biological issues associated with cell heterogeneity. Recent vigorous developments of microfluidics and combinatorial indexing strategies, coupled with lower sequencing costs, provide a strong support for the robustness of single-cell sequencing technology. Over thousands of cells analyzed in each run of single-cell experiment constitute a data revolution in single-cell biology, and this has resulted in the identification of unique data

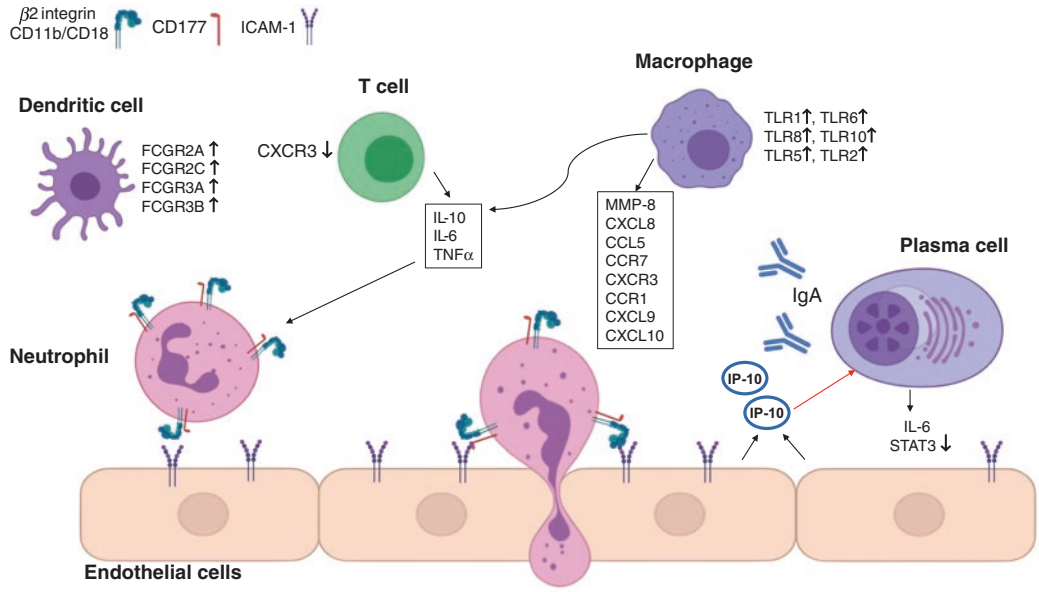

Fig. 1 KD-associated transcripts and involvement of neutrophils in KD. A diagram showing a monolayer of rectangular endothelial cells, at the bottom, with ICAM-1 surface expression. The circular T cell, macrophage, and oval plasma cells are presented with their potential targets. We illustrate a neutrophil expressing beta 2 integrin CD11b/CD18 and CD177 close to an endothelial cell and another neutrophil undergoing diapedesis to penetrate the endothelium

science problems. To date, single-cell gene expression analysis in mammalian tissues has revealed profound stage-specific molecular regulation phenomena. It is expected to improve our understanding of disease-associated cell subpopulations and signaling molecular mechanisms that are essential for determining lineage, morphogenesis, and growth. Therefore, several critical issues are expected to be investigated based on a single-cell analysis platform, by overcoming the heterogeneity of immune cells and the underlying biology of damaged heart tissues in KD.

Conclusion

Transcriptomics is essential for revealing the pathogenesis of KD. It is being increasingly used to monitor disease progression and treatment response and develop diagnostic and predictive biomarkers. Combined with genetic data, it has aided into the pathogenesis of KD using genome-wide association studies. It has provided a wealth of information about noncoding RNAs and their potential roles as biomarkers and/or in pathogenesis of these diseases. Rapidly improving sequencing technologies, including long-standing platforms such as single molecule real-time and droplet-based sequencing, are enabling researchers to quickly and economically characterize the application of isoforms in diseases. Thousands of single cells can be sequenced at a time, and even single-cell transcriptomes can be analyzed under in vivo conditions. There is no doubt that the application of NGS in characterizing the microbiome has produced basic information related to the development of KD. These studies will be the subject of further research. Despite these advances, relatively few studies have been performed on predictive biomarker detection owing to the lack of adequate design and functionality and, therefore, cannot be directly applied in clinical practice. In conclusion, the new methods for detecting, measuring, and combining various biomedical information will undoubtedly help in improving biomedical information, including molecular, genomic, cellular, and

clinical disease-associated factors. It is possible to understand and develop reasonable treatment methods not only for adult diseases but also for pediatric diseases, such as KD.

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References

1. Newburger JW, 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. https://doi.org/10.1161/01.CIR.0000145143.19711.78.
2. Newburger JW, 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. Pediatrics. 2004;114:1708–33. https://doi.org/10.1542/peds.2004-2182.
3. McCrindle BW, 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. https://doi.org/10.1161/CIR.0000000000000484.
4. Ko TM, et al. Genome-wide transcriptome analysis to further understand neutrophil activation and lncRNA transcript profiles in Kawasaki disease. Sci Rep. 2019;9:328. https://doi.org/10.1038/s41598-018-36520-y.
5. Fury W, et al. Transcript abundance patterns in Kawasaki disease patients with intravenous immunoglobulin resistance. Hum Immunol. 2010;71:865–73. https://doi.org/10.1016/j.humimm.2010.06.008.
6. Popper SJ, et al. Gene-expression patterns reveal underlying biological processes in Kawasaki disease. Genome Biol. 2007;8:R261. https://doi.org/10.1186/gb-2007-8-12-r261.
7. Abe J, et al. Gene expression profiling of the effect of high-dose intravenous Ig in patients with Kawasaki disease. J Immunol. 2005;174:5837–45. https://doi.org/10.4049/jimmunol.174.9.5837.
8. Nomura I, et al. Adrenomedullin is highly expressed in blood monocytes associated with acute Kawasaki disease: a microarray gene expression study. Pediatr Res. 2005;57:49–55. https://doi.org/10.1203/01.PDR.0000147745.52711.DD.
9. Popper SJ, et al. Gene transcript abundance profiles distinguish Kawasaki disease from adenovirus infection. J Infect Dis. 2009;200:657–66. https://doi.org/10.1086/603538.
10. Abe J, et al. Elevated granulocyte colony-stimulating factor levels predict treatment failure in patients with Kawasaki disease. J Allergy Clin Immunol. 2008;122:1008–1013.e8. https://doi.org/10.1016/j.jaci.2008.09.011.
11. Hoang LT, et al. Global gene expression profiling identifies new therapeutic targets in acute Kawasaki disease. Genome Med. 2014;6:541. https://doi.org/10.1186/s13073-014-0102-6.
12. Huang YH, Lo MH, Cai XY, Liu SF, Kuo HC. Increase expression of CD177 in Kawasaki disease. Pediatr Rheumatol Online J. 2019;17:13. https://doi.org/10.1186/s12969-019-0315-8.
13. Rowley AH, et al. The transcriptional profile of coronary arteritis in Kawasaki disease. BMC Genomics. 2015;16:1076. https://doi.org/10.1186/s12864-015-2323-5.
14. Ko TM, et al. CXCL10/IP-10 is a biomarker and mediator for Kawasaki disease. Circ Res. 2015;116:876–83. https://doi.org/10.1161/CIRCRESAHA.116.305834.
15. Feng S, Yadav SK, Gao F, Yi Q. Plasma levels of monokine induced by interferon-gamma/chemokine (C-X-X motif) ligand 9, thymus and activation-regulated chemokine/chemokine (C-C motif) ligand 17 in children with Kawasaki disease. BMC Pediatr. 2015;15:109. https://doi.org/10.1186/s12887-015-0424-6.
16. Matundan HH, et al. Myocardial fibrosis after adrenergic stimulation as a long-term sequela in a mouse model of Kawasaki disease vasculitis. JCI Insight. 2019;4:e126279. https://doi.org/10.1172/jci.insight.126279.
17. Lehman TJ, Walker SM, Mahnovski V, McCurdy D. Coronary arteritis in mice following the systemic injection of group B Lactobacillus casei cell walls in aqueous suspension. Arthritis Rheum. 1985;28:652–9. https://doi.org/10.1002/art.1780280609.
18. Suganuma E, Sato S, Honda S, Nakazawa A. A novel mouse model of coronary stenosis mimicking Kawasaki disease induced by Lactobacillus casei cell wall extract. Exp Anim. 2020;69:233–41. https://doi.org/10.1538/expanim.19-0124.
19. Murata H. Experimental candida-induced arteritis in mice. Relation to arteritis in the mucocutaneous lymph node syndrome. Microbiol Immunol. 1979;23:825–31. https://doi.org/10.1111/j.1348-0421.1979.tb02815.x.
20. Yoshikane Y, et al. JNK is critical for the development of Candida albicans-induced vascular lesions in a mouse model of Kawasaki disease. Cardiovasc Pathol. 2015;24:33–40. https://doi.org/10.1016/j.carpath.2014.08.005.
21. Oharaseki T, et al. Recognition of alpha-mannan by dectin 2 is essential for onset of Kawasaki disease-like murine vasculitis induced by Candida albicans cell-wall polysaccharide. Mod Rheumatol. 2020;30:350–7. https://doi.org/10.1080/14397595.2019.1601852.

22. Lau AC, Duong TT, Ito S, Yeung RS. Matrix metalloproteinase 9 activity leads to elastin breakdown in an animal model of Kawasaki disease. Arthritis Rheum. 2008;58:854–63. https://doi.org/10.1002/art.23225.
23. Lau AC, Duong TT, Ito S, Wilson GJ, Yeung RS. Inhibition of matrix metalloproteinase-9 activity improves coronary outcome in an animal model of Kawasaki disease. Clin Exp Immunol. 2009;157:300–9. https://doi.org/10.1111/j.1365-2249.2009.03949.x.
24. Hirao J, Sugita K. Circulating CD4+CD8+ T lymphocytes in patients with Kawasaki disease. Clin Exp Immunol. 1998;111:397–401. https://doi.org/10.1046/j.1365-2249.1998.00480.x.
25. Yilmaz A, et al. Activated myeloid dendritic cells accumulate and co-localize with CD3+ T cells in coronary artery lesions in patients with Kawasaki disease. Exp Mol Pathol. 2007;83:93–103. https://doi.org/10.1016/j.yexmp.2007.01.007.
26. Burns JC, et al. Characterization of circulating immune cells in acute Kawasaki disease suggests exposure to different antigens. Clin Exp Immunol. 2020;202:263–72. https://doi.org/10.1111/cei.13506.
27. Hsieh LE, et al. Characterization of the T cell response to Lactobacillus casei Cell Wall extract in children with Kawasaki disease and its potential role in vascular inflammation. Front Pediatr. 2021;9:633244. https://doi.org/10.3389/fped.2021.633244.
28. Jone PN, et al. Circulating microRNAs differentiate Kawasaki disease from infectious febrile illnesses in childhood. J Mol Cell Cardiol. 2020;146:12–8. https://doi.org/10.1016/j.yjmcc.2020.06.011.
29. Chu M, et al. Bone marrow-derived MicroRNA-223 works as an endocrine genetic signal in vascular endothelial cells and participates in vascular injury from Kawasaki disease. J Am Heart Assoc. 2017;6:e004878. https://doi.org/10.1161/JAHA.116.004878.
30. He M, et al. miR-483 targeting of CTGF suppresses endothelial-to-mesenchymal transition: therapeutic implications in Kawasaki disease. Circ Res. 2017;120:354–65. https://doi.org/10.1161/CIRCRESAHA.116.310233.
31. Kuo HC, et al. Next-generation sequencing identifies micro-RNA-based biomarker panel for Kawasaki disease. J Allergy Clin Immunol. 2016;138:1227–30. https://doi.org/10.1016/j.jaci.2016.04.050.
32. Rowley AH, et al. A study of cardiovascular miRNA biomarkers for Kawasaki disease. Pediatr Infect Dis J. 2014;33:1296–9. https://doi.org/10.1097/INF.0000000000000449.
33. Shimizu C, et al. Differential expression of miR-145 in children with Kawasaki disease. PLoS One. 2013;8:e58159. https://doi.org/10.1371/journal.pone.0058159.
34. Tsai FJ, et al. Identification of novel susceptibility loci for Kawasaki disease in a Han chinese population by a genome-wide association study. PLoS One. 2011;6:e16853. https://doi.org/10.1371/journal.pone.0016853.
35. Lee YC, et al. Two new susceptibility loci for Kawasaki disease identified through genome-wide association analysis. Nat Genet. 2012;44:522–5. https://doi.org/10.1038/ng.2227.
36. Onouchi Y, et al. A genome-wide association study identifies three new risk loci for Kawasaki disease. Nat Genet. 2012;44:517–21. https://doi.org/10.1038/ng.2220.
37. Ko TM, et al. Immunoglobulin profiling identifies unique signatures in patients with Kawasaki disease during intravenous immunoglobulin treatment. Hum Mol Genet. 2018;27:2671–7. https://doi.org/10.1093/hmg/ddy176.
38. Bai M, et al. CD177 modulates human neutrophil migration through activation-mediated integrin and chemoreceptor regulation. Blood. 2017;130:2092–100. https://doi.org/10.1182/blood-2017-03-768507.
39. Xu W, et al. Macrophages induce differentiation of plasma cells through CXCL10/IP-10. J Exp Med. 2012;209:1813–23, S1–2. https://doi.org/10.1084/jem.20112142.
40. Halbwachs L, Lesavre P. Endothelium-neutrophil interactions in ANCA-associated diseases. J Am Soc Nephrol. 2012;23:1449–61. https://doi.org/10.1681/ASN.2012020119.
41. Noval Rivas M, Arditi M. Kawasaki disease: pathophysiology and insights from mouse models. Nat Rev Rheumatol. 2020;16:391–405. https://doi.org/10.1038/s41584-020-0426-0.
42. Olin A, et al. Stereotypic immune system development in newborn children. Cell. 2018;174:1277–1292.e14. https://doi.org/10.1016/j.cell.2018.06.045.

Immune Responses in Kawasaki Disease

Kuender D. Yang

Abstract

Kawasaki disease (KD) is a febrile vasculitis associated with mucocutaneous lesions, lymphadenopathy and cardiovascular events. Typical KD mostly occurs in children less than 5 years of age but atypical KD complicated with macrophage activation syndrome (MAS) or KD shock syndrome (KDSS) occurs in relatively older children, even adults. The etiology of KD remains unclear; however, the immune response is known to mediate by an autoinflammatory innate immune response associated with an imbalance of adaptive immunity showing augmented T helper 17 (Th17)/Th1 responses with higher IL-6, IL-10, IP-10, and IL-17 levels and reduced Th2/Treg responses with lower IL-4, IL-5, FoxP3, and TGFβ expression. This acute autoinflammatory vasculitis may be induced by an exogenous antigen derived from pathogen-associated molecular pattern (PAMP) or an endogenous antigen derived from damage-associated molecular pattern (DAMP). The altered immunity would manifest typical or atypical KD under genetic and environmental backgrounds. Some patients of KD (3–5%) are complicated with KDSS associated with over-production of nitric oxide, coagulopathy and shock symptom, and few patients (1–2%) are complicated with MAS, showing hemophagocytosis, thrombocytopenia, and hyperferritinemia. KD patients with these variant complications usually manifest intravenous immunoglobulin (IVIG) resistance and require additional anti-inflammatory medication. The immune reaction of KD reveals a kinetic progression for early administration of IVIG within 4 days of the illness did not provide a better outcome, and early administration of corticosteroids alone exacerbated the prognosis, but a combination of corticosteroids with IVIG provided the best treatment response. Further studies are proposed to identify the immunopathogenesis of IVIG-resistance, MAS and KDSS, to protect hosts from antigen exposure, and genetic susceptibility, and to combat MAS and/or KDSS by blockade of mechanistic biomarkers, anti-signal transduction, manipulations of host milieu, hit the brakes for immunosuppression and anti-hemophagocytosis.

Keywords

Kawasaki disease (KD) · Kawasaki Disease Shock Syndrome (KDSS) · Macrophage Activation Syndrome (MAS) · Intravenous

K. D. Yang (✉)
MacKay Children's Hospital, Taipei, Taiwan

Department of Microbiology & Immunology, National Defense Medical Center, Taipei, Taiwan

Institute of Clinical Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan

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Immunoglobulin (IVIG) resistance · Th17/Treg imbalance · Immunotherapy

A Postinfectious Autoimmune Disease of Kawasaki Disease

Kawasaki disease (KD) is a febrile medium-sized vasculitis in children with at least 4 out of the 5 clinical features: (1) dysmorphic skin rashes, (2) bilateral nonpurulent conjunctivitis, (3) oral mucosal changes: dry fissured lips, injected lips, and/or strawberry tongue, (4) peripheral extremities changes: indurative angioedema of the hands and feet followed by skin desquamation, and (5) cervical lymphadenopathy (at least 1.5 cm in diameter) [1–4]. Pathogens such as *S. aureus*, streptococci, chlamydia, rhinovirus, coronavirus, enterovirus, or Epstein–Barr (EB) virus had been associated with KD [2–5]. An infectious disease is usually contagious, but it is not contagious transmission of KD in day care centers or hospital household staff. Siblings of KD patients reveal 6 to 10 times more chance to have KD than those without a KD history [6, 7]. Moreover, there is no any sequence readout of DNA and RNA viruses in sera from KD [8], suggesting a postinfectious disorder or an autoimmune disease. In East Asia, where Bacillus Calmette–Guérin (BCG) vaccination is applied to infants, 40% of KD patients have reactive skin erythema and/or scaling at the BCG inoculation site [2], suggesting the reactivation of BCG inoculation is related to cross-reaction of BCG antigen or bystander of hyperinflammatory reaction of KD. Taken together, KD may be caused by a common infectious agent which causes an asymptomatic infection but causes a postinfectious autoimmune vasculitis in children. It remains controversial if KD is a postinfectious hyperinflammation, autoinflammatory, or autoimmune disorder [9–11]. It is speculated that inflammation-inducing substances, such as those originating from pathogens and pathogen-associated molecular patterns (PAMPs), including toxins (superantigens), and others from injured or damaged-host cells called damage-associated molecular patterns (DAMPs) may cause hyperinflammatory response of KD [12].

A human coronavirus New Haven (HCoVNH) had been associated with an outbreak of KD in New Haven, showing RT-PCR detection of the positivity at 73% (8/11) versus 5% (1/22) in a case-control study [5]. The association of KD with HCoVNH was not replicated in Taiwan where a study showed undetectable virus RNA of HCoVNH or HCoV-NL63 in nasopharyngeal secretions using 53 consecutive KD patients [13]. However, the Taiwan study did not measure antibodies against HCoVNH or HCoV-NL63 in the serum. Recently, more than 1000 cases of KD-like multisystem inflammatory syndrome in children (MIS-C) which presented typical or atypical KD had been reported [14]. In patients with MIS-C, 80–100% patients had detectable anti-spike antibodies in blood but only 0–30% of patients had detectable RNA of SARS-CoV-2 in upper respiratory tract [14–19]. The algorithm for diagnosis and treatment of KD in children has been resorted to early recognition and treatment of the KD-like vasculitis in MIS-C for the immunotherapy with IVIG and corticosteroids. Interestingly, the MIS-C cases were mostly reported from Italy, France, the UK, and the USA [14–19], but not in China, Japan, and Korea, where the KD incidence is 10 times more than that in Western countries [1–4]. These studies suggest that children in Western countries are susceptible to coronavirus-related MIS-C, but not non–coronavirus-related KD. In contrast, children in Asian countries are susceptible to non–coronavirus-related KD vasculitis. It is a great concern that the Covid-19 associated MIS-C or cardiovascular events may occur after the mass Covid-19 vaccination in Western countries, where certain vaccine antigens with and without (w/wo) adjuvant may increase the risk of KD-like MIS-C [4].

Kinetic Progress on the Immunopathogenesis of Kawasaki Disease

Patients with KD or KD-like vasculitis reveal augmented immune reactions associated with hypercytokinemia and increases of C-reactive protein and procalcitonin levels [4]. This addressed the

hyperinflammatory responses on altered innate immunity. The augmented innate immunity is supported by our experimental mice model of KD showing higher TLR2 expression and monocytosis [20]. As shown in Fig. 1a, the initial immune response of KD may be mediated by a pathogen or an antigen derived from PAMP which ligates a pattern recognition receptor (PRR) such as toll-like receptors (TLRs) or C-type lectin receptors (CLRs) resulting in signal transduction of MyD88 (Myeloid differentiation primary response 88) and/or TRIF (Toll/interleukin-1 receptor containing adapter-inducing interferon-β) for augmented production of IL-1, IL-6, TNFα, and so on. These innate immune reactions are associated with early neutrophilia, and a thrombocytosis in the disease progression into convalescent stage [2, 11, 21, 22]. In addition to induction of innate immunity, the

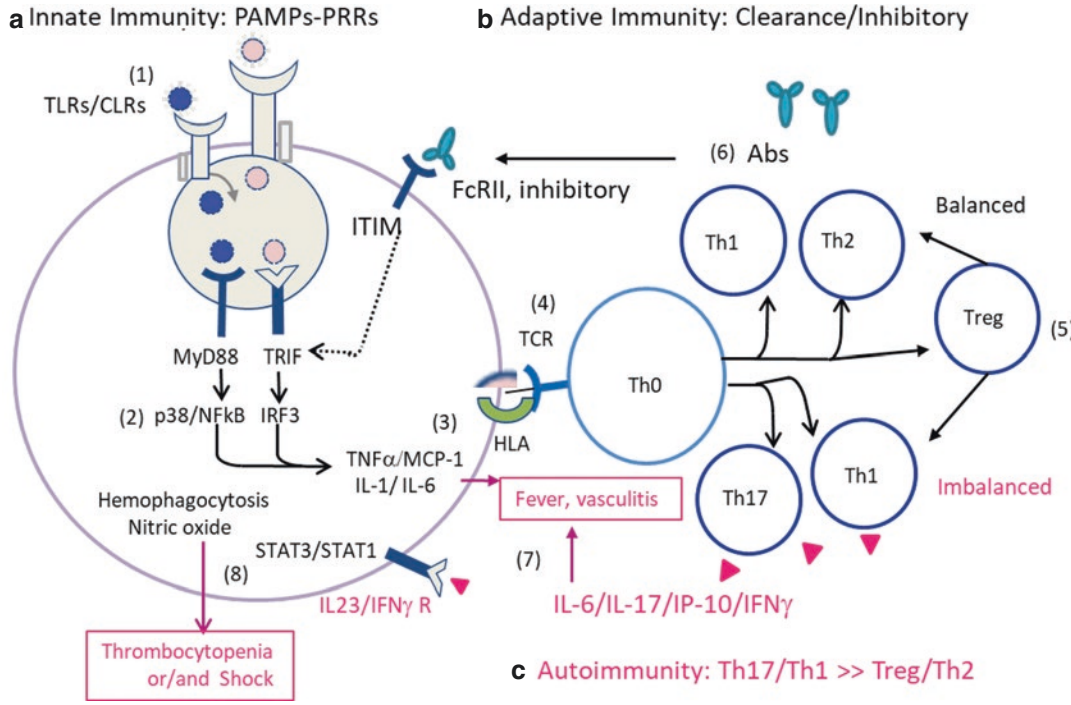

Fig. 1 Immunopathogenesis of KD without and with complication. (**a**) Innate immunity: The immune response is presumably triggered by an antigen (pathogen) derived from pathogen associated molecular pattern (PAMP) (pink circle) or from damage associated molecular pattern (DAMP) ((blue circle) which binds to a pattern recognition receptor (PRR) such as toll-like receptor (TLR, e.g., TLR2) or C-type lectin receptor (CLR), and induces signal transduction of MyD88 (Myeloid differentiation primary response 88) or TRIF (Toll/interleukin-1 receptor containing adapter-inducing interferon-β) for inflammatory responses, resulting in augmented production of IL-1, IL-6, TNFα, and so on. (**b**) Adaptive immunity: The adaptive response is mediated by antigen presentation to T cells through TCR (T cell receptor) and HLA (human leukocyte antigen) by which resting T cells (Tho) are amplified to proliferate and differentiate into T helper type 1 (Th1) cells, Th2 cells, Th17 cells and/or T regulatory (Treg) cells which provide cell immunity, antibody production (Abs), autoimmune reaction and/or immunoregulation, respectively. In a balanced adaptive immunity, the Th1 and Th2 cells will help clean and/or neutralize the antigen (pathogen), and the Treg cells or Abs that mediate FcRII (type II FcgR) inhibitory signal (ITIM, immunoreceptor tyrosine-based inhibitory motif) will inhibit the overt cell cytotoxicity or hypercytokinemia. (**c**) Autoimmunity: In case of imbalanced T cell response, the Th17 and Th1 mediators are augmented, and Treg and Th2 mediators are depressed, resulting in hypercytokinemia of IL-6, IL-17, IP-10, IL-23, and IFNγ, which mediate intractable fever and vasculitis. In certain conditions, for example, a Th17 mediator, such as IL-6, compromises NK cell cytotoxicity and promotes anti-apoptosis resulting in overloading of macrophage activation associated with phagocytosis of platelets or blood cells, called MAS (macrophage activation syndrome), and overproduction of nitric oxide for hypotension, called KDSS (Kawasaki disease shock syndrome), which are augmented by a Th1 mediator, such as IFNγ

internalized antigen by antigen presenting cells can be presented to T cells through recognition of TCR (T cell receptor) and HLA (human leukocyte antigen) by which resting T cells (Tho) are amplified to proliferate and differentiate into T helper type 1 (Th1) cells, Th2 cells, Th17 cells, and/or T regulatory (Treg) cells which provide an adaptive immunity associated with cell immunity, antibody production (Abs), autoimmune reaction, and/or immunoregulation, respectively. In a balanced adaptive immunity, the Th1 and Th2 cells will help clean and/or neutralize the antigen (pathogen) by cell immunity and/or antibody neutralization, and the Treg cells or the antibodies that mediate FcγRII (type II FcγR) inhibitory signal (ITIM, immunoreceptor tyrosine-based inhibitory motif) can inhibit the overt cell cytotoxicity or macrophage activation (Fig. 1b).

In case of imbalanced T cell response, the Th17 and Th1 mediators are augmented and Treg and Th2 mediators are depressed, resulting in autoimmunity associated with hypercytokinemia of IL-6, IL-17, IP-10, IL-23, and IFNγ, which mediate intractable fever and mid-sized vasculitis including coronary arterial lesion (CAL) [22, 23]. In certain conditions, for example, a Th17 mediator, such as IL-6, compromises NK cell cytotoxicity and promotes anti-apoptosis resulting in overloading of macrophage activation called macrophage activation syndrome (MAS), which is augmented by Th1 mediators, such as IFNγ and IP-10, resulting in hemophagocytosis of platelets or blood cells, associated with thrombocytopenia and hyperferritinemia [24]. In terms of KDSS, the hypotension may be derived from over induction of IFNγ, IL-10, and nitric oxide (NO) [25–27], which could be mediated through activation of STAT-1 and/or STAT3 (Fig. 1c).

The facts that early administration of IVIG within 4 days of the illness did not provide a better outcome [28], that early administration of corticosteroids alone exacerbated the outcomes of KD [29], and that late administration of corticosteroids in combination with IVIG significantly reduced the IVIG resistance and less progression of CAL [30] suggest a progressive immunopathogenesis of KD. It is, however, controversial that patients who were initially treated with IVIG only or IVIG and infliximab more often required an additional therapy for the IVIG resistance than those with IVIG and corticosteroids (21% vs 14% vs 0%, $P = 0.03$), but additional treatments for CAL more frequently occurred to patients initially received IVIG and corticosteroids than those received IVIG only or IVIG and infliximab (57% vs 21% vs 19%, $P = 0.001$) [31]. This suggests that anti-inflammatory therapies on different combinations comprising corticosteroids at right time and/or right dose may be needed for KD patients with variant immune aberrations. We have first demonstrated that the CD40L activation marker is highly expressed on T cells and platelets in children with KD [32], and overexpression of inducible nitric oxide synthase (iNOS) is associated with augmented nitric oxide (NO) production in KD patients before IVIG therapy [26]. The augmented immune reactions are reduced after IVIG therapy [26, 32]. In contrast, a T cell differentiation toward Th2 response is correlated to a better outcome of IVIG therapy since a higher eosinophil count associated with higher IL-5 level is a biomarker for success of IVIG treatment [33]; on the contrary, fewer eosinophil counts and lower IL-4 and IL-5 levels are associated with IVIG resistance [33, 34]. We also found that KD patients had a prominent Th17 expression but lower Treg FoxP3 expression before IVIG treatment [35]. This is related to altered Treg response on polymorphisms of TGFβ-signaling pathway genes such as TGFβ2 and SMAD3, which are associated with the susceptibility of KD [35], and related to depression of Treg immune responses [23]. Moreover, some of the KD patients associated with macrophage activation syndrome (MAS) presented with overproduction of IFN-gamma and its downstream mediators: IP-10 and TNFα [24]. These studies indicate that KD patients revealed a kinetic immune response showing early augmented innate immunity followed by late imbalance between Th17-Th1 and Th2-Treg responses, comparative to a kinetic immunopathology in a series of autopsy findings found in early necrotizing vasculitis with innate macrophage activation followed by a remodeling of coronary thrombosis with lymphocyte infiltration and aneurysm for-

mation [36, 37]. This also suggests that different immunotherapies may be required to modify the kinetic immunopathology according to disease stages variants of KD.

Immune Responses of Different KD Variants

Kawasaki disease can be categorized into different endotype and phenotypes in terms of age, gender, hemophagocytosis, hyperferritinemia, platelets, D-dimers, cytokines, IVIG resistance, and shock syndromes. Typical KD reveals a systemic vasculitis with fever more than 5 days, associated with at least 4 out of the 5 clinical features of KD described above. Patients with the typical KD criteria but fever fewer than 5 days can be diagnosed when coronary artery aneurysm (CAA) or lesion (CAL) is recognized. KD patients with prolong fever but fewer than four of the 5 characteristic KD symptoms are named atypical (incomplete) KD which usually occurs to patients with extreme ages, younger than 6 months of age or older than 5 years of age. Some other variants of KD present additional immune aberrations such as macrophage activation syndrome (MAS) or shock syndrome called KDSS are regarded as variants of KD [24, 27]. The variant of KD with MAS likely occurs to male with older age, atypical KD, intravenous immunoglobulin (IVIG) resistance, and persistent fever greater than 10 days with hemophagocytosis and thrombocytopenia. Another variant of KD presenting KDSS is frequently found in older age of female children with Hispanic origin [38–40].

As shown in Table 1, typical KD occurs to small children with age of 6 months to 5 years of age and a higher male to female ratio at 1.5. The KD patients complicated with MAS at 1–2% occur to a wider range of age distribution with a similar male to female ratio at 1.5. By contrast, the KD patients complicated with shock syndrome (KDSS) at 3–5% (1.4–7.0%) occur to older children with female predominance, particularly in Hispanics. A recent review reported that 14.8% KD patients developed KDSS [41], compared with those between 1.5 and 7% of KDSS reported in the literature [38–40]. Characteristically, KD patients complicated with MAS tend to have elevated IFNγ, splenomegaly, and thrombocytopenia associated with the highest levels of pro-BNP, ferritin, and triglycerides (Table 1). In contrast, patients with KDSS tend to have a shock syndrome with variable platelet counts due to thrombosis or coagulopathy, and significantly higher D-dimer (>1000–4000 ng/ml) levels and hypofibrinogenemia [25, 38–40].

Table 1 Immune responses in variant phenotypes of Kawasaki disease

Phenotypes	KD	MAS	KDSS
Occurrence	95%	1–2%	1.4–7.0%
Age	0.5 ~ 5.0 (2.0)	0.5 ~ 14 (>5.0)	2 ~ 12 (3.5)
Race	Asian	All races	Hispanic
Sex (male/female)	1.5	1.5	0.5
Cytokines	IL6, IL-10, IP-10	IL-6, INFγ, IL-18	IL-6, INFγ, IL-10
Pro-BNP (pg/ml)	>100	>1000	>1000
Ferritin (ng/ml)	100–200	>1000	>500
Splenomegaly	Rare	90–100%	Some
Platelets	>350,000/μl	Low	High or low
Coagulopathy	No	Some	Often
D-dimer (ng/ml)	<1000	<1000	>1000
Myocarditis	5%	46%	60%
IVIG resistant	15%	>50%	>50%
Mechanism	Th17 > Treg	Macrophage activation	Shock/coagulopathy
Fatality	0.1%	0–25%	0–6.8% (2%)

Abbreviations: *KD* Kawasaki disease, *MAS* macrophage activation syndrome, *KDSS* Kawasaki disease shock syndrome, *IVIG* intravenous immunoglobulin

Cytokine storm among KD without and with MAS or KDSS, showing augmented hypercytokinemia in IL-6, IL-10, IL-17, IP-10 (CXCL10), and MCP-1 (CCL2) are somehow different, especially higher IL-6, IL-18, and IFNγ levels in MAS, and higher IL-6, IL-10, and IFNγ levels in KDSS [25, 41]. The wide differences on sex ratio, race and age among KD with and MAS or KDSS suggest varied genetic background and environmental factors contributing to the susceptibility of different phenotypes. In KD with MAS, it is postulated that defects in the NK cell cytolytic function of KD patients result in an inability to lyse the infected macrophages, which causes a prolong macrophage activation and cytokine storm [42]. Heterozygous mutations in many genes such as PRF1, LYST, RAB27A, UNC13D, STXBP2, and/or STX11 have been found in 40% of patients with MAS, whose mutations could compromise cytolytic functions of NK cells and CD8 T cells [43]. Mice carrying heterozygous mutations in more than one of the genes involved in hemophagocytic lymphohistiocytosis (HLH) carry a significantly higher risk to develop MAS after viral infection [44]. Patients with systemic juvenile rheumatoid arthritis (JRA) tend to have a high rate of MAS, in which the combination of a genetic predisposition with underlying inflammatory state may contribute to the hyperinflammatory abnormalities seen in MAS [45, 46]. Patients with KDSS showed higher IVIG-resistant, higher neutrophil–lymphocyte ratio (NLR), and multisystemic presentations such as abdominal manifestations, hypoalbuminemia, and neurological manifestations in addition to presence of CAL [38–41]. Patients with KDSS are usually complicated with coagulopathy, embolism, and thrombosis, which may require certain antithrombotic and inotropic medications in addition to IVIG and/or corticosteroids. The cause of KDSS is unclear but may be related to genetic and milieu backgrounds which attribute to induction of hyperinflammation, nitric oxide production, and/or coagulopathy [26, 38–41], or an autoantibody-mediated thrombosis and thrombocytopenia, as seen in anti-PF4 autoimmune coagulopathy [47]. It is also not excluded that neutrophil activation and NET formation, which contributes to thrombosis as seen in heparin-induced thrombocytopenia [48], may be involved in the thrombosis found in KDSS. An important differential diagnosis of KDSS is toxic shock syndrome (TSS), which is caused by superantigen of enterotoxin derived from *Staphylococcus aureus* infections in skin or in women with tampon use [49]. The shock syndrome in KDSS is more frequently associated with pulmonary complications, acute kidney injury (AKI), pancreatitis, cholestasis, and neurological disorders [40]. The first line of treatment for KDSS includes IVIG and corticosteroids in pulses, and in severe cases refractory to the IVIG and corticosteroids, inotropic agents, anti-thrombotic agents, and anti-inflammatory treatments such as infliximab, anakinra, cyclosporin, or plasmapheresis may be needed as alternative treatment options. Typical KD usually has low mortality (<0.1%), but KD with KDSS or MAS tends to a higher mortality with a wide range between 0 and 25%, at average of 2% (Table 1).

Genetic and Epigenetic Immunoregulation of KD with and Without Complications

Kawasaki disease is prevalent in East Asia such as Japan, Korea, Mainland China, and Taiwan [2–4, 12, 50]. Several KD susceptibility genes (e.g., ITPKC, CASP3, CD40, and ORAI1) and human leukocyte antigens (HLAs) have been linked to KD [51]. In systemic JRA patients with MAS, over 40% of the patients had one or more heterozygous mutations of the PRF1, UNC13d, STX11, STXBP2, and RAB27a genes [52], suggesting a genetic background contributes to the complication of MAS. It is not clear whether this phenomenon also occurs to KD with MAS. Fourteen SNPs of 10 genes: PPIE, CD247, ACVR2B, FLT4, CUL1, IL2RA, MAP 2 K1, MAPK11, LBP, and CD24 are significantly associated with IVIG resistance of KD [53]. This study, however, demonstrates that a combination of 9 SNPs and 6 clinical features such as ESR, BNP, anemia, hypoalbuminemia, and so on predicts the IVIG resistance the best. This suggests a gene–environ-

ment interaction is involved in the susceptibility and complications of the KD variants.

We have therefore studied whether epigenetic regulation on CpG methylation of immune genes is associated with KD [54–57]. We have found that DNA hypomethylation on the promoter CpG islands of many immune activation genes was significantly higher DNA hypomethylation than hypermethylation in leukocytes before IVIG treatment [54–57]. We have found that the CpG methylation changes greater than 20% in acute stage of KD were prominently hypomethylated (97%) genes but only 3% hypermethylated genes [57]. The hypomethylated genes were correlated to enhanced gene (mRNA) expression, especially the toll-like receptors (TLRs). The TLR1, 2, 4, 5, 8, and 9 receptor genes were significantly hypomethylated and associated with augmented mRNA expression [55]. Other innate immunity genes such as FcgammaR2A, IL-10, and S100A8 were also significantly hypomethylated before IVIG treatment [55, 57]. The hypomethylated loci and augmented mRNA expression reciprocally reversed. In addition to DNA methylation changes, miRNA expression is also a good biomarker for KD, which differentiated KD from other febrile diseases by a set of 4 miRNA expression at C_T(miR-1246)-C_T (miR-4436b-5p) and C_T (miR-197-3p)-C_T (miR-671-5p) [58]. Moreover, the miRNA regulation of Treg expression has been characterized in KD patients [59]. The epigenetic control of Treg has been demonstrated mainly via FoxP3 expression [60, 61]. These epigenetic profiles and functional markers of various Treg populations (tTreg, iTreg and pTreg) can be regulated by inherited variants of T cell receptors and environmental factors making monitor of specific Treg populations suitable for prediction and prevention of Th17-mediated autoimmunity [61, 62]. Based on the immunopathogenesis of KD involved in an augmentation of Th17 response together with depressed T regulatory response which is regulated by epigenetic and genetic modifications s [23, 61–63], the development and differentiation of Treg populations regulated by genetic and epigenetic changes can be recognized as biomarkers and potentially therapeutic targets of KD with IVIG resistance.

Immunotherapies Based on Immune Response of KD

Before institution of IVIG for the treatment of KD, aspirin was considered a medication better than antibiotics or corticosteroids in 1970s [1, 29]. After institution of IVIG treatment in 1980s, the standard treatment has been evolved to a combined therapy of aspirin and IVIG since 1990s [64, 65]. The aspirin therapy, with high (80–100 mg/kg) or low (30–60 mg/kg) dose, does not appear to lower the rate of CAL [65, 66]. Different dosing of IVIG for KD has been clarified the best at single high dose 2 g/kg, which is better than 1 g/kg/day for 2 days, or 400 mg/kg/day for 5 days [65, 67]. However, 15% of KD patients are refractory to initial IVIG therapy and require additional doses of IVIG therapy or other anti-inflammatory therapies including pulse corticosteroids, anti-TNFα, anti-IL-1, and cyclosporin A. Some complications of KD such as shock syndrome (KDSS), macrophage activation syndrome (MAS) or coronary artery aneurysm (CAA) are frequently associated with IVIG resistance, suggesting different immune phenotypes may have fundamental immunopathogenesis but different genetic and epigenetic backgrounds which mediate variant phenotypes. Several scoring systems had been used to predict an intensified therapy needed [68–71]. A scoring system for predicting IVIG resistance (Kobayashi Score), which was useful for prediction and prevention of CAL after the combined IVIG and corticosteroids treatment in Japan [68, 69], but poor sensitivity and specificity was found in Western countries [70]. Intensification of the combination therapy for KD patients predicted to develop CAA based on observations of Z scores $\geq$2.5 for the CAL on the first echocardiogram is suggested as a universal indicator [71]. Taken together, KD patients in different countries or ethnicities may require varied criteria to predict complications and/or IVIG resistance and guide to an early intensified treatment. A new scoring system should include clinical symptoms/signs, immune parameters, genetic and epigenetic biomarkers to predict IVIG resistance and to prevent complications by a combined anti-inflammatory therapy.

Based on the immunopathogenesis of KD w/wo IVIG resistance described above, we suggest a stepwise guide in Fig. 2 to prevent or rescue IVIG-resistance and complications below:

1. *Identification of autoimmune antigens, PAMP and/or DAMP*. The pathogenesis of KD is likely derived from a postinfectious autoimmunity. Although the trigger factor for KD is not known, it is postulated that exogenous antigen (PAMP) or endogenous damaged substance (DAMP) may be involved. To avoid exposure of trigger factors (antigens) may prevent KD with complications. For instance, children with Covid-19 are usually mild or subclinical but some are susceptible to the occurrence of MIS-C 3 to 6 weeks after exposure to Covid-19 [4]. Children with MIS-C may be undetectable for viral RNA of Covid-19 but 80–100% detectable antibodies against spike protein [15–17]. This indicates that searching autoantibodies directed against exogenous or endogenous antigens may be needed in order to avoid autoimmune trig-

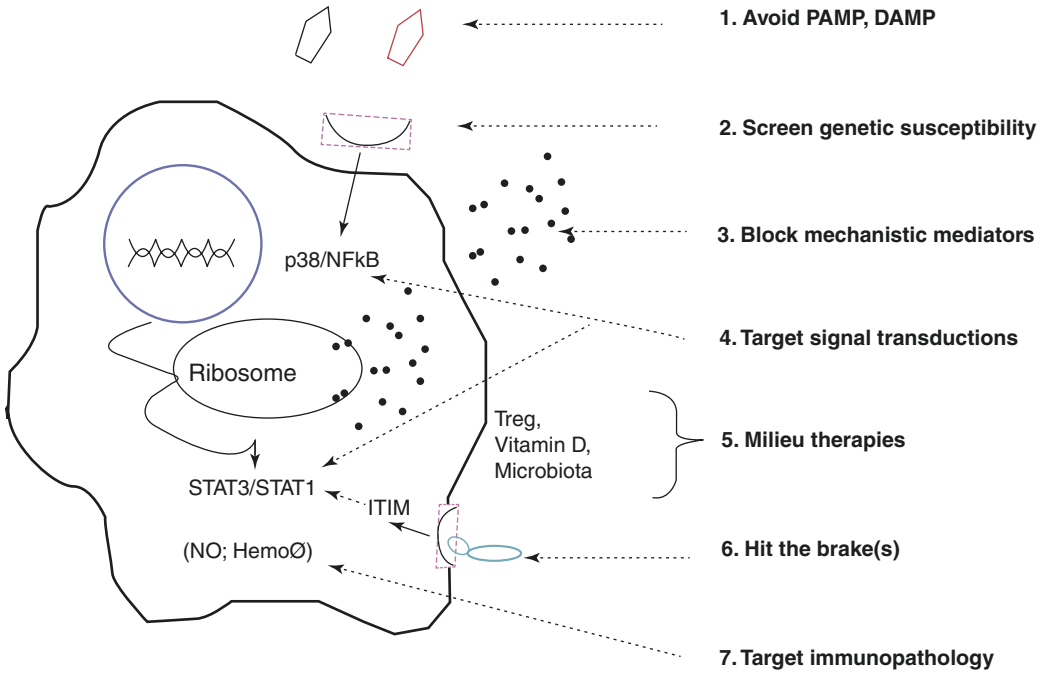

Fig. 2 Immunotherapies for KD refractory to conventional treatment. (1) Avoidance of autoimmune trigger factor: Although the trigger factor for KD is not known, it is postulated that exogenous antigen (PAMP) or endogenous damaged substance (DAMP) may be involved. To avoid exposure of trigger factors (antigens) may prevent KD with complications. (2) Screening of genetic susceptibility: To screen specific gene polymorphisms susceptible to IVIG resistance, CAA, MAS, and/or KDSS can guide an early prevention and precision treatment of life-threatening complications. (3) Blockade of mechanistic biomarkers: Anti-TNFα and anti-IL-1 have been used to rescue IVIG resistance. In addition, other Th17 and Th1 cytokines are also candidates for the target therapies. (4) Targeting of signal transductions: Overactivation of mitogen-activated protein kinases (MAPK) including p38 phosphorylation has been described in KD, and strategies to target the MAPK pathway for the treatment of cytokine storm has been postulated. (5) Milieu manipulations of immunoregulation: Certain internal and exogenous milieu that could provide a better homeostasis of Treg enhancement with polarizing FoxP3 expression may benefit KD patients with hyperinflammatory responses. (6) Hit the brakes on the immunoregulation by immunoreceptor tyrosine-based inhibitory motif (ITIM) for inhibiting cytokine production. A ligation of immunosuppressing receptors has been shown to shut down hyperinflammatory responses of leukocytes, which may be useful for KD patients refractory to IVIG therapy. (7) Anti-hemophagocytosis can be made by targeting nitric oxide (NO) production or hemophagocytosis mediate by IFNγ and TNFα inhibition or downexpression of their downstream STAT-1 (Signal transducer and activator of transcription 1) activation

ger factors for KD although high-throughput sequencing of viral genomes in blood from KD patients has not been done.

2. *Screening of genetic variants.* KD has been associated with certain polymorphisms of immune genes and HLA variants in regard to disease susceptibility and severity [51, 72–75]. We have also found that DNA polymorphisms of Treg pathway genes such as TGFβ2 and SMAD3 are associated with the KD susceptibility [35], and the gene expression of TLR1, 2, 4, 5, 8, and 9 receptors is involved in the immunopathogenesis of KD with and without complications [55]. These results suggest that identifying the risk genetic variants for severity and/or autoimmunity of KD could help develop genetic screening tests for predicting and preventing KD with and without complications. To screen specific gene polymorphisms susceptible to IVIG resistance, CAA, MAS and/or KDSS may guide an early precision treatment to prevent life-threatening complications.
3. *Blockade of mechanistic biomarkers*: Hypercytokinemia, such as augmented TNF-alpha and IL-6 expression, has been found in KD patients with IVIG resistance [76, 77]. Therefore, some studies have shown that anti-TNF-alpha (infliximab) or anti-IL-1 (anakinra) could rescue the resistance of IVIG treatment for KD [77–79]. However, another study showed that two of the four KD patients with IVIG resistance who were responsive to anti-IL-6 treatment developed CAA [80]. These studies suggest that a single target directed against one cytokine action may be ineffective, and a combined strategy or a sequential targeting could be required for eliminating the cytokine storm mediated by a couple of hyper-inflammatory cytokinemia found in IVIG resistance, MAS or KDSS. Given the fact that Th17 and Th1 mediators: Il-6, IL-17A, TNF-alpha, and IP-10 are more prominently increased in KD [65, 76, 80, 81], targeting IL-17A and anti-TNF-alpha might be considered in KD patients with IVIG resistance. Some patients with KD could have acute kidney injury, particularly those with KDSS associated with hypercytokinemia may require continuous renal replacement therapy and/or plasma exchange [49]. Occasionally, extracorporeal membrane oxygenation (ECMO) is required for KD patients with life-threatening cardiac dysfunction or KDSS who are refractory to the treatment of IVIG and pulsed corticosteroids [82, 83].
4. *Targeting signal transduction*. Employing phosphorylated proteomic analyses have recently demonstrated that activation of mitogen-activated kinase proteins (MAPK) signal transduction is involved in the pathogenesis of KD [84, 85]. A synthetic lipid-modified sialoglycopeptide which could insert into cell membranes and mediate a cis-binding to Siglec-9 has been shown to inhibit the MAPK activation for therapeutic effects on experimental autoimmune inflammation [86]. As a result, a specific inhibition of MAPK by an antibody or a modified sialoglycan to ligate Siglec-9 may provide anti-inflammatory response for the treatment of KD refractory to IVIG treatment.
5. *Milieu regulation of Treg immunity.* Epigenetic changes in DNA methylation and/or miRNA expressing profiles in the Treg pathways have been found in KD patients [33–35, 55]. It is known that Treg cell development and induction are significantly affected by endogenous milieu such as vitamins and metabolites from microbiota [87–91]. Vitamin D deficiency has been correlated to KD with IVIG resistance [90, 92]. In addition to vitamin D, microbiota in coordination with mesenchymal stem cells has recently been shown to combat experimental autoimmune diseases [93]. Moreover, MSCs or the exosomes derived from MSCs, which are useful in treating inflammatory diseases [94–96] may be also useful for immunoregulation of cytokine storm in KD with IVIG resistance. Since T cell regulatory functions can be influenced by epigenetic modulations of FoxP3 [59–63], and MSC or their exosomes could provide homeostasis of Treg immune responses [94–97], MSCs or their exosomes may be used to modulate the Th17/Treg imbalance in patients with hyperinflam-

matory response in KD patients with IVIG resistance or complications.

6. *Hit the brakes on enhancement of immunoinhibitory receptors*: Inhibition of hyperinflammation is known to mediate via immunoreceptor tyrosine-based inhibition motif (ITIM) through its cytoplasmic tail. The ITIM-containing receptors belong to the immunoglobulin receptor superfamily possessing a consensus sequence of I/V/LxYxxL/V (where x represents any amino acid) for docking SH2 domain, containing protein-tyrosine phosphatases including SHIP-1, Shp1, and Shp2 [98]. The inhibitory FcgR2B of IgG has been shown to mediate immunomodulation through inhibitory ITIM [98, 99]. In KD patients, polymorphisms of FcgR2B have been implicated in the IVIG resistance in Caucasians [100]. Besides, certain studies have shown that the Fc fragments of IgG play a pivotal role on immunosuppression of autoimmune disorders [98, 100–102]. The Fc portions of all IgG isotypes are glycosylated with an N-glycan at asparagine-297 residue in which 30 N-glycans have been identified and implicated in varied effector functions [103–105]. The N-glycans of Fc domain with a galactosylated glycans are associated with pro-inflammatory diseases, and higher levels of sialogalactosylation on the N-glycans of Fc domains are associated with higher anti-inflammatory activity in different Fc antibody preparations [104]. An Fc domain fusion to a sialoglycoprotein, CD24, called CD24Fc protects virus-mediated respiratory inflammation in an animal study [106], and has been used in a phase 3 clinical trial for nonantiviral immunomodulation in Covid-19 treatment [107]. The highly sialylated CD24 could induce immunosuppression by ligation of sialoglycan to sialic acid immunoglobulin-like lectin-10 (Siglec 10) [108–110], mediate a driving force to cancer [108], damp tissue damage induced inflammation [109], and induce immune tolerance of pregnancy [110]. A synthetic membrane insertable lipid-modified sialoglycan has been shown to induce cis-binding to Siglec-9 for immunomodulation and inhibit in vitro neutrophil overactivation of neutrophil extracellular traps (NETosis), associated with Covid-19 infection, mediated by ITIM-associated SHP-1 [111]. These glycan immunomodulators may be replicated to treat KD patients with IVIG resistance.
7. *Anti-hemophagocytosis.* KD patients with MAS [24, 25, 27] or KDSS [11, 112] may have IVIG resistance associated with prolong fever, anemia, hyperferritinemia, and hypertriglyceridemia, compatible with secondary hemophagocytic lymphohistiocytosis (sHLH) [113]. Macrophage activation is usually associated with elevated circulating sCD163 and Th1 mediators, such as IL-18, IFN-gamma, and TNF-alpha, which induce Stat-1 and NFkB activation resulting in coagulopathy, hemophagocytosis, and induction of nitric oxide (NO) for vascular insults [112–114]. The autoimmune-induced MAS can be found in patients with rheumatic diseases including JRA, systemic lupus erythematosus, and KD [24, 112, 115, 116]. In this situation, a combination of IVIG with pulse corticosteroids, cyclosporin-A, anti-IL-1, and/or anti-TNFα administration may be required [24, 78, 116, 117].

In summary, the autoimmune vasculitis of KD with and without complications is mediated by an altered hyperinflammation toward augmented Th17/Th1 mediators: IL-6, IL-10, IP-10, IFN-gamma, and IL17A, and downexpression of Treg-signal transduction of FoxP3 and TGF-β, presumably through genetic variants of HLA, FcgR2A and/or epigenetic dysregulation for vasculitis. To clarify the immunopathogenesis among KD w/wo IVIG resistance, CAA, MAS, and/or KDSS can make early prediction, protection, prevention and precision treatment of the KD with life-threatening complications possible. Standard immunotherapies for KD have evolved to a combination of IVIG and aspirin therapy with and without additional pulse therapy of corticosteroids. While KD patients are resistant to these therapies, additional anti-inflammatory therapies based on the immunopathogenesis

described above might be provided to reverse the hyperinflammation of KD with IVIG resistance, CAA, MAS, or/and KDSS.

References

1. Kawasaki T, Kosaki F, Okawa S, Shigematsu I, Yanagawa H. A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. Pediatrics. 1974;54:271–6.
2. Wang CL, Wu YT, Liu CA, Kuo HC, Yang KD. Kawasaki disease: infection, immunity and genetics. Pediatr Infect Dis J. 2005;24:998–1004.
3. Chang L, Yang HW, Lin TY, Yang KD. Perspective of immunopathogenesis and immunotherapies for Kawasaki disease. Front Pediatr. 2021;9:697632. https://doi.org/10.3389/fped.2021.697632.
4. Chen MR, Kuo HC, Lee YJ, Chi H, Li SC, Lee HC, Yang KD. Phenotype, susceptibility, autoimmunity, and immunotherapy between Kawasaki disease and coronavirus disease-19 associated multisystem inflammatory syndrome in children. Front Immunol. 2021;12:632890. https://doi.org/10.3389/fimmu.2021.632890.
5. Esper F, Shapiro ED, Weibel C, Ferguson D, Landry ML, Kahn JS. Association between a novel human coronavirus and Kawasaki disease. J Infect Dis. 2005;191(4):499–502.
6. Burns JC, Newburger JW. Genetics insights into the pathogenesis of Kawasaki disease. Circ Cardiovasc Genet. 2012;5(3):277–8.
7. Dajani AS, Taubert KA, Gerber MA, Shulman ST, Ferrieri P, Freed M, et al. Diagnosis and therapy of Kawasaki disease in children. Circulation. 1993;87:1776–80.
8. Torii Y, Horiba K, Hayano S, Kato T, Suzuki T, Kawada JI, et al. Comprehensive pathogen detection in sera of Kawasaki disease patients by high-throughput sequencing: a retrospective exploratory study. BMC Pediatr. 2020;20(1):482.
9. Rhim JW, Kang HM, Han JW, Lee KY. A presumed etiology of Kawasaki disease based on epidemiological comparison with infectious or immune-mediated diseases. Front Pediatr. 2019;7:202.
10. Marrani E, Burns JC, Cimaz R. How should we classify Kawasaki disease? Front Immunol. 2018;9:2974.
11. Sakurai Y. Autoimmune aspects of Kawasaki disease. J Investig Allergol Clin Immunol. 2019;29(4):251–61.
12. Lee KY. Pneumonia, acute respiratory distress syndrome, and early immune-modulator therapy. Int J Mol Sci. 2017;18(2):388.
13. Chang LY, Lu CY, Shao PL, Lee PI, Lin MT, Fan TY, et al. Viral infections associated with Kawasaki disease. J Formos Med Assoc. 2014;113(3):148–54.
14. Levin M. Childhood multisystem inflammatory syndrome - a new challenge in the pandemic. N Engl J Med. 2020;383:393–5.
15. Riphagen S, Gomez X, Gonzales-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during Covid-19 pandemic. Lancet. 2020;395(10237):1607–8.
16. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet. 2020;395(10239):1771–8.
17. Cheung EW, Zachariah P, Gorelik M, Boneparth A, Kernie SG, Orange JS, et al. Multisystem inflammatory syndrome related to Covid-19 in previously healthy children and adolescents in New York City. JAMA. 2020;8:e2010374.
18. Pouletty M, Borocco C, Ouldali N, Caseris M, Basmaci R, Lachaume N, et al. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-Covid-19): a multicentre cohort. Ann Rheum Dis. 2020;79(8):999–1006.
19. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med. 2020;383(4):334–46.
20. Lin IC, Kuo HC, Lin YJ, Wang FS, Wang L, Huang SC, Chien SJ, Huang CF, Wang CL, Yu HR, Chen RF, Yang KD. Augmented TLR2 expression on monocytes in both human Kawasaki disease and a mouse model of coronary arteritis. PLoS One. 2012;7(6):e38635.
21. Cho HJ, Bak SY, Kim SY, Yoo R, Baek HS, Yang S, et al. High neutrophil: lymphocyte ratio is associated with refractory Kawasaki disease. Pediatr Int. 2017;59(6):669–74.
22. Jia S, Li C, Wang G, Yang J, Zu Y. The T helper type 17/regulatory T cell imbalance in patients with acute Kawasaki disease. Clin Exp Immunol. 2010;162(1):131–7.
23. Guo MM, Tseng WN, Ko CH, Pan HM, Hsieh KS, Kuo HC. Th17- and Treg-related cytokine and mRNA expression are associated with acute and resolving Kawasaki disease. Allergy. 2015;70(3):310–8.
24. Jinkawa A, Shimizu M, Nishida K, Kaneko S, Usami M, Sakumura N, et al. Cytokine profile of macrophage activation syndrome associated with Kawasaki disease. Cytokine. 2019;119:52–6.
25. Li Y, Zheng Q, Zou L, Wu J, Guo L, Teng L, et al. Kawasaki disease shock syndrome: clinical characteristics and possible use of IL-6, IL-10 and IFN-γ as biomarkers for early recognition. Pediatr Rheumatol Online J. 2019;17:1.
26. 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(4):560–5.
27. Lin Y, Shi L, Deng Y-j, Liu Y, Zhang H-w. Kawasaki disease shock syndrome complicated with macrophage activation syndrome in a 5-month old boy: a case report. Medicine (Baltimore). 2019;98(4):e14203.

28. Downie ML, Manlhiot C, Collins TH, Chahal N, Yeung RSM, McCrindle BW. Factors associated with development of coronary artery aneurysms after Kawasaki disease are similar for those treated promptly and those with delayed or no treatment. Int J Cardiol. 2017;236:157–61.
29. Kato H, Koike S, Yokoyama T. Kawasaki disease: effect of treatment on coronary artery involvement. Pediatrics. 1979;63(2):175–9.
30. Chen S, Dong Y, Yin Y, Krucoff MW. Intravenous immunoglobulin plus corticosteroid to prevent coronary artery abnormalities in Kawasaki disease: a meta-analysis. Heart. 2013;99:76–82.
31. Dionne A, Burns JC, Dahdah N, Tremoulet AH, Gauvreau K, de Ferranti SD, Baker AL, Son MB, Gould P, Fournier A, Newburger JW, Friedman KG. Treatment intensification in patients with Kawasaki disease and coronary aneurysm at diagnosis. Pediatrics. 2019;143(6):e20183341.
32. Wang CL, Wu YT, Liu CA, Lin MW, Lee CJ, Huang LT, et al. Expression of CD40 ligand on CD4+ T-cells and platelets correlated to the coronary artery lesion and disease progress in Kawasaki disease. Pediatrics. 2003;111(2):E140–7.
33. Kuo HC, Yang KD, Liang CD, Bong CN, Yu HR, Wang L, et al. The relationship of eosinophilia to intravenous immunoglobulin treatment failure in Kawasaki disease. Pediatr Allergy Immunol. 2007;18(4):354–9.
34. Kuo HC, Wang CL, Liang CD, Yu HR, Huang CF, Wang L, et al. Association of lower eosinophil-related T helper 2 (Th2) cytokines with coronary artery lesions in Kawasaki disease. Pediatr Allergy Immunol. 2009;20(3):266–72.
35. Kuo HC, Onouchi Y, Hsu YW, Chen WC, Huang JD, Huang YH, et al. Polymorphisms of transforming growth factor-β signaling pathway and Kawasaki disease in the Taiwanese population. J Hum Genet. 2011;56(12):840–5.
36. Takahashi K, Oharaseki T, Naoe S, Wakayama M, Yokouchi Y. Neutrophilic involvement in the damage to coronary arteries in acute stage of Kawasaki disease. Pediatr Int. 2005;47(3):305–10.
37. Kobayashi M, Matsumoto Y, Ohya M, Harada K, Kanno H. Histologic and immunohistochemical evaluation of infiltrating inflammatory cells in Kawasaki disease arteritis lesions. Appl Immunohistochem Mol Morphol. 2020;29(1):62–7.
38. Kanegaye JT, Wilder MS, Molkara D, Frazer JR, Pancheri J, Tremoulet AH, et al. Recognition of a Kawasaki disease shock syndrome. Pediatrics. 2009;123(5):e783–9.
39. Gamez-Gonzalez LB, Moribe-Quintero I, Cisneros-Castolo M, Varela-Ortiz J, Muñoz-Ramírez M, Garrido-García M, et al. Kawasaki disease shock syndrome: unique and severe subtype of Kawasaki disease. Pediatr Int. 2018;60:781–90.
40. Watanabe T. Clinical features of acute kidney injury in patients with Kawasaki disease. World J Clin Pediatr. 2018;7(3):83–8.
41. Quick RD, Sehgal I, Feldman A, Murphey D, Fernandez M, Hauger SB. Kawasaki disease shock syndrome: identifying risks. Open Forum Infect Dis. 2019;6(Supplement_2):S557.
42. Latino GA, Manlhiot C, Yeung RS, Chahal N, McCrindle BW. Macrophage activation syndrome in the acute phase of Kawasaki disease. J Pediatr Hematol Oncol. 2010;32(7):527–31.
43. Zhang M, Behrens EM, Atkinson TP, Shakoory B, Grom AA, Cron RQ. Genetic defects in cytolysis in macrophage activation syndrome. Curr Rheumatol Rep. 2014;16:439.
44. Sepulveda FE, Garrigue A, Maschalidi S, Garfa-Traore M, Ménasché G, Fischer A, de Saint BG. Polygenic mutations in the cytotoxicity pathway increase susceptibility to develop HLH immunopathology in mice. Blood. 2016;127(17):2113–21.
45. Strippoli R, Caiello I, De Benedetti F. Reaching the threshold: a multilayer pathogenesis of macrophage activation syndrome. J Rheumatol. 2013;40:761.
46. Han SB, Lee SY. Macrophage activation syndrome in children with Kawasaki disease: diagnostic and therapeutic approaches. World J Pediatr. 2020;16(6):566–74.
47. Nguyen T, Medvedev N, Delcea M, Greinacher A. Anti-platelet factor 4/polyanion antibodies mediate a new mechanism of autoimmunity. Nat Commun. 2017;8:14945.
48. Gollomp K, Kim M, Johnston I, Hayes V, Welsh J, Arepally GM, et al. Neutrophil accumulation and NET release contribute to thrombosis in HIT. JCI Insight. 2018;3(18):e99445.
49. Gottlieb M, Long B, Koyfman A. The evaluation and management of toxic shock syndrome in the emergency department: a review of the literature. J Emerg Med. 2018;54(6):807–14.
50. Holman RC, Christensen KY, Belay ED, Steiner CA, Effler PV, Miyamura J, et al. Racial/ethnic differences in the incidence of Kawasaki syndrome among children in Hawaii. Hawaii Med J. 2010;69(8):194–7.
51. Onouchi Y. The genetics of Kawasaki disease. Int J Rheum Dis. 2018;21(1):26–30.
52. Vastert SJ, van Wijk R, D'Urbano LE, de Vooght KM, de Jager W, Ravelli A, Magni-Manzoni S, Insalaco A, Cortis E, van Solinge WW, Prakken BJ, Wulffraat NM, de Benedetti F, Kuis W. Mutations in the perforin gene can be linked to macrophage activation syndrome in patients with systemic onset juvenile idiopathic arthritis. Rheumatology (Oxford). 2010;49(3):441–9.
53. Chen L, Song S, Ning Q, Zhu D, Jia J, Zhang H, Zhao J, Hao S, Liu F, Chu C, Huang M, Chen S, Xie L, Xiao T, Huang M. Prediction for intravenous immunoglobulin resistance combining genetic risk loci identified from next generation sequencing and laboratory data in Kawasaki disease. Front Pediatr. 2020;8:462367.
54. Kuo HC, Chang JC, Kuo HC, Yu HR, Wang CL, Lee CP, et al. Identification of an association between

genomic hypomethylation of FCGR2A and susceptibility to Kawasaki disease and intravenous immunoglobulin resistance by DNA methylation array. Arthritis Rheumatol. 2015;67(3):828–36.
55. Huang YH, Li SC, Huang LH, Chen PC, Lin YY, Lin CC, et al. Identifying genetic hypomethylation and upregulation of toll-like receptors in Kawasaki disease. Oncotarget. 2017;8(7):11249–58.
56. Chen KD, Huang YH, Guo M, Lin TY, Weng WT, Yang HJ, et al. The human blood DNA methylome identifies crucial role of beta-catenin in the pathogenesis of Kawasaki disease. Oncotarget. 2018;9(47):28337–50.
57. Huang LH, Kuo HC, Pan CT, Lin YS, Huang YH, Li SC. Multiomics analyses identified epigenetic modulation of the S100A gene family in Kawasaki disease and their significant involvement in neutrophil transendothelial migration. Clin Epigenetics. 2018;10(1):135.
58. Kuo HC, Hsieh KS, Ming-Huey Guo M, Weng KP, Ger LP, Chan WC, Li SC. Next-generation sequencing identifies micro-RNA-based biomarker panel for Kawasaki disease. J Allergy Clin Immunol. 2016;138(4):1227–30.
59. Ni FF, Li CR, Li Q, Xia Y, Wang GB, Yang J. Regulatory T cell microRNA expression changes in children with acute Kawasaki disease. Clin Exp Immunol. 2014;178(2):384–93.
60. Freudenberg K, Lindner N, Dohnke S, Garbe AI, Schallenberg S, Kretschmer K. Critical role of TGF-β and IL-2 receptor signaling in Foxp3 induction by an inhibitor of DNA methylation. Front Immunol. 2018;9:125.
61. Shevach EM, Thornton AM. tTregs, pTregs, and iTregs: similarities and differences. Immunol Rev. 2014;259(1):88–102.
62. Zhao C, Li X, Yang Y, Li Z, Li M, Tan Q, Liang W, Liu Z. An analysis of Treg/Th17 cells imbalance associated microRNA networks regulated by moxibustion therapy on Zusanli (ST36) and Shenshu (BL23) in mice with collagen induced arthritis. Am J Transl Res. 2019;11(7):4029–45.
63. Bettelli E, Carrier Y, Gao W, Korn T, Strom TB, Oukka M, Weiner HL, Kuchroo VK. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature. 2006;441(7090):235–8.
64. Berkman SA, Lee ML, Gale RP. Clinical uses of intravenous immunoglobulins. Ann Intern Med. 1990;112(4):278–92.
65. 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(17):e927–99.
66. Kuo HC, Yang KD, Chang WC, Ger LP, Hsieh KH. Kawasaki disease: an update on diagnosis and treatment. Pediatr Neonatol. 2012;53:4–11.
67. Terai M, Shulman ST. Prevalence of coronary artery abnormalities in Kawasaki disease is highly dependent on gamma globulin dose but independent of salicylate dose. J Pediatr. 1997;131(6):888–93.
68. Kobayashi T, Saji T, Otani T, Takeuchi K, Nakamura T, Arakawa H, et al. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial. Lancet. 2012;379(9826):1613–20.
69. Miyata K, Kaneko T, Morikawa Y, Sakakibara H, Matsushima T, Misawa M, Takahashi T, Nakazawa M, Tamame T, Tsuchihashi T, Yamashita Y, Obonai T, Chiga M, Hori N, Komiyama O, Yamagishi H, Miura M, Post RAISE Group. Efficacy and safety of intravenous immunoglobulin plus prednisolone therapy in patients with Kawasaki disease (Post RAISE): a multicentre, prospective cohort study. Lancet Child Adolesc Health. 2018;2(12):855–62.
70. Arane K, Mendelsohn K, Mimouni M, Mimouni F, Koren Y, Brik Simon D, et al. Japanese scoring systems to predict resistance to intravenous immunoglobulin in Kawasaki disease were unreliable for Caucasian Israeli children. Acta Paediatr. 2018;107(12):2179–84.
71. Burns JC. Revisiting once again steroids for the treatment of acute Kawasaki disease. J Am Heart Assoc. 2020;9:e018300.
72. Kato S, Kimura M, Tsuji K, Kusakawa S, Asai T, Juji T, et al. HLA antigens in Kawasaki disease. Pediatrics. 1978;61(2):252–5.
73. Oh J, Han JW, Lee SJ, Lee KY, Suh BK, Koh DK, et al. Polymorphisms of HLA genes in Korean children with Kawasaki disease. Pediatr Cardiol. 2008;29(2):402–8.
74. Huang FY, Chang TY, Chen MR, Hsu CH, Lee HC, Lin SP, et al. Genetic variations of HLA-DRB1 and susceptibility to Kawasaki disease in Taiwanese children. Hum Immunol. 2007;68(1):69–74.
75. Chen MR, Chang ZY, Chiu NC, Chi H, Yang KD, Chang L, et al. Validation of genome-wide associated variants for Kawasaki disease in a Taiwanese case-control sample. Sci Rep. 2020;10(1):11756.
76. Wang Y, Qian SY, Yuan Y, Wang Q, Gao L, Chen X, et al. Do cytokines correlate with refractory Kawasaki disease in children? Clin Chim Acta. 2020;506:222–7.
77. Hu P, Jiang GM, Wu Y, Huang BY, Liu SY, Zhang DD, et al. TNF-alpha is superior to conventional inflammatory mediators in forecasting IVIG nonresponse and coronary arteritis in Chinese children with Kawasaki disease. Clin Chim Acta. 2017;471:76–80.
78. Tremoulet AH. Adjunctive therapies in Kawasaki disease. Int J Rheum Dis. 2018;21(1):76–9.
79. Cohen S, Tacke CE, Straver B, Meijer N, Kuipers IM, Kuijpers TW. A child with severe relapsing Kawasaki disease rescued by IL-1 receptor blockade and extracorporeal membrane oxygenation. Ann Rheum Dis. 2012;71(12):2059–61.

80. Nozawa T, Imagawa T, Ito S. Coronary-artery aneurysm in tocilizumab-treated children with Kawasaki's disease. N Engl J Med. 2017;377(19):1894–6.
81. Hamada H, Suzuki H, Abe J, et al. Inflammatory cytokine profiles during Cyclosporin treatment for immunoglobulin-resistant Kawasaki disease. Cytokine. 2012;60(3):681–5.
82. Best D, Millar J, Kornilov I, Sinelnikov Y, Chiletti R, Rycus P, et al. Extracorporeal membrane oxygenation for Kawasaki disease: two case reports and the extracorporeal life support organization experience 1999-2015. Perfusion. 2017;32(7):609–12.
83. Zhang H, Xie L, Xiao T. Extracorporeal membrane oxygenation support for cardiac dysfunction due to Kawasaki disease shock syndrome. Front Pediatr. 2019;7:221.
84. Consiglio CR, Cotugno N, Sardh F, Pou C, Amodio D, Rodriguez L, et al. The immunology of multisystem inflammatory syndrome in children with COVID-19. Cell. 2020;183(4):968–981.e7.
85. Li SM, Liu WT, Yang F, Yi QJ, Zhang S, Jia HL. Phosphorylated proteomics analysis of human coronary artery endothelial cells stimulated by Kawasaki disease patients serum. BMC Cardiovasc Disord. 2019;19(1):21.
86. Delaveris CS, Chiu SH, Riley NM, Bertozzi CR. Modulation of immune cell reactivity with cis-binding Siglec agonists. Proc Natl Acad Sci U S A. 2021;118(3):e2012408118.
87. Arpaia N, Campbell C, Fan X, Dikiy S, van der Veeken J, deRoos P, et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. Nature. 2013;504(7480):451–5.
88. Castellani ML, Shaik-Dasthagirisaheb YB, Tripodi D, Anogeianaki A, Felaco P, Toniato E, et al. Interrelationship between vitamins and cytokines in immunity. J Biol Regul Homeost Agents. 2010;24(4):385–90.
89. Mucida D, Park Y, Kim G, Turovskaya O, Scott I, Kronenberg M, et al. Reciprocal TH17 and regulatory T cell differentiation mediated by retinoic acid. Science. 2007;317(5835):256–60.
90. Jun JS, Jung YK, Lee DW. Relationship between vitamin D levels and intravenous immunoglobulin resistance in Kawasaki disease. Korean J Pediatr. 2017;60(7):216–20.
91. Rhodes JM, Subramanian S, Laird E, Griffin G, Kenny RA. Perspective: vitamin D deficiency and Covid-19 severity - plausibly linked by latitude, ethnicity, impacts on cytokines, ACE2, and thrombosis. J Intern Med. 2020;289(1):97–115.
92. Stagi S, Rigante D, Lepri G, Matucci Cerinic M, Falcini F. Severe vitamin D deficiency in patients with Kawasaki disease: a potential role in the risk to develop heart vascular abnormalities? Clin Rheumatol. 2016;35(7):1865–72.
93. Li X, Lu C, Fan D, Lu X, Xia Y, Zhao H, et al. Human umbilical mesenchymal stem cells display therapeutic potential in rheumatoid arthritis by regulating interactions between immunity and gut microbiota via the aryl hydrocarbon receptor. Front Cell Dev Biol. 2020;8:131.
94. Bassi ÊJ, Moraes-Vieira PM, Moreira-Sá CS, Almeida DC, Vieira LM, Cunha CS, et al. Immune regulatory properties of allogeneic adipose-derived mesenchymal stem cells in the treatment of experimental autoimmune diabetes. Diabetes. 2012;61(10):2534–45.
95. Li Y, Li H, Cao Y, Wu F, Ma W, Wang Y, et al. Placenta-derived mesenchymal stem cells improve airway hyperresponsiveness and inflammation in asthmatic rats by modulating the Th17/Treg balance. Mol Med Rep. 2017;16(6):8137–45.
96. Hough KP, Chanda D, Duncan SR, Thannickal VJ, Deshane JS. Exosomes in immunoregulation of chronic lung diseases. Allergy. 2017;72(4):534–44.
97. Shiue SJ, Rau RH, Shiue HS, Hung YW, Li ZX, Yang KD, Cheng JK. Mesenchymal stem cell exosomes as a cell-free therapy for nerve injury-induced pain in rats. Pain. 2019 Jan;160(1):210–23. https://doi.org/10.1097/j.pain.0000000000001395.
98. Coxon CH, Geer MJ, Senis YA. ITIM receptors: more than just inhibitors of platelet activation. Blood. 2017;129(26):3407–18.
99. Smith KG, Clatworthy MR. FcgammaRIIB in autoimmunity and infection: evolutionary and therapeutic implications. Nat Rev Immunol. 2010;10(5):328–43.
100. Shrestha S, Wiener H, Olson AK, Edberg JC, Bowles NE, et al. Functional FcγRIIB gene variants influence intravenous immunoglobulin (IVIG) response in Kawasaki disease (KD) patients. J Allergy Clin Immunol. 2011;128(3):677–80.
101. Thiruppathi M, Sheng JR, Li L, Prabhakar BS, Meriggioli MN. Recombinant IgG2a Fc (M045) multimers effectively suppress experimental autoimmune myasthenia gravis. J Autoimmun. 2014;52:64–73.
102. Debré M, Bonnet MC, Fridman WH, et al. Infusion of Fcγ fragments for treatment of children with acute immune thrombocytopenic purpura. Lancet. 1993;342:945–9.
103. Jefferis R. Glycosylation as a strategy to improve antibody-based therapeutics. Nat Rev Drug Discov. 2009;8:226–34.
104. Alter G, Ottenhoff THM, Joosten SA. Antibody glycosylation in inflammation, disease and vaccination. Semin Immunol. 2018;39:102–10.
105. Yamada K, et al. Galactosylation of IgG1 modulates FcgammaRIIB-mediated inhibition of murine autoimmune hemolytic anemia. J Autoimmun. 2013;47:104–10.
106. Tian RR, Zhang MX, Liu M, Fang X, Li D, Zhang L, Zheng P, Zheng YT, Liu Y. CD24Fc protects against viral pneumonia in simian immunodeficiency virus-infected Chinese rhesus monkeys. Cell Mol Immunol. 2020;17(8):887–8.
107. OncoImmune, Inc. CD24Fc as a non-antiviral immunomodulator in COVID-19 treatment (SAC-COVID). https://clinicaltrials.gov/ct2/show/NCT04317040

108. Altevogt P, Sammar M, Hüser L, Kristiansen G. Novel insights into the function of CD24: a driving force in cancer. Int J Cancer. 2021;148(3):546–59.
109. Chen GY, Tang J, Zheng P, Liu Y. CD24 and Siglec-10 selectively repress tissue damage-induced immune responses. Science. 2009;323(5922):1722–5.
110. Sammar M, Siwetz M, Meiri H, Fleming V, Altevogt P, Huppertz B. Expression of CD24 and Siglec-10 in first trimester placenta: implications for immune tolerance at the fetal-maternal interface. Histochem Cell Biol. 2017;147(5):565–74.
111. Delaveris C, Wilk A, Riley N, Stark J, Yang S, Rogers A, et al. Synthetic Siglec-9 agonists inhibit neutrophil activation associated with COVID-19. ChemRxiv. 2020; https://doi.org/10.26434/chemrxiv.13378148.
112. Crayne CB, Albeituni S, Nichols KE, Cron RQ. The immunology of macrophage activation syndrome. Front Immunol. 2019;10:119.
113. Karakike E, Giamarellos-Bourboulis EJ. Macrophage activation-like syndrome: a distinct entity leading to early death in sepsis. Front Immunol. 2019;10:55.
114. Wang F, Zhang S, Jeon R, Vuckovic I, Jiang X, Lerman A, et al. Interferon gamma induces reversible metabolic reprogramming of M1 macrophages to sustain cell viability and pro-inflammatory activity. EBioMedicine. 2018;30:303–16.
115. Grom AA, Horne A, De Benedetti F. Macrophage activation syndrome in the era of biologic therapy. Nat Rev Rheumatol. 2016;12(5):259–68.
116. Pilania RK, Jindal AK, Johnson N, Prithvi A, Vignesh P, Suri D, et al. Macrophage activation syndrome in children with Kawasaki disease: an experience from a tertiary care hospital in Northwest India. Rheumatology (Oxford). 2021;60(7):3413–9.
117. Lind-Holst M, Hartling UB, Christensen AE. High-dose anakinra as treatment for macrophage activation syndrome caused by refractory Kawasaki disease in an infant. BMJ Case Rep. 2019;12(8):e229708.

Anemia in Kawasaki Disease

Ying-Hsien Huang and Ho-Chang Kuo

Abstract

Kawasaki disease (KD) is the most common acute coronary vasculitis syndrome that mainly affects genetically susceptible kids under 5 years of age. Aside from the standard diagnostic five criteria, patients with KD may also experience a variety of nonspecific clinical symptoms and signs. Anemia is the most common clinical feature in KD patients. In 2001, the scientists have the discovery of a liver-derived peptide hormone named as hepcidin began revolutionizing the understanding of anemia's relation to a number of inflammatory diseases, including KD. This chapter focuses on hepcidin-induced iron deficiency's relation to transient hyposideremia, anemia, and disease outcomes in KD patients, and goes on to suggest possible routes of KD study.

Keywords

Kawasaki disease · Anemia · Hepcidin
HAMP · Iron

Y.-H. Huang · H.-C. Kuo (✉)
Department of Pediatrics, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan

Kawasaki Disease Center, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan

Kawasaki Disease Is the Most Common Vasculitis of the Coronary Arteries in Children

Kawasaki disease (KD) is an acute multisystem vasculitis syndrome that mainly affects genetically susceptible infants and kids under 5 years of age. Although the cause of KD is not clearly known, it is temporarily defined as an infection–immune–genetic pathogenesis for this mysterious disease [1]. Tomisaku Kawasaki is the first doctor to publish 50 cases of KD in English in 1974 [2]. KD shows signs and symptoms such as high fever for several days, conjunctivitis, diffuse mucosal inflammation, polymorphous skin rashes, peeling of the skin on the hands and feet (especially on their tips), and nonsuppurative lymphadenopathy [1]. Inflammation in small- and medium-sized blood vessels, particularly the coronary arteries, may be also manifested in KD patients. The most serious complication in KD is coronary artery lesions (CAL), including myocardial infarction and coronary artery aneurysm. If left untreated, 20% of the affected kids may suffer from a sequelae of vasculitis with coronary aneurysms [3]. Currently, a single dose of 2 mg/Kg intravenous immunoglobulin (IVIG) is the main treatment for coronary artery lesions (CAL) in KD patients [4]. The global prevalence of KD among children is the highest in Japan ($218/10^5$) and the lowest (4.7/105) in kids of European descent, while the incidence in Taiwan

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is 66/10^5 [1]. During our recent study period, the incidence of KD in Taiwan more than doubled from 28.58 to 60.08 per 100,000 [5]. Therefore, the prevalence of KD in Asia is nearly 10 times higher than in Europe and the USA. However, for clinicians in the pediatric emergency department, the biggest challenge is to identify KD itself in the early stage, because KD shares many of the same clinical signs with other childhood diseases with high fever [6]. Even worse, 20–30% of KD patients do not fully meet the diagnostic criteria and are considered to suffer an incomplete KD, making the diagnosis even more challenging for inexperienced pediatricians [7, 8].

Anemia in Patients with Kawasaki Disease

Aside from the standard diagnostic criteria, patients with KD may also experience a variety of nonspecific clinical symptoms, such as uveitis, aseptic meningitis, abdominal pain, hydrocystic gallbladder, skin rash at the site of BCG-Carinella inoculation, impaired liver function, hypoalbuminemia, and anemia [9–12]. Among them, anemia is the most common clinical feature in KD patients and is considered to have a longer duration of active inflammation [13–16]. A study involving 783 people including 441 KD patients and 342 febrile controls showed that hemoglobin level is one of the seven variables with the largest absolute value of the diagnostic coefficient [17]. In addition, Lin et al. observed that hemoglobin is a useful marker for telling KD shock syndrome from toxic shock syndrome in pediatric intensive care units [18]. Although severe hemolytic anemia that requires blood transfusion is rare, it may be related to IVIG infusion [14, 15, 19]. The main cause of hemolysis is usually related to anti-A and anti-B IgM antibodies and anti-Rh IgG antibodies [20]. In fact, the IVIG products used today are generally safe and effective. They consist of at least 98% IgG and very low anti-A (1:8) and anti-B (1:4) IgM antibodies, but no anti-D IgG antibodies [22, 31]. In addition, Rh-negative blood types are much less common in the Asian populations (0.3%) than in the Caucasian populations (15%). The phenomena and literature concerning hemolysis after IVIG in KD patients may thus be more commonly reported in European ancestry than Asian ancestry. We also found that there were no significant differences in total bilirubin and haptoglobin levels between KD patients before and after IVIG treatment [11]. Therefore, we believe that the key etiological link can explain the relationship between KD and anemia.

Anemia associated with inflammation represents a serious, highly common clinical problem [21]. Anemia of chronic disease is usually observed in various inflammatory states, such as infections, inflammatory diseases, and certain cancers [22–25]. In 2000, Krause et al. described a peptide that was first called liver-expressed antimicrobial peptide-1 or LEAP-1 but later named "hepcidin" due to its liver expression and antibacterial activity [26]. It is understood that hepcidin plays a vital role in preventing the subsequent iron influx into the plasma: duodenal absorption, macrophage release, mobilization of iron stored in liver cells, and inflammatory anemia [21, 27]. In anemia associated with inflammatory diseases such as infections [39, 40], autoimmune diseases [41, 42], severe diseases [43, 44], obesity [28], and acute myocardial infarction [29], abnormally elevated levels of hepcidin have also been observed.

Hepcidin Expression Is Associated with the Prognosis of Kawasaki Disease

We have previously reported that before receiving IVIG treatment, the plasma hepcidin and IL-6 levels of KD patients were higher than those of febrile controls [30]. After IVIG treatment, the levels of hepcidin and IL-6 decreased significantly. Interestingly, changes in hepcidin levels are related to the resistance to IVIG treatment and the formation of CAL, which supports the theory that inflammation markers and increased IVIG anergy may be related to the development of CAL in KD patients [30].

It is proven that IVIG can effectively reduce the incidence of CAL [4], but it is still unclear what role aspirin plays and how much aspirin should be administered on KD patients. In the

past few decades, even before IVIG was used, aspirin-related practices have been administered in KD treatment [3]. Moreover, anemia and significant bleeding are associated with the use of aspirin [31]. In a study of 851 patients with KD, we have reported that high-dose aspirin in acute-phase KD does not benefit the disease outcomes but may be harmful in reducing disease inflammation [32]. In addition, this is the first study to show that high-dose aspirin can lower hemoglobin levels and hinder the ability to lower hepcidin levels after IVIG treatment. Therefore, high-dose aspirin may not be an essential part of acute-phase KD treatment. Nevertheless, more randomized placebo-controlled studies are needed to clarify the function of high-dose aspirin in KD.

Iron Deficiency Caused by Hepcidin Is Related to Transient Hypoferremia and Anemia in KD Patients

Hepcidin is essential in coordinating iron metabolism and the pathogenesis of inflammatory anemia [33, 34]. After hepcidin interacts with ferroportin, the ferroportin is internalized and degraded, which ultimately leads to a decrease in iron chelation and iron absorption in the cells [35]. Currently, ferroportin is the only known exporter of mammalian iron and is essential for transporting iron from one cell type to another [35]. Hepcidin not only controls the absorption of iron, but also has a direct inhibitory effect on erythropoiesis [36]. Moreover, it is also proved that hepcidin can directly affect the proliferation and survival of erythroid precursors, because the formation of erythrocyte colony [37] is consistent with the observation of transient erythrocytopenia in bone marrow aspiration in patients with KD [38]. In our previous study, hemoglobin levels kept on decreasing significantly after IVIG treatment, showing that myelosuppression in KD patients does not quickly reverse after IVIG treatment. In our age-matched 27 health controls and 117 KD patients, the hemoglobin level increased 3 weeks after IVIG treatment, and the hemoglobin level was completely restored during the 6-month follow-up (Fig. 1). Thus, we recommend that patients with KD do not need to supplement iron.

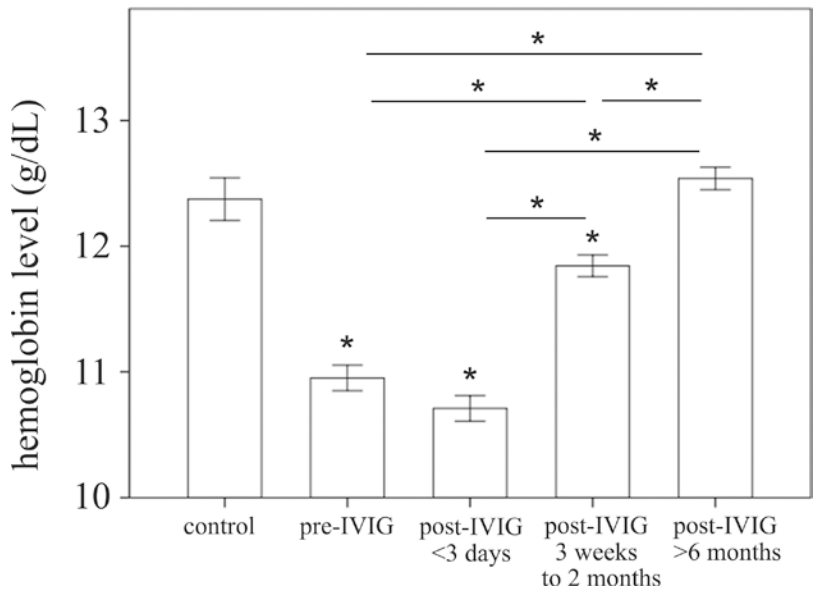

Fig. 1 Comparison of hemoglobin levels in age-matched healthy controls ($N = 27$) with Kawasaki disease (KD) ($N = 117$) patients before and after receiving intravenous immunoglobulin therapy. The data are expressed as mean ± standard error. * indicates $p < 0.05$ between groups (reproduced with permission from https://encyclopedia.pub/3623)

HAMP Promoter Hypomethylation and Elevated Hepcidin Levels Are Biomarkers of Kawasaki Disease

The genome-wide DNA methylation method shows that DNA methylation occurs in the epigenetic regulation mechanism, which is used for the transcriptional inhibition of HAMP in alcohol-related hepatocellular carcinoma [39]. In our previous study, univariate analysis showed that the methylation status of the HAMP promoter was significantly and negatively correlated with plasma hepcidin levels in KD patients and controls [40]. Since DNA methylation is the most famous control mechanism of gene expression, our in vitro research results also show that promoter DNA methylation under epigenetic regulation can be used as a regulatory mechanism for the transcription regulation of HAMP genes. In addition, these findings highlight the epigenetic hypomethylation of the HAMP promoter and the upregulation of hepcidin expression. These results establish a new significance for the epigenetic hypomethylation of HAMP in KD patients and indicate that a significant increase in the level of hepcidin can be used as a biomarker for KD. In 2021, we further demonstrated a novel scoring system, which has good ability to distinguish children with Kawasaki disease from other kids with high fever and highlights the importance of eosinophils in Kawasaki disease. Using this novel scoring system to evaluate factors, including hemoglobin, average red blood cell hemoglobin, and average red blood cell hemoglobin concentration level, can help first-line doctors diagnose and treat Kawasaki disease as soon as possible [41].

Other Studies on Hepcidin in Kawasaki Disease

Macrophages play a vital role in regulating iron homeostasis, which is closely related to polarization during innate immunity. The iron homeostasis of macrophages is related to the functional polarization and plasticity of these cells and plays an extreme role in the process of inflammation, immune regulation, and inflammation regression [42]. According to the Mosser and Edwards model, macrophages are grouped by their functional characteristics into three populations, including host defense (M1), wound healing (M2a), and immune regulation (M2b/c). Under a conceptual framework these three basic macrophage populations can be blended into a large number of different macrophage subpopulations [43]. Polarization characteristics usually refer to the cytokine profile that has been extensively studied in KD patients. However, no studies have yet been made to resolve the exact macrophage polarization in KD. Since iron is an essential growth factor for most bacteria and parasites, they have developed various mechanisms to separate iron from the host. Doing so makes M1-macrophages a major iron storage site under inflammatory conditions [42]. In contrast, M2-macrophages increase ferroportin to promote iron release [44]. However, little is known about whether iron homeostasis affects the ability of the macrophage polarization program and molecular mechanisms involved in the KD disease process.

Conclusion

Inflammation-induced hepcidin can bring about transient hypoironemia, anemia, and disease outcomes in acute-phase KD (Fig. 2, published Int J Mol Sci. 2017 Apr 12; 18 (4): 820. doi: 10.3390/ijms18040820, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5412404/). However, further research is needed to better clarify the role of hepcidin in the pathogenesis of KD.

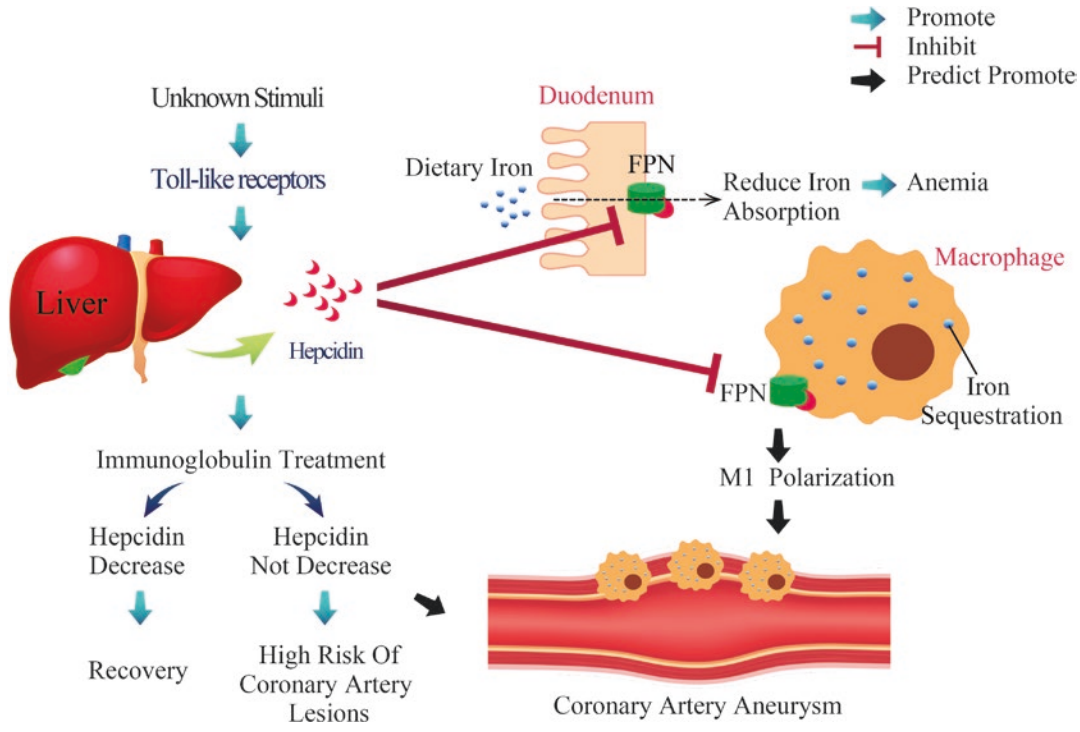

Fig. 2 Proposed mechanism of transient anemia and coronary artery lesions caused by hepcidin in patients with Kawasaki disease. Although the exact cause of Kawasaki disease (KD) is still uncertain, we have reported that KD stimulates the abnormal upregulation of most TLRs, and these TLR arteries upregulate the expression of Hepcidin. After hepcidin interacts with ferroportin, the ferroportin is internalized and degraded, which ultimately leads to the reduction of intracellular iron chelation and duodenal iron absorption. Hepcidin not only controls the absorption of iron, but also has a direct inhibitory effect on erythropoiesis, which can cause transient hypoironemia and anemia in patients with KD. The iron homeostasis of macrophages is related to the functional polarization and plasticity of these cells and makes M1-macrophages a major iron storage site under inflammatory conditions. However, little is known about whether iron homeostasis affects the macrophage polarization program and the ability of the molecular mechanisms involved in the KD disease process. (Reproduced with permission from Int J Mol Sci. 2017 Apr 12; 18 (4): 820. doi: 10.3390/ijms18040820)

References

1. Wang CL, Wu YT, Liu CA, Kuo HC, Yang KD. Kawasaki disease: infection, immunity and genetics. Pediatr Infect Dis J. 2005;24:998–1004.
2. Kawasaki T, Kosaki F, Okawa S, Shigematsu I, Yanagawa H. A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. Pediatrics. 1974;54:271–6.
3. Newburger JW, Takahashi M, Burns JC, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. N Engl J Med. 1986;315:341–7.
4. Newburger JW, Takahashi M, Beiser AS, et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. N Engl J Med. 1991;324:1633–9.
5. Huang YH, Lin KM, Ho SC, Yan JH, Lo MH, Kuo HC. Increased incidence of Kawasaki disease in Taiwan in recent years: a 15 years nationwide population-based cohort study. Front Pediatr. 2019;7:121.
6. Hao S, Jin B, Tan Z, et al. A classification tool for differentiation of Kawasaki disease from other febrile illnesses. J Pediatr. 2016;176:114–20. e8
7. 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.
8. Liu YC, Lin MT, Wang JK, Wu MH. State-of-the-art acute phase management of Kawasaki disease after 2017 scientific statement from the American Heart Association. Pediatr Neonatol. 2018;59:543–52.

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. Tseng HC, Ho JC, Guo MM, et al. Bull's eye dermatoscopy pattern at bacillus Calmette-Guerin inoculation site correlates with systemic involvements in patients with Kawasaki disease. J Dermatol. 2016;43:1044–50.
11. Huang YH, Kuo HC, Huang FC, et al. Hepcidin-induced iron deficiency is related to transient anemia and hypoferremia in Kawasaki disease patients. Int J Mol Sci. 2016;17:715.
12. Kuo HC, Hsu YW, Wu MS, Chien SC, Liu SF, Chang WC. Intravenous immunoglobulin, pharmacogenomics, and Kawasaki disease. J Microbiol Immunol Infect. 2016;49:1–7.
13. Alves NR, Magalhaes CM, Almeida Rde F, Santos RC, Gandolfi L, Pratesi R. Prospective study of Kawasaki disease complications: review of 115 cases. Rev Assoc Med Bras. 2011;57:295–300.
14. Fukushige J, Takahashi N, Ueda Y, Ueda K. Incidence and clinical features of incomplete Kawasaki disease. Acta Paediatr. 1994;83:1057–60.
15. Kuo HC, Wang CL, Liang CD, et al. Persistent monocytosis after intravenous immunoglobulin therapy correlated with the development of coronary artery lesions in patients with Kawasaki disease. J Microbiol Immunol Infect. 2007;40:395–400.
16. Kuo HC, Yang KD, Liang CD, et al. The relationship of eosinophilia to intravenous immunoglobulin treatment failure in Kawasaki disease. Pediatr Allergy Immunol. 2007;18:354–9.
17. Ling XB, Lau K, Kanegaye JT, et al. A diagnostic algorithm combining clinical and molecular data distinguishes Kawasaki disease from other febrile illnesses. BMC Med. 2011;9:130.
18. Lin YJ, Cheng MC, Lo MH, Chien SJ. Early differentiation of Kawasaki disease shock syndrome and toxic shock syndrome in a pediatric intensive care unit. Pediatr Infect Dis J. 2015;34:1163–7.
19. Nakagawa M, Watanabe N, Okuno M, Kondo M, Okagawa H, Taga T. Severe hemolytic anemia following high-dose intravenous immunoglobulin administration in a patient with Kawasaki disease. Am J Hematol. 2000;63:160–1.
20. Thorpe SJ. Specifications for anti-a and anti-B in intravenous immunoglobulin: history and rationale. Transfusion. 2015;55(Suppl 2):S80–5.
21. Nemeth E, Ganz T. Anemia of inflammation. Hematol Oncol Clin North Am. 2014;28:671–81. vi
22. Keel SB, Abkowitz JL. The microcytic red cell and the anemia of inflammation. N Engl J Med. 2009;361:1904–6.
23. Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med. 2005;352:1011–23.
24. Hohaus S, Massini G, Giachelia M, et al. Anemia in Hodgkin's lymphoma: the role of interleukin-6 and hepcidin. J Clin Oncol. 2010;28:2538–43.
25. Lee SH, Jeong SH, Park YS, et al. Serum prohepcidin levels in chronic hepatitis C, alcoholic liver disease, and nonalcoholic fatty liver disease. Korean J Hepatol. 2010;16:288–94.
26. Krause A, Neitz S, Magert HJ, et al. LEAP-1, a novel highly disulfide-bonded human peptide, exhibits antimicrobial activity. FEBS Lett. 2000;480:147–50.
27. Girelli D, Nemeth E, Swinkels DW. Hepcidin in the diagnosis of iron disorders. Blood. 2016; 127:2809–13.
28. del Giudice EM, Santoro N, Amato A, et al. Hepcidin in obese children as a potential mediator of the association between obesity and iron deficiency. J Clin Endocrinol Metab. 2009;94:5102–7.
29. Sasai M, Iso Y, Mizukami T, et al. Potential contribution of the hepcidin-macrophage axis to plaque vulnerability in acute myocardial infarction in human. Int J Cardiol. 2017;227:114–21.
30. Kuo HC, Yang YL, Chuang JH, et al. Inflammation-induced hepcidin is associated with the development of anemia and coronary artery lesions in Kawasaki disease. J Clin Immunol. 2012;32:746–52.
31. Gaskell H, Derry S, Moore RA. Is there an association between low dose aspirin and anemia (without overt bleeding)? Narrative review. BMC Geriatr. 2010;10:71.
32. Kuo HC, Lo MH, Hsieh KS, Guo MM, Huang YH. High-dose aspirin is associated with anemia and does not confer benefit to disease outcomes in Kawasaki disease. PLoS One. 2015;10:e0144603.
33. Le NT, Richardson DR. Ferroportin1: a new iron export molecule? Int J Biochem Cell Biol. 2002;34:103–8.
34. Ward DM, Kaplan J. Ferroportin-mediated iron transport: expression and regulation. Biochim Biophys Acta. 1823;2012:1426–33.
35. Nemeth E, Tuttle MS, Powelson J, et al. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. Science. 2004;306:2090–3.
36. Kim A, Nemeth E. New insights into iron regulation and erythropoiesis. Curr Opin Hematol. 2015;22:199–205.
37. Dallalio G, Law E, Means RT Jr. Hepcidin inhibits in vitro erythroid colony formation at reduced erythropoietin concentrations. Blood. 2006;107:2702–4.
38. Frank GR, Cherrick I, Karayalcin G, Valderrama E, Lanzkowsky P. Transient erythroblastopenia in a child with Kawasaki syndrome: a case report. Am J Pediatr Hematol Oncol. 1994;16:271–4.
39. Udali S, Guarini P, Ruzzenente A, et al. DNA methylation and gene expression profiles show novel regulatory pathways in hepatocellular carcinoma. Clin Epigenetics. 2015;7:43.
40. Huang YH, Kuo HC, Li SC, Cai XY, Liu SF, Kuo HC. HAMP promoter hypomethylation and increased

hepcidin levels as biomarkers for Kawasaki disease. J Mol Cell Cardiol. 2018;117:82–7.
41. Tsai CM, Chu CH, Liu X, et al. A novel score system of blood tests for differentiating Kawasaki disease from febrile children. PLoS One. 2021;16:e0244721.
42. Jung M, Mertens C, Brune B. Macrophage iron homeostasis and polarization in the context of cancer. Immunobiology. 2015;220:295–304.
43. Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation. Nat Rev Immunol. 2008;8:958–69.
44. Corna G, Campana L, Pignatti E, et al. Polarization dictates iron handling by inflammatory and alternatively activated macrophages. Haematologica. 2010;95:1814–22.

Psychological or Mental Issues in Kawasaki Disease

Liang-Jen Wang and Ho-Chang Kuo

Abstract

Kawasaki disease (KD) is characterized by multisystem vasculitis, which may affect blood perfusion and cause inflammatory changes in the brain. This chapter aims to systematically review the research on KD psychology or psychological problems. A comprehensive search of studies published before April 5, 2021 was conducted on MEDLINE through the PubMed database to identify relevant articles. Both current clinical data and population-based cohorts indicate that patients with KD have no increased risk of mental/psychological sequelae, including intellectual disability, attention deficit/hyperactivity disorder, or autism. The results indicate that KD seems to have no effect on developmental milestones or cognitive function later in life. However, caregivers of KD patients with coronary artery lesion (CAL) may be stressed that CAL can cause unpredictable sequelae to their children. Such caregivers may need support to perform their parenting duties. Future research is necessary to clarify the subtle effects of KD-related systemic vasculitis on the central nervous system.

Keywords

Kawasaki disease · Psychiatry · Cognition
Caregivers · Complication

Background

Kawasaki disease (KD) is a disease that mainly affects children under 5 years of age and involves multisystem vasculitis of unknown etiology [1, 2]. Although it occurs all over the world, the incidence of KD is particularly high in East Asia, especially Japan, South Korea, and Taiwan [3, 4]. The main clinical features of KD include persistent fever, diffuse mucosal inflammation, bilateral non-suppurative conjunctivitis, non-suppurative cervical lymphadenopathy, rigid angioedema of the hands and feet, and pleomorphic rash [5–7]. Although its etiology is not yet clear, both genetic and environmental factors are related to the occurrence of KD [8, 9]. Intravenous immunoglobulin (IVIG) infusion is the standard treatment for acute KD, but 10–20% of patients show resistance to IVIG treatment and are at risk of complications [10], the most serious of which is cardiovascular complications (such as coronary

L.-J. Wang (✉)
Department of Child and Adolescent Psychiatry, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan

H.-C. Kuo
Department of Pediatrics and Kawasaki Disease Center, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan

Chang Gung University College of Medicine, Kaohsiung, Taiwan

H.-C. Kuo (ed.), *Kawasaki Disease*, https://doi.org/10.1007/978-981-19-2944-1_16

aneurysm) [11]. However, KD is also characterized by multisystem vasculitis, which may affect blood perfusion and cause inflammatory changes in the brain [12, 13]. A study has shown that 1–30% of KD patients will experience central nervous system (CNS) symptoms [14].

KD and Cognition

KD patients with central nervous system involvement may show a variety of symptoms and signs, including irritability, lethargy, aseptic meningitis, cranial nerve palsy [15], and prolonged partial seizures with bilateral subdural effusion [16]. Endothelial cell dysfunction in patients with KD may not be limited to coronary vessels. Previous studies have shown that migraine and Raynaud's phenomenon may be the consequences of KD [17]. In addition, coma and white matter damage on brain magnetic resonance imaging (MRI) have been observed in KD patients [12]. However, few studies have focused on whether KD is related to the sequelae of cognitive impairment [18, 19]. A study conducted in Ottawa, Ontario recruited 32 KD patients aged between 4 and 18 and their siblings as control subjects. Compared with the control group, KD patients were found to show no differences in cognition or academic performance, but a KD deficit was found to be related to internalization and attention behavior [18]. In another clinical study conducted in northern India, 20 KD patients between 5 and 10 years old were recruited together with 20 patients with mild intermittent asthma as comparison subjects [19]. The researchers found that there were no significant differences between the two groups in terms of social adaptation, cognitive function, or behavioral function.

The case of a 7-year-old boy with KD complicated with cerebrovascular inflammation and encephalitis was observed. After a single dose of immunoglobulin, pulse methylprednisolone therapy was started, which resulted in a gradual improvement in consciousness, an eventual complete recovery of motor and cognitive functions, and the regression of brain magnetic resonance lesions [20]. A prospective study (clinical cohort) reported the neurological sequelae of 115 KD patients [21]. Even within a few months of the acute phase of the disease, KD may have a variety of complications, eventually leading to permanent sequelae. Behavior changes during rehabilitation were observed in approximately 20% of children with KD [21].

A previous study conducted in Taiwan included a clinical cohort (168 KD patients and 81 healthy controls) and a national cohort (4286 KD patients and 50,038 controls) retrieved from the Taiwan National Health Insurance Research Database. Clinical data and population-based cohorts consistently indicate that KD does not increase the risk of future cognitive impairment in children [22]. Another retrospective cohort study of 612 KD patients recruited in Taiwan showed that the prevalence of neurodevelopmental disorders, especially epilepsy and Tourette syndrome (TS), in children with KD is higher than that in the general pediatric population in Taiwan. There is no significant difference in the prevalence of intellectual disability (ID) and developmental language impairment between KD patients in Taiwan or worldwide [23].

KD and ADHD

Attention deficit/hyperactivity disorder (ADHD) is a common neuropsychiatric disease in children and adolescents. According to reports, the prevalence of school-age children worldwide is about 3–10% [24], and that in Taiwan is 7.5% [25]. The core symptoms of ADHD are inattention, hyperactivity, and impulsivity, which have a significant negative impact on the overall aspects of academic performance, interpersonal relationships, and family function [26, 27]. The underlying pathophysiological mechanism of ADHD is complex and multidimensional. The risk factors for ADHD are generally categorized as prenatal, perinatal, and postnatal [28, 29]. Among the postnatal factors, several childhood diseases have been identified as increasing the risk of ADHD, including head injuries, meningitis, encephalitis, epilepsy, and exposure to toxins or drugs [30]. A recent study based on the national population showed an asso-

ciation between ADHD and allergic/autoimmune diseases [31]. The release of inflammatory cytokines caused by allergic/autoimmune diseases may interfere with the neurotransmitter system and brain maturation involved in the pathophysiology of ADHD [32]. However, there are currently no studies investigating whether physiological abnormalities in KD (cerebral hypoperfusion and inflammation) are related to subsequent development of symptoms of ADHD.

A previous population-based study conducted in Taiwan recruited 651 KD patients and 3255 controls, indicating that KD patients may not increase the risk of ADHD [33]. Another retrospective cohort study of 612 KD patients recruited in Taiwan showed that the prevalence of neurodevelopmental disorders in children with KD is higher than the general pediatric population in Taiwan, especially epilepsy and Tourette syndrome (TS). Nevertheless, the prevalence of ADHD was not significantly different between KD patients and those in Taiwan or worldwide [23].

KD and Autism Spectrum Disorders

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder that affects up to 1.1% of children in the United States [34] and 0.3% of children in Taiwan [35]. Children with autism show characteristic impairments in mutual social interaction, delayed and abnormal communication skills, and a restricted repertoire of activities and interests [36]. Recent studies have shown that some patients with ASD have decreased cerebral perfusion, evidence of neuroinflammation, and increased oxidative stress markers [37]. A number of independent SPECT and positron emission tomography (PET) studies have shown that there is insufficient perfusion in several areas of the autistic brain, the most notable being the temporal regions and areas particularly related to language understanding and auditory processing. Several studies have shown that reduced blood flow to these areas correlates with many clinical features associated with ASD, including repetitive, self-stimulatory, and stereotypical behaviors, as well as barriers to communication, sensory perception, and social interaction. Hyperbaric oxygen therapy (HBOT) has achieved clinical success in a variety of cerebral hypoperfusion syndromes, including cerebral palsy, fetal alcohol syndrome, closed head injury, and stroke [37]. It has been reported that HBOT is beneficial to many individuals with ASD who have certain physiological abnormalities, including cerebral hypoperfusion, inflammation, mitochondrial dysfunction, and oxidative stress [38]. A previous population-based retrospective cohort study showed that patients with KD have no increased risk of ASD [39].

KD and Caregiver Pressure

Intravenous immunoglobulin (IVIG) has been the standard treatment for acute KD [10]. However, 10–20% of patients still show resistance to IVIG treatment and have a high risk of coronary complications [40]. Among them, CAL is the most serious [11]. Current research shows that 20–24% of children with KD still suffer from CAL even if they receive IVIG treatment [41, 42]. Moreover, KD patients, as well as their caregivers, may consistently worry about patients' potential risk of cardiac event-related death [43]. However, our data show that caregivers of patients with CAL are under greater parenting pressure than caregivers of patients without CAL. Children with persistent CAL may develop complications [44], so caregivers may worry, feel stressed, and feel helpless in the face of the uncertainty of the child's risk of myocardial infarction and the possibility of sudden death. This finding indicates that parental stress or mental health of caregivers of patients with CAL require particular assistance.

Conclusion

Both current clinical data and population-based cohorts indicate that patients with KD have no increased risk of mental/psychological sequelae, including intellectual disability, hyperactivity, or autism (summarized in Table 1). The results are

Table 1 Summary of current studies regarding to psychological/mental issues in Kawasaki disease

Topic	Study	Design	Country	Case number	Main findings
KD and cognition	King et al., 2000	Cohort analytic study	Canada	KD: *n* = 32 Siblings: *n* = 32	No effect on cognitive development or academic performance
	Nishad et al., 2010	3-month follow-up	India	KD: *n* = 20 Siblings: *n* = 20	No significant difference in social adaptation, cognitive function and behavioural functioning
	Alves et al., 2011	Prospective study (clinical cohort)	Brazil	KD: *n* = 115	Behavioral changes over convalescence were observed in around 20% children
	Wang and Kuo, 2018	Clinical Study plus a nationwide cohort	Taiwan	Clinical Study: 168 KD and 81 controls Nationwide Cohort: 4286 KD patients and 50,038 controls	Both the clinical data and the population-based cohort consistently demonstrated that KD does not increase a child's risk of future cognitive impairment
	Lin et al. 2019	Retrospective cohort study	Taiwan	612 KD patients	The prevalence of ID was not significantly different between this study patients and those in Taiwan or worldwide
KD and ADHD	Kuo et al. 2016	Retrospective cohort study	Taiwan	651 KD patients 3255 controls	Patients with KD may not have an increased risk of ADHD
	Lin et al. 2019	Retrospective cohort study	Taiwan	612 KD patients	The prevalence of ADHD was not significantly different between our study patients and those in Taiwan or worldwide
KD and autism	Kuo et al. 2014	Retrospective cohort study	Taiwan	563 KD patients 2815 controls	Patients with KD are not at increased risk of autism
	Lin et al. 2019	Retrospective cohort study	Taiwan	612 KD patients	The prevalence of autism was not significantly different between this study patients and those in Taiwan or worldwide

good news for caregivers and KD patients, reassuring them that KD seems to have no effect on developmental milestones or cognitive function later in life. However, future research is necessary to clarify the subtle effects of KD-related systemic vasculitis on the central nervous system.

References

1. Newburger JW, Takahashi M, Burns JC. Kawasaki Disease. J Am Coll Cardiol. 2016;67(14):1738–49.
2. Hara T, Nakashima Y, Sakai Y, Nishio H, Motomura Y, Yamasaki S. Kawasaki disease: a matter of innate immunity. Clin Exp Immunol. 2016;186(2):134–43.
3. Singh S, Vignesh P, Burgner D. The epidemiology of Kawasaki disease: a global update. Arch Dis Child. 2015;100(11):1084–8.
4. Uehara R, Belay ED. Epidemiology of Kawasaki disease in Asia, Europe, and the United States. J Epidemiol. 2012;22(2):79–85.
5. Zhu FH, Ang JY. The clinical diagnosis and Management of Kawasaki Disease: a review and update. Curr Infect Dis Rep. 2016;18(10):32.
6. Rowley AH. The complexities of the diagnosis and Management of Kawasaki Disease. Infect Dis Clin N Am. 2015;29(3):525–37.
7. Kuo HC, Yang KD, Chang WC, Ger LP, Hsieh KS. Kawasaki disease: an update on diagnosis and treatment. Pediatr Neonatol. 2012;53(1):4–11.
8. Galeotti C, Kaveri SV, Cimaz R, Kone-Paut I, Bayry J. Predisposing factors, pathogenesis and therapeutic intervention of Kawasaki disease. Drug Discov Today. 2016;21(11):1850–7.
9. Kuo HC, Chang JC, Kuo HC, Yu HR, Wang CL, Lee CP, et al. Identification of an association between genomic hypomethylation of FCGR2A and susceptibility to Kawasaki disease and intravenous immunoglobulin resistance by DNA methylation array. Arthritis Rheumatol. 2015;67(3):828–36.
10. Eleftheriou D, Levin M, Shingadia D, Tulloh R, Klein NJ, Brogan PA. Management of Kawasaki disease. Arch Dis Child. 2014;99(1):74–83.
11. Chen KY, Curtis N, Dahdah N, Kowalski R, Cheung M, Burgner DP. Kawasaki disease and cardiovascular risk: a comprehensive review of subclinical vascular changes in the longer term. Acta Paediatr. 2016;105(7):752–61.
12. Gitiaux C, Kossorotoff M, Bergounioux J, Adjadj E, Lesage F, Boddaert N, et al. Cerebral vasculitis in severe Kawasaki disease: early detection by magnetic resonance imaging and good outcome after intensive treatment. Dev Med Child Neurol. 2012;54(12):1160–3.
13. Korematsu S, Uchiyama S, Miyahara H, Nagakura T, Okazaki N, Kawano T, et al. The characterization of cerebrospinal fluid and serum cytokines in patients with Kawasaki disease. Pediatr Infect Dis J. 2007;26(8):750–3.
14. Hikita T, Kaminaga T, Wakita S, Ogita K, Ikemoto H, Fujii Y, et al. Regional cerebral blood flow abnormalities in patients with Kawasaki disease. Clin Nucl Med. 2011;36(8):643–9.
15. Emiroglu M, Alkan G, Kartal A, Cimen D. Abducens nerve palsy in a girl with incomplete Kawasaki disease. Rheumatol Int. 2016;36(8):1181–3.
16. Bailie NM, Hensey OJ, Ryan S, Allcut D, King MD. Bilateral subdural collections--an unusual feature of possible Kawasaki disease. Eur J Paediatr Neurol. 2001;5(2):79–81.
17. Constantinescu CS. Migraine and Raynaud phenomenon: possible late complications of Kawasaki disease. Headache. 2002;42(3):227–9.
18. King WJ, Schlieper A, Birdi N, Cappelli M, Korneluk Y, Rowe PC. The effect of Kawasaki disease on cognition and behavior. Arch Pediatr Adolesc Med. 2000;154(5):463–8.
19. Nishad P, Singh S, Sidhu M, Malhi P. Cognitive and behaviour assessment following Kawasaki disease--a study from North India. Rheumatol Int. 2010;30(6):851–4.
20. Stojanovic VD, Radovanovic TD, Koprivsek KM, Vijatov Ethuric GV, Doronjski AD. Kawasaki disease complicated with cerebral Vasculitis and severe encephalitis. Ann Indian Acad Neurol. 2020;23(2):228–32.
21. Alves NR, Magalhaes CM, Almeida Rde F, Santos RC, Gandolfi L, Pratesi R. Prospective study of Kawasaki disease complications: review of 115 cases. Rev Assoc Med Bras (1992). 2011;57(3):295–300.
22. Wang LJ, Kuo HC. Cognitive development after Kawasaki disease- clinical study and validation using a Nationwide population-based cohort. Circ J. 2018;82(2):517–23.
23. Lin CH, Lin WD, Chou IC, Lee IC, Hong SY. Heterogeneous neurodevelopmental disorders in children with Kawasaki disease: what is new today? BMC Pediatr. 2019;19(1):406.
24. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry. 2007;164(6):942–8.
25. Gau SS, Chong MY, Chen TH, Cheng AT. A 3-year panel study of mental disorders among adolescents in Taiwan. Am J Psychiatry. 2005;162(7):1344–50.
26. American Psychiatric Association. Diagnostic and Statistical Manual of Mental disorders. Washington DC: American Psychiatric Association; 2013.
27. Spencer TJ, Biederman J, Mick E. Attention-deficit/hyperactivity disorder: diagnosis, lifespan, comorbidities, and neurobiology. J Pediatr Psychol. 2007;32(6):631–42.
28. Galera C, Cote SM, Bouvard MP, Pingault JB, Melchior M, Michel G, et al. Early risk factors for hyperactivity-impulsivity and inattention trajectories from age 17 months to 8 years. Arch Gen Psychiatry. 2011;68(12):1267–75.

29. Sagiv SK, Epstein JN, Bellinger DC, Korrick SA. Pre- and postnatal risk factors for ADHD in a nonclinical pediatric population. J Atten Disord. 2013;17(1):47–57.
30. Millichap JG. Etiologic classification of attention-deficit/hyperactivity disorder. Pediatrics. 2008;121(2):e358–65.
31. Chen MH, Su TP, Chen YS, Hsu JW, Huang KL, Chang WH, et al. Comorbidity of allergic and autoimmune diseases among patients with ADHD: a Nationwide population-based study. J Atten Disord. 2017;21(3):219–27.
32. Schmitt J, Buske-Kirschbaum A, Roessner V. Is atopic disease a risk factor for attention-deficit/hyperactivity disorder? A systematic review. Allergy. 2010;65(12):1506–24.
33. Kuo HC, Chang WC, Wang LJ, Li SC, Chang WP. Association of Attention deficit hyperactivity disorder and Kawasaki disease: a nationwide population-based cohort study. Epidemiol Psychiatr Sci. 2016;25(6):573–80.
34. Kogan MD, Blumberg SJ, Schieve LA, Boyle CA, Perrin JM, Ghandour RM, et al. Prevalence of parent-reported diagnosis of autism spectrum disorder among children in the US, 2007. Pediatrics. 2009;124(5):1395–403.
35. Chen CY, Liu CY, Su WC, Huang SL, Lin KM. Factors associated with the diagnosis of neurodevelopmental disorders: a population-based longitudinal study. Pediatrics. 2007;119(2):e435–43.
36. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. In: DSM-IV-TR (Text Revision). Washington, DC: American Psychiatric Association; 2000. p. 85–93.
37. Rossignol DA, Rossignol LW. Hyperbaric oxygen therapy may improve symptoms in autistic children. Med Hypotheses. 2006;67(2):216–28.
38. Rossignol DA, Bradstreet JJ, Van Dyke K, Schneider C, Freedenfeld SH, O'Hara N, et al. Hyperbaric oxygen treatment in autism spectrum disorders. Med Gas Res. 2012;2(1):16.
39. Kuo HC, Wu CM, Chang WP, Kuo CN, Yeter D, Lin CY, et al. Association between Kawasaki disease and autism: a population-based study in Taiwan. Int J Environ Res Public Health. 2014;11(4):3705–16.
40. Qiu H, He Y, Rong X, Ren Y, Pan L, Chu M, et al. Delayed intravenous immunoglobulin treatment increased the risk of coronary artery lesions in children with Kawasaki disease at different status. Postgrad Med. 2018;130(4):442–7.
41. Joshi M, Tulloh R. Kawasaki disease and coronary artery aneurysms: from childhood to adulthood. Futur Cardiol. 2017;13(5):491–501.
42. Kuo HC. Preventing coronary artery lesions in Kawasaki disease. Biom J. 2017;40(3):141–6.
43. Miura M, Kobayashi T, Kaneko T, Ayusawa M, Fukazawa R, Fukushima N, et al. Association of Severity of coronary artery aneurysms in patients with Kawasaki disease and risk of later coronary events. JAMA Pediatr. 2018;172(5):e180030.
44. Wang LJ, Tsai ZY, Chang LS, Kuo HC. Cognitive development of children with Kawasaki disease and the parenting stress of their caregivers in Taiwan: a case-control study. BMJ Open. 2021;11(6):e042996.

Infection or not in Kawasaki Disease

Nan-Chang Chiu

Abstract

Kawasaki disease (KD) is considered to be related to an infection by its clinical presentations, epidemiological studies, and laboratory findings. Many factors, e.g., age distribution, seasonality, cluster phenomenon, show the compatibility of KD with infection. Superantigen-produced bacteria, i.e., streptococci and staphylococci, have been suspected to be the causative agents, but no consistent evidence. Several viruses, e.g., enteroviruses, adenovirus, Epstein–Barr virus, reveal association with KD in some studies. Though indirect evidences of many infectious agents were reported, no definite pathogens can be identified. KD-like children were noted in COVID-19 pandemic. It is named as multisystem inflammatory syndrome in children or pediatric multisystem inflammatory syndrome later and considered to be distinct from KD. Infection is more likely to be a trigger for a special subsequently immune reaction that causes vasculitis in the genetic predisposing children who present as KD.

Keywords

Infection · Transmission · Bacteria · Virus
COVID-19

N.-C. Chiu (✉)
MacKay Children's Hospital, Taipei, Taiwan
e-mail: ncc88@mmh.org.tw

What Is Infection?

Infection is an organism's body tissues been invaded by disease-causing agents, their multiplication, and the immune reaction of host tissues to the infectious agents and the toxins they produce. A wide range of pathogens can cause infections, bacteria and viruses are the most prominent agents but also other unusual types, i.e., fungi, parasites, prions. The immune system of the host reacts to infections with an innate response, often involving inflammation, followed by an adaptive response. Infectious diseases can be passed from person to person through body secretions, insects, or other means and also known as transmissible diseases or communicable diseases.

An infection usually has clinical presentation, such as fever or other inflammatory symptoms/signs, but can also be subclinical, silent, or occult. Colonization is another situation. The presence of a microorganism on/in a host, with growth and multiplication of the microorganism, but without interaction between host and microorganism is called colonization instead of true infection.

Robert Koch proposed the Koch's postulates to define infection or not in 1884, which require that first, the infectious agent is identifiable only in patients who have the disease, and not in healthy controls, and second, patients who contract the infectious agent also develop the disease. However, it can't be applied to all the infectious diseases in modern practice for ethical reasons

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and new scientific evidence. Epidemiological study of who, why and where disease occurs, and what determines whether various populations have a disease, is another important tool used to understand infectious diseases. When a patient reveals inflammatory symptoms and/or signs, infection will be considered as the possible reason. Other information regarding the possibility of transmissible characters, i.e., contact or cluster with other similar presentation patients, travel or occupational history related to a specific endemic community, needs to be collected. Next, it requires to find the possible causing agent via isolation of the agent in culture, microscopic visualization or molecular detection of the pathogen in tissue lesions, and/or detection of a specific host immune response to the microorganism. If a special microorganism is found and further studies reveal similar correlation, it can be regarded as an infectious disease caused by that microorganism.

Fever is the key symptom for the diagnosis of Kawasaki disease (KD). With other inflammatory symptoms/signs of the diagnostic criteria, infection by some kinds of pathogens have been considered as a very possible reason. Some epidemiological data also support the linkage to infectious origin. Unfortunately, there are no special bacterial or viral causes proved to be the pathogen of KD. Besides, KD isn't contagious; it doesn't transmit from one person to another, at least not so significantly. Therefore, KD is unlikely caused by a pathogen alone. At present, KD is widely thought to be triggered by an infection or an abnormal immune response to infection in some genetic susceptible children.

Clinical and Epidemiological Evidence

Clinical Presentation of Vasculitis

KD presents symptoms and signs of vasculitis. Many idiopathic vasculitides have been suggested to be induced and/or reactivated by infections [1]. In large vessel vasculitis, *Mycobacterium tuberculosis* in Takayasu arteritis and *Chlamydia pneumoniae*, parvovirus B19, and human herpes viruses in giant cell arteritis are thought to have some association [2, 3]. Hepatitis B and C viruses have been linked to polyarteritis nodosa, which involved medium size vessels [4, 5]. KD affects the coronary arteries, one of the medium size vessels, but clinical presentation is different from polyarteritis nodosa. Other infectious agents suspected to have linkage with vasculitis include human immunodeficiency virus, cytomegalovirus, varicella zoster virus, *Staphylococcus aureus*, *Treponema pallidum*, *Borrelia burgdorferi*, rickettsiaceae, etc. Although many observations suggest a link between infections and the development of vasculitis, no direct proof exists [6, 7].

Age Distribution

The predominant age of KD is less than 5 years, with peak incidence at 9–11 months of age and a relatively low incidence in the first 6 months [8]. It is compatible with the typical peak age for common childhood infections, especially similar to many pediatric respiratory transmitted viral infections [9–11]. The age distribution corresponds with the timing of a significant decrease in passive immunity from mothers and progressively increasing reaction of immune system to different infectious agents contacted throughout childhood [12]. KD rarely occurs in adults, suggesting that virtually all adults may have related symptomatic or subclinical infections during their childhood and already developed a protective immune response.

Gender

KD occurs more commonly in the male gender with an approximate 1.5:1 male to female ratio [13, 14]. The reason of male preponderance is unclear but similar to many pediatric infectious diseases.

Seasonality

Several countries have distinct seasonality in KD [15]. The peak months of KD in Taiwan are during the summer season [14, 15]. Two seasonal

peaks, winter and late spring were found in Japan and Korea [9, 16–18]. Winter-early spring is the predominant time in the USA, Canada, Europe, and many other temperate areas [19]. Though the seasonality is different in variable areas, it is highly suggestive of a viral etiology in these areas. However, there is variable or no evidence of seasonal variation in some areas, such as China and Australia [20, 21]. A global study of the seasonality of KD found a winter peak and summer/autumn nadir in non-tropical regions of the northern hemisphere, but less clear seasonality in the southern hemisphere [22].

Tropospheric Wind

Tropospheric wind currents from the northern Pacific have been stated to have an apparent association with KD incidence of Hawaii, southern California and Japan [23]. A northern desert wind has also been reported from Chile [24]. Westerly winds were found to be associated with increased fungal particles in the atmosphere and increased incidence of KD over the Greater Toronto Area of Canada [25]. A hypothesis is that an airborne agent originating in central Asia may trigger KD. This putative trigger is blown to various geographical regions of the world in the troposphere, where found to have a high density of fungal spores, and by entering the upper respiratory tract results in KD. Data relating incidence to wind patterns from other regions of the world are still needed to confirm the relevance to KD.

Intra-Family Transmission

A strong association with infection was suggested in a household study from Taiwan. Around two-thirds of their KD cases had positive contact with ill household members prior to the disease onset and more than ninety percent of families had clusters of infectious illness [26]. A Japanese epidemiologic study found that in KD patients when the fertility rate was higher, the adjusted mean patient age was lower. It suggests that sibling-to-sibling transmission is likely [27]. Simultaneous or sequential cases in siblings, twins, or other contacts were reported in Japanese outbreaks, and twins occurred more frequently than non-twins siblings [28]. Nonetheless, when a new KD patient was diagnosed, only rare sequential KD patients occurred within their family in general [29]. Outside family like daycare setting, transmission isn't found. An explanation for the possibility is that an agent that generally causes an asymptomatic infection through close contact, but will only lead to KD in children with underlying genetic predisposition.

Recurrence

Recurrent KD occurs in about 1% or fewer in western countries, and in 2–4% of those of Asian ethnicity [15, 30, 31]. Patients with incomplete clinical KD signs, more serious initial presentation, and less than 3 years of age have higher recurrence rate [32–34]. The relatively low recurrence rate suggests that KD is more likely due to an infectious process rather than an autoimmune disease.

Cluster Phenomenon

Epidemics and clusters of KD have been noted in countries throughout the world [35–38]. Exposure to some environmental triggers, e.g., an infectious agent or by regional weather conditions, may be a factor. Though cluster may indicate an infectious illness, the phenomenon is not as significant as caused by a highly transmissible infectious agent. An unfound microorganism with mostly silent transmission but causing illness in children with specific genes is therefore postulated.

Laboratory Evidence

Pathological Discovery

Pathological study in KD patients found persistent inflammation in various organs such as

lung, spleen, salivary glands, and lymph nodes even 6–8 weeks after the acute phase [39]. A persistent infectious agent may be involved. KD antigen localized to homogeneous intracytoplasmic inclusion bodies was observed. It resembles inclusion bodies formed by viral protein and nucleic acid aggregates [40]. Upregulated interferon-stimulated genes in both KD lung and coronary artery tissues were identified [41]. All these provide additional support for the hypothesis of a viral etiology. An observation of single synthetic KD monoclonal antibody, derived from IgA plasma cell receptor sequences in KD arterial tissue, binding to ciliated bronchial epithelium in the majority of KD patients, suggests a specific etiologic agent and against the diverse etiologic agent hypothesis [42]. Unfortunately, no specific infectious cause can be confirmed by pathological method till now.

Bacterial Infections and Superantigens

Concomitant infections are common at diagnosis of KD. In a Canada's study, one-third of children with typical KD had one or more confirmed infections at the time of KD diagnosis [43]. In a Spain nationwide pediatric network study, around one-sixth children with KD had positive microbiological findings being found and in another one-sixth have a previous recent infection during the 4 weeks preceding KD diagnosis [44]. More than half of the identified organisms were bacteria. Whether these isolated microorganisms are true pathogens or only colonization, or even just coincident is uncertain.

KD has similar clinical features of fever, desquamation rash, and mucous membrane erythema to toxic shock syndrome (TSS) and streptococcal toxic shock syndrome (STSS). While major complication of KD is coronary artery involvement, hypotension is a central symptom of TSS and STSS. The three diseases are speculated to share a superantigen-mediated etiology [45]. Patients with both KD and TSS at the same time have been reported [46, 47]. A superantigen-mediated disease demonstrates a disproportionate number of T cells expressing T-cell receptor Vβ families that have been stimulated by the superantigen; a "skewed" T-cell receptor repertoire [48]. A skewed T-cell receptor repertoire may stimulate Vβ families T-cell receptor [49, 50]. Though some KD patients were found to have a skewed T-cell receptor repertoire but not all have Vβ change [51]. The reason might be that superantigens induced T-cell repertoire changes can only be detected in peripheral blood during a short period. Superantigen-secreting *S. aureus* in patients complicated by coronary artery disease was noted initially [52]. However, subsequent multicentre study in the United States and Japan did not find significant differences between KD patients and controls with regard to overall isolation rates of superantigen producing bacteria [53, 54]. A significantly higher IgM titer to multiple superantigens in patients with KD than controls has been demonstrated [55]. In contrast, some studies provided no evidence of the involvement of superantigens in KD [56, 57]. These incongruent findings suggest that KD may be a response to one or many of a variety of superantigens in genetically susceptible individuals.

Some other bacteria may have association with KD. Strong association with *Bordetella pertussis* was demonstrated by epidemiological data [58]. KD-specific serum possesses molecular structures similar to microbe-associated molecular patterns (MAMPs) from *Bacillus cereus*, *Bacillus subtilis*, *Yersinia pseudotuberculosis*, and *S. aureus*. KD-specific MAMPs may induce vascular inflammation, leading to the occurrence of KD [59]. Reactivation of Bacillus Calmette-Guérin (BCG) scar has been regarded as an important clinical manifestation in KD, suggesting that *Mycobacteria* might be involved in KD. Though BCG vaccination associated with KD has been reported [60], the relationship remains uncertain. Other association between KD and bacterial infections include *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* [61, 62]. The relationship between KD and bacterial infection remains controversial.

Viral Infections

Viruses are speculated as the most possible infectious agents that cause or trigger the illness of KD. A group of viruses or a single unrecognized virus may be the etiology. In a Taiwan's study, viruses were isolated in 7.5% and detected by polymerase chain reaction in 50.4% of KD patients. Various viruses were found to be significantly more in KD patients than in controls, including enterovirus, adenovirus, human rhinovirus, and coronavirus [63].

The cumulative incidence of KD was found to be significantly higher in the enterovirus-infected cohort than in the non-enterovirus-infected cohort by Taiwan National Health Insurance Research Database. A high association exists between KD and previous enterovirus infection in Taiwanese children according to the results [64]. Also from the same database, a significantly higher cumulative incidence of KD in the adenovirus-infected cohort than that in the control was found [65]. Detection of adenovirus by polymerase chain reaction in patients with suspected KD is not uncommon in one US study [66]. However, other investigation found no evidence to suggest a link between KD and adenovirus in Japan [67].

Epstein–Barr virus (EBV) is another suspected virus. EBV DNA sequence was detected in high ratio of KD patients [68]. Coronary artery involvement may be related to deoxyuridine 5′-triphosphate nucleotidohydrolase, an EBV-encoded protein; it stimulates monocyte-derived macrophages through Toll-like receptor 2-dependent signaling [69]. But in Japanese children, the EBV seropositivity rates were not significantly different between the less than 11 months old KD patients and controls. The rate in 1 to 6 years old children with KD was even significantly lower than those in corresponding age controls [70].

Several other viruses have been implicated as potential causes of KD, including parvovirus B19, herpesvirus type 6, influenza virus, parainfluenza type 3 virus, human immunodeficiency virus, measles, rotavirus, dengue virus, varicella, cytomegalovirus, etc. None of them has emerged to be a proved agent [71–79]. However, we still cannot deny the possibility of an unfound viral pathogen for KD.

A new human coronavirus (HCoV) NL-63 was found and suspected to have association with KD in 2005 [80]. Subsequent studies could not have similar correlation and it is clear now that the elusive etiologic agent of KD is not HCoV NL-63 [81–83]. During coronavirus disease 2019 (COVID-19) pandemic, finding of the Kawasaki-like manifestation patients let the linkage of KD and coronavirus become one important issue again [84].

SARS-CoV-2 Infection

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Compared with adults, it is less frequent in children, with a milder course [85]. However, an increase in the number of SARS-CoV-2 infected children presenting with a phenotype resembling KD was noted by scattered case reports and then observational cohort studies at Italy, United Kingdom, and France [86–89]. These KD-like patients suggest that SAR-CoV-2 could be a trigger for KD and indicate the potential timing of an increase in incidence of the disease in COVID-19 epidemics [90]. Though severe SARS-CoV-2 infected children may have similar clinical manifestations of KD, some differences exist. Multisystem inflammatory syndrome in children (MIS-C) named by the US Centers for Disease Control and Prevention and the World Health Organization, or pediatric multisystem inflammatory syndrome (PMIS) named by the National Health Service in United Kingdom are defined for critically COVID-19 infected children with overlapping features of toxic shock syndrome, atypical KD, and other severe clinical findings [91–93]. Overlapping portions with KD include rash, conjunctivitis, lymphadenopathy, extremity edema, fissured lips, and cardiac involvement. MIS-C/PMIS patients are different from KD or KD shock syndrome as older age of presentation, more profound form of inflammation, more gastrointestinal manifestation, higher propensity towards left ventricle dysfunction and

shock, and unalike laboratory findings including lymphopenia, thrombocytopenia, elevated troponin, elevated NT-proBNP, elevated D-dimer, and elevated ferritin [94]. The difference in race/ethnicity is also noted between KD and MIS-C/PMIS. MIS-C/PMIS seems to have less propensity towards children of east Asian and Pacific Islander descent, but is more common in Hispanic/Latino and black ethnic groups [95–97]. In Japan, the highest KD incidence country, there is no dramatic increase in KD incidence or changes in its clinical features observed during the local COVID-19 epidemic [98]. Italian survey found that SARS-CoV-2 infections might determine KD and MIS-C/PIMS as two distinct inflammatory diseases in children [99]. SARS-CoV-2 seems not the etiology of typical KD.

Conclusion

Infection must play an important role in KD, but it is not the whole story. From the available data, there isn't any pathogen identified as the single agent to cause KD. Several infectious microorganisms have been found to have an association with KD. How they work to proceeding to the clinical presentation of KD is not fully explained and/or proved. The most acceptable theory at present may be that one or several infectious agents may trigger a special immunological process in some genetic predisposing patients and lead to KD [100–102].

References

1. van Timmeren MM, Heeringa P, Kallenberg CG. Infectious triggers for vasculitis. Curr Opin Rheumatol. 2014;26:416–23.
2. Castillo-Martínez D, Amezcua-Guerra L. Self-reactivity against stress-induced cell molecules: the missing link between Takayasu's arteritis and tuberculosis? Med Hypotheses. 2012;78:485–8.
3. Cooper R, D'Arcy S, Kirby M, Al-Buhtori M, Rahman MJ, Proctor L, et al. Infection and temporal arteritis: a PCR-based study to detect pathogens in temporal artery biopsy specimens. J Med Virol. 2008;80:501–5.
4. Guillevin L, Mahr A, Callard P, Godmer P, Pagnoux C, Leray E, et al. Hepatitis B virus-associated polyarteritis nodosa: clinical characteristics, outcome, and impact of treatment in 115 patients. Medicine (Baltimore). 2005;84:313–22.
5. Saadoun D, Terrier B, Semoun O, Sene D, Maisonobe T, Musset L, et al. Hepatitis C virus-associated polyarteritis nodosa. Arthritis Care Res. 2011;63:427–35.
6. Lidar M, Lipschitz N, Langevitz P, Shoenfeld Y. The infectious etiology of vasculitis. Autoimmunity. 2009;42:432–8.
7. Mohan N, Kerr G. Infectious etiology of vasculitis: diagnosis and management. Curr Rheumatol Rep. 2003;5:136–41.
8. Kobayashi T, Ayusawa M, Suzuki H, Abe J, Ito S, Kato T, et al. Revision of diagnostic guidelines for Kawasaki disease (6th revised edition). Pediatr Int. 2020;62:1135–8.
9. Makino N, Nakamura Y, Yashiro M, Sano T, Ae R, Kosami K, et al. Epidemiological observations of Kawasaki disease in Japan, 2013-2014. Pediatr Int. 2018;60:581–7.
10. Liu WK, Liu Q, Chen DH, Tan WP, Cai Y, Qiu SY, et al. Epidemiology of HBoV1 infection and relationship with meteorological conditions in hospitalized pediatric patients with acute respiratory illness: a 7-year study in a subtropical region. BMC Infect Dis. 2018;18:329.
11. Panayiotou C, Richter J, Koliou M, Kalogirou N, Geroriou E, Chritodoulou C. Epidemiology of respiratory syncytial virus in children in Cyprus during three consecutive winter seasons (2010–2013): age distribution, seasonality and association between prevalent genotypes and disease severity. Epidemiol Infect. 2014;142:2406–11.
12. Chuang CY, Kao CL, Huang LM, Lu CY, Shao PL, Lee PI, et al. Human bocavirus as an important cause of respiratory tract infection in Taiwanese children. J Microbiol Immunol Infect. 2011;44:323–7.
13. Lee KY, Han JW, Lee JS. Kawasaki disease may be a hyperimmune reaction of genetically susceptible children to variants of normal environmental flora. Med Hypotheses. 2007;69:642–51.
14. Huang YH, Lin KM, Ho SC, Yan JH, Lo MH, Kuo HC. Increased incidence of Kawasaki disease in Taiwan in recent years: a 15 years nationwide population-based cohort study. Front Pediatr. 2019;7:121.
15. Huang WC, Huang LM, Chang IS, Chang LY, Chiang BL, Chen PJ, et al. Epidemiologic features of Kawasaki disease in Taiwan, 2003–2006. Pediatrics. 2009;123:e401–5.
16. Makino N, Nakamura Y, Yashiro M, Ae R, Tsuboi S, Aoyama Y, et al. Descriptive epidemiology of Kawasaki disease in Japan, 2011–2012: from the results of the 22nd nationwide survey. J Epidemiol. 2015;25:239–45.
17. Ae R, Makino N, Kosami K, Kuwabara M, Matsubara Y, Nakamura Y. Epidemiology, treatments, and cardiac complications in patients with Kawasaki disease: the nationwide survey in Japan, 2017–2018. J Pediatr. 2020t;225:23–29.e2.

18. Kim GB, Eun LY, Han JW, Kim SH, Yoon KL, Han MY, et al. Epidemiology of Kawasaki disease in South Korea: a Nationwide survey 2015–2017. Pediatr Infect Dis J. 2020;39:1012–6.
19. Uehara R, Belay ED. Epidemiology of Kawasaki disease in Asia, Europe, and the United States. J Epidemiol. 2012;22:79–85.
20. Piao JH, Jin LH, Lv J, Zhou Y, Jin CJ, Jin ZY. Epidemiological investigation of Kawasaki disease in Jilin province of China from 2000 to 2008. Cardiol Young. 2010;20:426–32.
21. Saundankar J, Yim D, Itotoh B, Payne R, Maslin K, Jape G, et al. The epidemiology and clinical features of Kawasaki disease in Australia. Pediatrics. 2014;133:e1009–e14.
22. Burns JC, Herzog L, Fabri O, Tremoulet AH, Rodó X, Uehara R, et al. Kawasaki disease global climate consortium. Seasonality of Kawasaki disease: a global perspective. PLoS One. 2013;8:e74529.
23. Rodo X, Curcoll R, Robinson M, Ballester J, Burns JC, Cayan DR, et al. Tropospheric winds from northeastern China carry the etiologic agent of Kawasaki disease from its source to Japan. Proc Natl Acad Sci U S A. 2014;111:7952–7.
24. Jorquera H, Borzutsky A, Hoyos-Bachiloglu R, García A. Association of Kawasaki disease with tropospheric winds in Central Chile: is wind-borne desert dust a risk factor? Environ Int. 2015;78:32–8.
25. Manlhiot C, Mueller B, O'Shea S, Majeed H, Bernknopf B, Labelle M, et al. Environmental epidemiology of Kawasaki disease: linking disease etiology, pathogenesis and global distribution. PLoS One. 2018;13:e0191087.
26. Tsai HC, Chang LY, Lu CY, Shao PL, Fan TY, Cheng AL, et al. Transmission of acute infectious illness among cases of Kawasaki disease and their house members. J Formos Med Assoc. 2015;114:72–6.
27. Nagao Y, Urabe C, Nakamura H, Hatano N. Predicting the characteristics of the aetiological agent for Kawasaki disease from other paediatric infectious diseases in Japan. Epidemiol Infect. 2016;144:478–92.
28. Kottek A, Shimizu C, Burns JC. Kawasaki disease in monozygotic twins. Pediatr Infect Dis J. 2011;30:1114–6.
29. Fujita Y, Nakamura Y, Sakata K, Hara N, Kobayashi M, Nagai M, et al. Kawasaki disease in families. Pediatrics. 1989;84:666–9.
30. Nakamura Y, Yanagawa H. A case-control study of recurrent Kawasaki disease using the database of the nationwide surveys in Japan. Eur J Pediatr. 1996;155:303–7.
31. Belay ED, Maddox RA, Holman RC, Curns AT, Ballah K, Schonberger LB. Kawasaki syndrome and risk factors for coronary artery abnormalities, United States, 1994–2003. Pediatr Infect Dis J. 2006;25:245–9.
32. Nakada T. Clinical features of patients with recurrent Kawasaki disease. Nippon Rinsho. 2008;66:296–300.
33. Zou LX, Gong FQ. Clinical features of recurrent Kawasaki disease in 20 children. Zhongguo Dang Dai Er Ke Za Zhi. 2008;10:617–9.
34. Maddox RA, Holman RC, Uehara R, Callinan LS, Guest JL, Schonberger LB, et al. Recurrent Kawasaki disease, United States and Japan. Pediatr Int. 2015;57:1116–20.
35. Rypdal M, Rypdal V, Burney JA, Cayan D, Bainto E, Skochko S, et al. Clustering and climate associations of Kawasaki Disease in San Diego County suggest environmental triggers. Sci Rep. 2018;8:16140.
36. Burns JC, DeHaan LL, Shimizu C, Bainto EV, Tremoulet AH, Cayan DR, et al. Temporal clusters of Kawasaki disease cases share distinct phenotypes that suggest response to diverse triggers. J Pediatr. 2021;229:48–53.e1.
37. Hearn J, McCrindle BW, Mueller B, O'Shea S, Bernknopf B, Labelle M, et al. Spatiotemporal clustering of cases of Kawasaki disease and associated coronary artery aneurysms in Canada. Sci Rep. 2018;8:17682.
38. Nakamura Y, Yanagawa I, Kawasaki T. Temporal and geographical clustering of Kawasaki disease in Japan. Prog Clin Biol Res. 1987;250:19–32.
39. Amano S, Hazama F, Kubagawa H, Tasaka K, Haebara H, Hamashima Y. General pathology of Kawasaki disease. On the morphological alterations corresponding to the clinical manifestations. Acta Pathol Jpn. 1980;30:681–94.
40. Rowley AH, Baker SC, Shulman ST, Fox LM, Takahashi K, Garcia FL, et al. Cytoplasmic inclusion bodies are detected by synthetic antibody in ciliated bronchial epithelium during acute Kawasaki disease. J Infect Dis. 2005;92:1757–66.
41. Rowley AH. Is Kawasaki disease an infectious disorder? Int J Rheum Dis. 2018;21:20–5.
42. Rowley AH, Baker SC, Shulman ST, Garcia FL, Guzman-Cottrill JA, Chou P, et al. Detection of antigen in bronchial epithelium and macrophages in acute Kawasaki disease by use of synthetic antibody. J Infect Dis. 2004;90:856–65.
43. Benseler SM, McCrindle BW, Silverman ED, Tyrrell PN, Wong J, Yeung RS. Infections and Kawasaki disease: implications for coronary artery outcome. Pediatrics. 2005;116:e760–6.
44. Fernández-Cooke E, Tascón AB, Antón-López J, Grasa Lozano CD, Sánchez-Manubens J, Calvo C. Working Group for the Study of Kawasaki disease (KAWA-RACE). Previous or coincident infections with suspected Kawasaki disease. Should we change our approach? An Pediatr. 2019;90:213–8.
45. Matsubara K, Fukaya T. The role of superantigens of group a *streptococcus* and *Staphylococcus aureus* in Kawasaki disease. Curr Opin Infect Dis. 2007;20:298–303.
46. Anderson DG, Warner G, Barlow E. Kawasaki disease associated with streptococcal infection within a family. J Paediatr Child Health. 1995;31:355–7.
47. Daves HD, Kirk V, Jadavji T, Kotzin BL. Simultaneous presentation of Kawasaki disease

and toxic shock syndrome in an adolescent male. Pediatr Infect Dis J. 1996;15:1136–8.
48. Abe J, Kotzin BL, Jujo K, Melish ME, Glode MP, Kohsaka T, et al. Selective expansion of T cells expressing T-cell receptor variable regions V beta 2 and V beta 8 in Kawasaki disease. Proc Natl Acad Sci U S A. 1992;89:4066–70.
49. Brogan PA, Shah V, Clarke LA, Dillon MJ, Klein N. T cell activation profiles in Kawasaki syndrome. Clin Exp Immunol. 2008;151:267–74.
50. Yoshioka T, Matsutani T, Iwagami S, Toyosaki-Maeda T, Yutsudo T, Tsuruta Y, et al. Polyclonal expansion of TCRBV2-and TCRBV6-bearing T cells in patients with Kawasaki disease. Immunology. 1999;96:465–72.
51. Pietra BA, De Inocencio J, Giannini EH, Hirsch R. TCR Vβ family repertoire and T cell activation markers in Kawasaki disease. J Immunol. 1994;153:1881–8.
52. Leung DY, Sullivan KE, Brown-Whitehorn TF, Fehringer AP, Allen S, Finkel TH, et al. Association of toxic shock syndrome toxin-secreting and exofoliative toxin-secreting *staphylococcal aureus* with Kawasaki syndrome complicated by coronary artery disease. Pediatr Res. 1997;42:268–72.
53. Leung DY, Meissner HC, Shulman ST, Mason WH, Gerber MA, Glode MP, et al. Prevalence of superantigen secreting bacteria in patients with Kawasaki disease. J Pediatr. 2002;140:742–6.
54. Horita N, Yokota S, Fuse S, Takamuro M, Tomita H, Sato K, et al. The throat flora and its mitogenic activity in patients with Kawasaki disease. Microbiol Immunol. 2004;48:899–903.
55. Matsubara K, Fukaya T, Miwa K, Shibayama N, Nigami H, Harigaya H, et al. Development of serum IgM antibodies against superantigens of *Staphylococcus aureus* and *streptococcus pyogenes* in Kawasaki disease. Clin Exp Immunol. 2006;143:427–34.
56. Terai M, Miwa K, Williams T, Kabat W, Fukuyama M, Okajima Y, et al. The absence of evidence of staphylococcal toxin involvement in the pathogenesis of Kawasaki disease. J Infect Dis. 1995;172:558–61.
57. Morita A, Imada Y, Igarashi H, Yutsudo T. Serologic evidence that streptococcal superantigens are not involved in the pathogenesis of Kawasaki disease. Microbiol Immunol. 1997;41:895–900.
58. Pellegrino P, Carnovale C, Perrone V, Salvati D, Gentili M, Brusadelli T, et al. Kawasaki disease and pertussis epidemics. Epidemiology. 2014;25:310–1.
59. Kusuda T, Nakashima Y, Murata K, Kanno S, Nishio H, et al. Kawasaki disease-specific molecules in the sera are linked to microbe-associated molecular patterns in the biofilms. PLoS One. 2014;9:e113054.
60. Yamada H, Ohta H, Hasegawa S, Azuma Y, Hasegawa M, Kadoya R, et al. Two infants with tuberculid associated with Kawasaki disease. Hum Vaccin Immunother. 2016;12:2772–6.
61. Wang JN, Wang SM, Liu CC, Wu JM. *Mycoplasma pneumoniae* infection associated with Kawasaki disease. Acta Paediatr. 2001;90:594–5.
62. Normann E, Naas J, Gnarpe J, Backman H, Gnarpe H. Demonstration of *chlamydia pneumoniae* in cardiovascular tissues from children with Kawasaki disease. Pediatr Infect Dis J. 1999;18:72–3.
63. Chang LY, Lu CY, Shao PL, Lee PI, Lin MT, Fan TY, et al. Viral infections associated with Kawasaki disease. J Formos Med Assoc. 2014;113:148–54.
64. Weng KP, Wei JC, Hung YM, Huang SH, Chien KJ, Lin CC, et al. Enterovirus infection and subsequent risk of Kawasaki disease: a population-based cohort study. Pediatr Infect Dis J. 2018;81:170–7.
65. Huang SH, Chen CY, Weng KP, Chien KJ, Hung YM, Hsieh KS, et al. Adenovirus infection and subsequent risk of Kawasaki disease: a population-based cohort study. J Chin Med Assoc. 2020;83:302–6.
66. Jaggi P, Kajon AE, Mejias A, Ramilo O, Leber A. Human adenovirus infection in Kawasaki disease: a confounding bystander? Clin Infect Dis. 2013;56:58–64.
67. Shike H, Shimizu C, Kanegaye JT, Foley JL, Schnurr DP, Wold LJ, et al. Adenovirus, adeno-associated virus and Kawasaki disease. Pediatr Infect Dis J. 2005;24:1011–4.
68. Kikuta H, Matsumoto S, Yanase Y, Kawasaki T, Mizuno F, Osato T. Recurrence of Kawasaki disease and Epstein-Barr virus infection. J Infect Dis. 1990;162:1215.
69. Ariza ME, Glaser R, Kaumaya PT, Jones C, Williams MV. The EBV-encoded dUTPase activates NF-kappa B through the TLR2 and MyD88-dependent signaling pathway. J Immunol. 2009;182:851–9.
70. Fuse S, Fujinaga E, Mori T, Hotsubo T, Kuroiwa Y, Morii M. Children with Kawasaki disease are not infected with Epstein-Barr virus. Pediatr Infect Dis J. 2010;29:286–7.
71. Holm JM, Hansen LK, Oxhoj H. Kawasaki disease associated with parvovirus B19 infection. Eur J Pediatr. 1995;154:633–4.
72. Hagiwara K, Komura H, Kishi F, Kaji T, Yoshida T. Isolation of human herpesvirus-6 from an infant with Kawasaki disease. Eur J Pediatr. 1992;151:867–8.
73. Banday AZ, Arul A, Vignesh P, Singh MP, Goyal K, Singh S. Kawasaki disease and influenza-new lessons from old associations. Clin Rheumatol. 2021;2:1–9.
74. Johnson D, Azimi P. Kawasaki disease associated with *Klebsiella pneumoniae* bacteremia and parainfluenza type 3 virus infection. Pediatr Infect Dis J. 1985;4:100–3.
75. Muniain-Ezcurra M, Bueno-Mariscal C, Rodriguez-Bano J, Domínguez-Castellano A, Balonga-Tomás B, Ríos-Villegas MJ, et al. Kawasaki disease and parvovirus B19 infection in an adult HIV-1-infected patient. Clin Microbiol Infect. 1998;4:609–10.
76. Kuijpers TW, Herweijer TJ, Scholvinck L, Wertheim-Van Dillen PM, Van De Veer EM. Kawasaki disease

associated with measles virus infection in a monozygotic twin. Pediatr Infect Dis J. 2000;19:350–3.
77. Matsuno S, Utagawa E, Sugiura A. Association of rotavirus infection with Kawasaki syndrome. J Infect Dis. 1983;148:177.
78. Sopontammarak S, Pruekprasert P. Concomitant dengue hemorrhagic fever with Kawasaki disease. Southeast Asian J Trop Med Public Health. 2000;31:190–2.
79. Lee DH, Huang HP. Kawasaki disease associated with chickenpox: report of two sibling cases. Acta Paediatr Taiwan. 2004;45:94–6.
80. Esper F, Shapiro ED, Weibel C, Ferguson D, Landry ML, Kahn JS. Association between a novel human coronavirus and Kawasaki disease. J Infect Dis. 2005;191:499–502.
81. Ebihara T, Endo R, Ma X, Ishiguro N, Kikuta H. Lack of association between New Haven coronavirus and Kawasaki disease. J Infect Dis. 2005;192:351–2.
82. Shimizu C, Shike H, Baker SC, Garcia F, van der Hoek L, Kuijpers TW, et al. Human coronavirus NL63 is not detected in the respiratory tracts of children with acute Kawasaki disease. J Infect Dis. 2005;192:1767–71.
83. Dominguez SR, Anderson MS, Glodé MP, Robinson CC, Holmes KV. Blinded case-control study of the relationship between human coronavirus NL63 and Kawasaki disease. J Infect Dis. 2006;194:1697–701.
84. Lai CC. Another compelling evidence suggesting infectious diseases as the cause of Kawasaki disease? J Chin Med Assoc. 2020;83:801–2.
85. Laws RL, Chancey RJ, Rabold EM, Chu VT, Lewis NM, Fajans M, et al. Symptoms and transmission of SARS-CoV-2 among children: Utah and Wisconsin, March-May 2020. Pediatrics. 2021;147:e2020027268.
86. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet. 2020;395:1771–8.
87. Jones VG, Mills M, Suarez D, Hogan CA, Yeh D, Segal JB, et al. COVID-19 and Kawasaki disease: novel virus and novel case. Hosp Pediatr. 2020;10:537–40.
88. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet. 2020;395:1607–8.
89. Toubiana J, Poirault C, Corsia A, Bajolle F, Fourgeaud J, Angoulvant F, et al. Kawasaki-like multisystem inflammatory syndrome in children during the COVID-19 pandemic in Paris, France: prospective observational study. BMJ. 2020;369:m2094.
90. Ouldali N, Pouletty M, Mariani P, Beyler C, Blachier A, Bonacorsi S, et al. Emergence of Kawasaki disease related to SARS-CoV-2 infection in an epicentre of the French COVID-19 epidemic: a time-series analysis. Lancet Child Adolesc Health. 2020;4:662–8.
91. Royal College of Paediatrics and Child Health. Guidance paediatric multisystem inflammatory syndrome temporally associated with Cov-19. 2020. https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19
92. Centers for Disease Control and Prevention. Multisystem inflammatory syndrome in children (MIS-C) 2020. https://www.cdc.gov/mis-c/
93. World Health Organization. Multisystem inflammatory syndrome in children and adolescents with COVID-19. 2020. https://www.who.int/publications/i/item/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19
94. Loke YH, Berul CI, Harahsheh AS. Multisystem inflammatory syndrome in children: Is there a linkage to Kawasaki disease? Trends Cardiovasc Med. 2020;30:389–96.
95. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA. 2020;324:259–69.
96. Centers for Disease Control and Prevention. Multisystem inflammatory syndrome in children (MIS-C) health department-reported cases of multisystem inflammatory syndrome in children (MIS-C) in the United States. 2021. https://www.cdc.gov/mis-c/cases/index.html.
97. Broad J, Forman J, Brighouse J, Sobande A, McIntosh A, Watterson C, et al. Post-COVID-19 paediatric inflammatory multisystem syndrome: association of ethnicity, key worker and socioeconomic status with risk and severity. Arch Dis Child. 2021;106:1–8. https://doi.org/10.1136/archdischild-2020-320388.
98. Lio K, Uda K, Hatay H, Yasui F, Honda T, Sanada T, et al. Kawasaki disease or Kawasaki-like disease: influence of SARS-CoV-2 infections in Japan. Acta Paediatr. 2021;110:600–1.
99. Cattalini M, Della Paolera S, Zunica F, Bracaglia C, Giangreco M, Verdoni L, et al. Defining Kawasaki disease and pediatric inflammatory multisystem syndrome- temporally associated to SARS-CoV-2 infection during SARS-CoV-2 epidemic in Italy: results from a national, multicenter survey. Pediatr Rheumatol Online J. 2021;19:29.
100. Wang CL, Wu YT, Liu CA, Kuo HC, Yang KD. Kawasaki disease: infection, immunity and genetics. Pediatr Infect Dis J. 2005;24:998–1004.
101. Nakamura A, Ikeda K, Hamaoka K. Aetiological significance of infectious stimuli in Kawasaki disease. Front Pediatr. 2019;7:244.
102. Huang SM, Huang SH, Weng KP, Chien KJ, Lin CC, Huang YF. Update on association between Kawasaki disease and infection. J Chin Med Assoc. 2019;82:172–4.

Kawasaki Disease Shock Syndrome and Mild KD

I-Hsin Tai and Yun-Ching Fu

Abstract

Kawasaki disease shock syndrome (KDSS), although rare, represents the most severe form of Kawasaki disease on the spectrum and is often correlated with profound cardiovascular sequelae. In this chapter, we describe the incidence, pathophysiology, clinical presentation, and diagnostic clues of KDSS and compare it with other types of shock that share similar clinical profiles as well as with hemodynamically stable Kawasaki disease (also called "mild KD"). We also highlight the importance of early therapeutic strategy as this results in better clinical outcomes and lower mortality rates.

Keywords

Kawasaki disease shock syndrome · Coronary aneurysm · IVIG-resistant · Early goal strategy

Introduction

Among children with Kawasaki disease (KD), a very small group of patients develop hemodynamic instability, which requires the utilization of volume expanders or inotropic agents. In 1994, Senzaki et al. reported KD complicated with acute myocarditis and pre-renal azotemia in two patients, respectively [1]. These cases provided an important insight into the development of ventricular dysfunction and intravascular fluid depletion in extremely severe cases of KD. In 2009, Kanegaye et al. introduced the term "Kawasaki disease shock syndrome" (KDSS) to distinguish this form of KD from hemodynamically normal KD. KDSS has an even higher possibility of developing intravenous immunoglobulin (IVIG) resistance or coronary artery aneurysms [2, 3]. It also appears that Hispanic people have higher incidence rates of KDSS than Asians or Caucasians [3].

Definition of KDSS

In the presence of KD, including the complete or incomplete type, any of the following conditions is an indication to initiate volume expansion, administer vasoactive agents, or transfer to an intensive care unit: systolic hypotension for age (infants 0–28 days of age, <60 mm Hg; infants 1–12 months of age, <70 mm Hg; children 1–10 years of age, <70 + [2 × age] mm Hg; youth >10 years of age, <90 mm Hg), a decrease in systolic blood pressure from baseline by >20%, or physical signs of poor end-organ perfusion (tachycardia, prolonged capillary filling time,

I.-H. Tai
China Medical University Children's Hospital, Taichung, Taiwan

Y.-C. Fu (✉)
Taichung Veterans General Hospital, Taichung, Taiwan

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cool limbs, diminished or bounding pulses, oliguria, or changes in consciousness not accounted for by other conditions), regardless of the measured blood pressure. Patients who fulfill the above criteria are considered to have KDSS.

Interracial Incidence

According to a study in Taiwan, which investigated the largest Asian cohort since 2013, the incidence of KDSS was **1.45** per 100 KD patients [4], with most cases occurring in winter. Maddox et al. reported the estimated prevalence and incidence of KD and KDSS in the United States using the Kids' inpatient database, national inpatient sample, IBM MarketScan, etc. From 2016 to 2018, the KD-associated hospitalization rates for children <5 years of age were 19.8 (2016), 19.6 (2017), and 19.3 (2018) per 100,000 [5]. There was no indication of an increase in the KD rate over time. However, rates of potential KDSS among children <18 years of age, ranging from 0 to 0.7 per 100,000, demonstrated an increase; coding indicated potential KDSS among approximately **2.8–5.3%** of KD hospitalizations. Furthermore, Gámez-González et al. suggested **that 5%** [6, 7] of Hispanic KD patients met the definition of KDSS.

Etiology (Shock Mechanism)

The underlying etiology and pathogenesis of KDSS are multifactorial and can be cardiogenic (hypokinesia or valvular insufficiency) or distributive, with capillary leakage [8] and cytokine dysregulation.

Cardiogenic Shock Component (Hypokinesia)

Takahashi and Matsuura observed positive cardiac uptake of gallium-67 in 60–80% of patients with KD [9, 10]. Positive gallium uptake by the myocardium is generally believed to be mediated by the infiltration of leukocytes. Evidence derived from numerous biopsies supports the fact that KD is characterized by medium-sized arteritis and varied degrees of myocarditis [10, 11]. Because myocarditis in most KD patients is very mild, the subjects' hemodynamic status remains stable. It is worth noting that similar cardiogenic shock has been reported in Kawasaki-like illness caused by COVID-19 [12], which should be treated seriously.

Cardiogenic Shock Component (Valvular Insufficiency)

Valvular insufficiency has been considered a standard parameter, which should be routinely evaluated via transthoracic echocardiography in children with acute Kawasaki disease (KD). There is a wide variation [13–19] in the information on the prevalence of valvular regurgitation after "mild KD," depending on the time between KD onset and evaluation, and the evaluation modalities used. Moreover, a study by Akagi et al. reported a cohort comprising 65 patients with KD (2 months–6 years) and 113 age-matched normal controls; the cohort showed a similar percentage of subjects presenting with background valvular insufficiency, indicating that there was an overestimation of the population-sizes of valvular insufficiency, since some investigations may treat physiological mitral regurgitation as new-onset pathological symptom after KD [16].

In mild KD, the presence of valvulitis, myocarditis, or left ventricular dilatation leading to mitral regurgitation in the acute stage may spontaneously improve in the convalescent stage.

With increasing inflammation severity, damaging effects on the endocardium and myocardium also increased. In acute [13, 20] or convalescent [21] stage of KD, rupture of the mitral chordae tendineae may occur due to ischemia of the ventricular posterior wall, and progress to severe mitral regurgitation, also known as free mitral regurgitation. The high degree of valvular dysfunction in KD, whether mitral or aortic regurgitation, may also compromise the left ventricular function and give rise to shock status [21, 22].

More severe mitral regurgitation is indicative of poor prognosis in KD, such as coronary aneurysm formation [19].

Distributive Shock Component

Increased vascular permeability in the acute phase is a hallmark of KD, contributing to the hand and foot edema seen in this disease. This increased vascular permeability is also a factor in the development of KDSS. In a recent cohort study in Mexico, all children with KDSS developed hypoalbuminemia [6], which caused subsequent pleural effusion, pericardial effusion, and ascites. In extremely critical circumstances, retropharyngeal edema [23] and tamponade [24] may lead to mortality. As previously stated, hypoalbuminemia is an independent predictive factor of IVIG resistance [25]. This association may partially explain the high comorbidity of KDSS and IVIG-resistant KD.

Clinical Manifestations (Database Limitation Is Addressed in the End of the Section)

KDSS may present as the complete or incomplete type of the disease before the onset of shock, although the incomplete type [26] of KD seems to be more common according to studies performed in different races [7, 27]. Whether this type is correlated with a more severe form of KD, such as KDSS, because of delayed diagnosis and subsequent IVIG administration, requires further investigation.

A total of 103 subjects from 42 retrospective studies or case reports of children with KDSS were reviewed and summarized by Gamez-Gonzalez et al [6]. Cardiovascular complications were summarized for all 103 patients, while non-cardiovascular organ failure symptoms resulting from KDSS-related poor perfusion were collected from 63 patients as follows:

Cardiovascular manifestations of KDSS (Fig. 1) patients included transient coronary dilatation in 72.5% (75/103), coronary artery aneurysm in 65% (67/103), left ventricular dysfunction, which was defined as an ejection fraction <50% via transthoracic echocardiography, in 44.6% (46/103), and new-onset atrioventricular regurgitation in 27.2% (28/103) patients; the most common was mitral regurgitation (13.6%). Pericardial effusion was present in 20.4% (21/103) of the patients, and giant coronary aneurysms occurred in 4.8% (5/103) of KDSS patients. Three patients experienced ischemic heart attacks during the acute phase of KDSS.

Non-cardiovascular manifestations of KDSS (summarized in Fig. 2) included neurologic alterations in 53.9% patients; the most common were aseptic meningitis, encephalopathy, and obnubilation. Pulmonary symptoms were present in

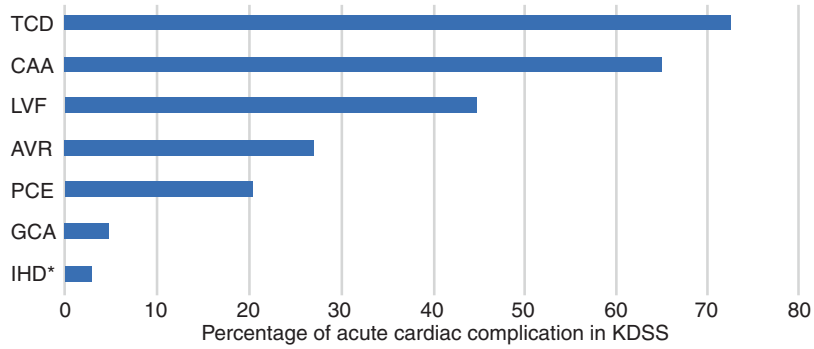

Fig. 1 #Modified and summarized from Gamez-Gonzalez et al. [6]. TCD denotes transient coronary dilation; CAA, coronary artery aneurysm; LVF, left ventricular failure; AVR, acquired valvular regurgitation; PCE, pericardial effusion; GCA, giant coronary aneurysm; IHD, ischemia heart disease. *All the cardiac complication be approached by transthoracic echocardiography except for IHD, which was revealed by electrocardiogram

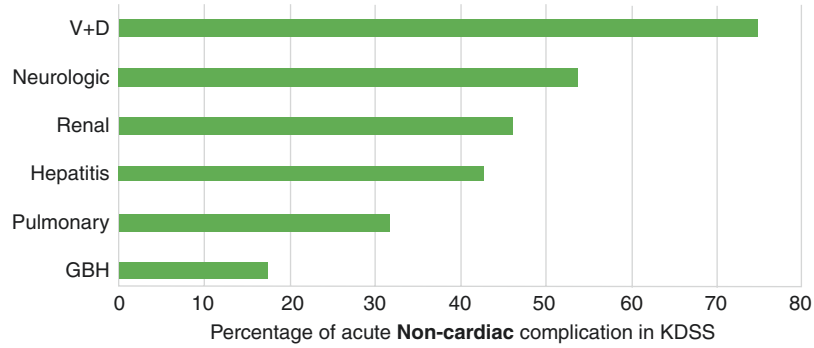

Fig. 2 #Modified and summarized from Gamez-Gonzalez et al. [5]. V + D denotes vomiting and diarrhea; GBH, gallbladder hydrops

31.7% (20/63) of the patients; the most common symptoms were pleural effusion and pneumonia [28]. Renal involvement was present in 46% of the patients. Although acute renal failure was the most common presentation, there were also two case reports regarding KDSS-related proteinuria, and one of renal insufficiency requiring dialysis. KDSS can have common gastrointestinal symptoms including vomiting, diarrhea, hepatitis, and gallbladder hydrops given the nature of vascular inflammation. KDSS can also present with severe manifestations, such as upper gastrointestinal bleeds and bowel perforation presenting as coffee ground vomitus or tarry stool [7].

Hypoalbuminemia is an independent predictive factor of IVIG resistance. In one case series composed of 12 KDSS patients [6], all of the subjects had hypoalbuminemia and consequent pleural effusion, pericardial effusion, and ascites. Retropharyngeal edema and tamponade have also been reported in KDSS patients. Additionally, an indirect relationship between the severity of edema and the development of coronary aneurysms has been reported [25].

IVIG Non-Responders: Children with KDSS have been reported to be more susceptible to IVIG nonresponse. In a Hispanic cohort study conducted in 2013 (including 214 KD patients and 11 KDSS patients), Gamez-Gonzalez et al. reported that the IVIG-resistance rate was 60% among KDSS patients. Later in 2015, Chen et al. from Mackay Memorial Hospital, Taiwan, revealed that KDSS resembles severe vasculitis, and 22.2% of the patients need a second IVIG infusion.

Database Limitation

Appropriate sample size is crucial to the research investigation and associated with higher reliability. Therefore, the investigation has value compared with previous case reports despite of a few limitations such as the retrospective analysis led to limited or absent clinical and laboratory data for some KDSS patients; the possibility of population bias, in which patients with shock are not considered to have KD until coronary abnormalities are identified. Multicenter, well-designed studies have been undertaken to reflect the complete spectrum of KDSS.

Conditions that Mimic Kawasaki Disease Shock Syndrome

Toxic Shock Syndrome

Despite the fact that KDSS and nonmenstrual toxic shock syndrome (TSS) share similar clinical features as well as disease course timelines and often cause confusion in clinical practice, it is not difficult to make a correct diagnosis. Early differentiation of KDSS from TSS is mandatory because these two shock syndromes require different treatment strategies. Lin and colleagues at Kaohsiung Chang Gung Memorial Hospital analyzed the demographic, echocardiographic imaging, and laboratory test results of dozens of children with KDSS or TSS who were admitted to the pediatric intensive care unit (Table 1). The results showed that KDSS was more common

Table 1 Demographic, Echocardiography, Laboratory of KDSS & TSS groups[#]

Variables	KDSS (n = 17)	TSS (n = 16)	P value
Demographic, Mean ± SD			
Age, months	36.8 ± 41.1	113.3 ± 55.6	<0.001
Fluid challenge, mL/kg	10.9 ± 18.3	29.7 ± 32.6	0.048
Maximal dopamine dose, μg/kg/min	7.3 ± 5.5	12.3 ± 7.5	0.035
Mortality, n(%)	0(0)	2(13)	NS
Echocardiography, n(%)			
Valvulitis[*]	9 (52.9)	0 (0)	0.022
LV dysfunction	6 (35.3)	1 (14.3)	NS
PE	2 (11.8)	0 (0)	NS
CAA	9 (52.9)	0 (0)	0.022
Laboratory, median (range)			
WBC, 10^3/μL	14.6 (0.5–20.6)	17.3 (0.45–39.2)	NS
Hemoglobin, g/dL	10 (7.9–13.8)	13.7 (8.3–18.4)	<0.001
Platelet, 10^3/μL	312 (116–518)	184.5 (31–629)	0.021
CRP, mg/L	164.8 (70–352.2)	135 (0.3–367.1)	NS
ESR, mm/h	55 (21–127)	72 (23–111)	NS
Creatinine, mg/dL	0.45 (0.3–1.8)	1.53 (0.5–3.89)	0.001
Albumin	2.45 (1.6–3.0)	2.6 (1.7–3.1)	NS

[#] Modified and summarized from Tables by Lin et al. [29]
* Valvulitis was defined by a cut-off grade above "moderate" for tricuspid regurgitation and "mild" for mitral regurgitation, or any degree of aortic valve regurgitation. CAA denotes coronary artery aneurysms

Table 2 Severity comparison between KDSS & septic shock, presenting as median value[#]

	KDSS (N = 9)	Septic shock (N = 18)	P value
Duration of illness pre-admission, days	9	3	**0.004**
Length of hospital stay, days	9	28	**<0.001**
Fluid resuscitation (first aid), mL/kg	60	63	0.27
Duration of inotropic, hour	40	26	0.76
platelet counts, 10^9/L	140	258	**0.02**
INR	1.3	1.4	1.00

[#] Modified and summarized from Tables by McCrindle et al. [30]

among younger children (mean age 36.8-month-old) than TSS. TSS appeared to be more progressive and caused renal failure more often than KDSS. Hence, additional fluid challenge and higher target dopamine doses are required when making an early treatment plan for TSS. Left ventricular (LV) dysfunction leads to cardiogenic shock in KDSS, but not in TSS. Moreover, coronary artery aneurysm formation has a definite value in identifying KDSS.

Septic Shock

The clinical profile and illness severity comparison (Table 2) between patients with KDSS and septic shock were first described in 2020 by McCrindle et al. Children with KDSS had a longer duration of illness pre-admission than septic shock patients [(9 (7,14) days vs. 3 (1,5) days; p = 0.004]. Children with KDSS had a shorter duration of hospital stay than septic

shock patients [9 (6,14) days vs. 28 (15,37) days; $p < 0.001$]. There was no significant difference in the median fluid resuscitation volume before ICU admission between KDSS and septic shock patients [60 (40,80) vs. 63 (60,110), $p = 0.27$]. Moreover, there was no significant difference in the inotropic therapy duration between KDSS and septic shock patients [40 (20,44) h vs. 26 (7,59) h; $p = 0.76$].

Adverse Effect of IVIG

There is concern regarding co-administration of IVIG and sedatives.

Although IVIG infusions are usually well tolerated, adverse reactions can include hypotension, chills, and, rarely, anaphylactic reactions. The risk of adverse reactions is correlated with the dose and rate of IVIG infusion. An echocardiogram is the preferred imaging modality to detect coronary artery changes in acute KD; however, the quality of the images can be compromised in case of an irritable crying child. Thus, sedation is often required prior to an echocardiogram in children younger than 3 years of age. According to the study by Nguyen et al. [31] from Rady Children's Hospital, all infusion reactions occurred within 4 h of starting IVIG. No hypotension reactions occurred after 4 h. Thus, these authors propose that it is safe to co-administer IVIG with sedatives at least 4 h after initiation of IVIG infusion.

Treatment

Principle: Early recognition and treatment is mandatory for better prognosis despite the etiologies of shock itself!! The treatment of KDSS is combination of high-dose IVIG along with a standard regimen for cardiogenic/distributive shock (inotropic agents, vasoactive agents, volume resuscitation if not contraindicated) which should be initiated as soon as possible due to the presence of poor perfusion. Furthermore, considering that IVIG resistance is not uncommon in KDSS patients, early aggressive adjunctive therapy should be considered with first time IVIG if high-risk IVIG resistance is identified through specific predictive models (Table 3) as appropriate [32–36]. Although corticosteroid is usually the first choice, anti-TNF-α monoclonal antibody or TNF-α inhibitor should be considered before staphylococcal and streptococcal toxin-mediated diseases can be excluded. The role of empirical antibiotics in KDSS treatment remains crucial because the frequency of microorganism isolation from KDSS patients was 8.7%. Based on the numerous case reports reviewed [6], vasoactive agents are required in 66.9% (69/103) of the patients. However, it is worth noting that not

Table 3 Predictive score for IVIG resistance or coronary artery aneurysm

Score	Kobayashi [16]	Egami [17]	Sano [19]	Formosa [20]	PNI [18]
Cohort	Japan	Japan	Japan	Taiwan	Taiwan
Aim	IVIG-R	IVIG-R	IVIG-R	IVIG-R	IVIG-R, CAA
Year	2006.06	2006.03	2007.03	2015.03	2020.04
Development	546	320	112	181	275
Validation	204	0	0	67	0
Variables	7	5	3	3	2
Statistics	Sen 86	Sen 78	Sen 77	Sen 90.9	Sen 70.4
	Spe 67	Spe 76	Spe 86	Spe 81.3	Spe 65.7

Summary of five currently available predictive model for IVIG-resistance, PNI score was designed to assist the prediction for coronary aneurysm development. IVIG-R denotes to IVIG resistance; CAA, coronary artery aneurysm; Sen, sensitivity; Spe, specificity.

all KDSS patients require vasoactive agents for clinical improvement.

Mortality

From the same database, the mortality rate of KDSS was 6.8% according to Gamez-Gonzalez et al. in 2018. The causes of death were myocardial infarction, brain hemorrhage, bronchopneumonia, and complications from KD-associated cardiac surgery. By reviewing other studies involved records of mortality, we found that a retrospective 11-patient cohort study conducted in France. Although multiple organ failure occurred in 8 patients and acute kidney injury in 10 patients, all patient survived without sequelae [37]. Huang et al. from Chang Gung Memorial Hospital, Taiwan analyzed characteristics of 26 children with KD requiring intensive care from total 1065 KD patients [38] and found that shock sydrome noted in 73% (19/26) of the intensive care patients. No in-hospital mortality was revealed.

Significant Difference between KDSS and Mild KD

Reviewed data regarding KDSS and mild KD were summarized as Table 4.

Conclusion (Take Home Message)

1. Evidence showed that KDSS, the extreme worse form of KD in the spectrum, has interracial incidence (Hispanic > North America > Asia).
2. The shock type is mainly cardiogenic (inclusive of akinesia- or valvular dysfunction-related) or distributive.
3. The percentage of hypoalbuminemia, IVIG non-responder, and giant coronary aneurysm significantly elevated in KDSS compared with that of mild KD.
4. How to early differentiate KDSS from TSS:
   (1) Age: KDSS < TSS (5-year-old as the boundary).
   (2) Course: TSS progressive faster and invariably required vasoactive agents.
   (3) Shock type: cardiogenic shock seldom observed in TSS.
   (4) Coronary aneurysm indicated KDSS.
5. KDSS combined therapies were inclusive of administration of IVIG, vasoactive agents, broad spectrum antibiotics, and other adjunctive therapy of KD in acute phase.
6. KDSS basically has low mortality rate.

Table 4 Significant Difference between KDSS and Mild KD

	KDSS	Mild KD	*P* value
Age, months [2, 4]	23.2 (10.4–45.9)	17.78 (9.17–34.78)	**0.031**
Coronary artery aneurysm, % [4, 7]	15.9	7	**<0.001**
Giant coronary aneurysm, % [7]	27	0	**<0.001**
IVIG non-responder, % [7]	60	12	**<0.001**
Platelet counts, 10^9/L [3]	148 (97–302)	410 (331–491)	**<0.001**
Mortality, % [7]	10	0	0.051

The above numbers are expressed as the median (IQR) where appropriate

References

1. Senzaki H, Suda M, Noma S, Kawaguchi H, Sakakihara Y, Hishi T. Acute heart failure and acute renal failure in Kawasaki disease. Acta Paediatr Jpn. 1994;36(4):443–7.
2. Park WY, Lee SY, Kim GB, et al. Clinical aspects for differential diagnosis of Kawasaki disease shock syndrome: a case control study. BMC Pediatr. 2021;21(1):25.
3. Kanegaye JT, Wilder MS, Molkara D, et al. Recognition of a Kawasaki disease shock syndrome. Pediatrics. 2009;123(5):e783–9.
4. Lin MT, Fu CM, Huang SK, Huang SC, Wu MH. Population-based study of Kawasaki disease shock syndrome in Taiwan. Pediatr Infect Dis J. 2013;32(12):1384–6.
5. Maddox RA, Person MK, Kennedy JL, et al. Kawasaki disease and Kawasaki disease shock syndrome hospitalization rates in the United States, 2006-2018. Pediatr Infect Dis J. 2021;40(4):284–8.
6. Gamez-Gonzalez LB, Moribe-Quintero I, Cisneros-Castolo M, et al. Kawasaki disease shock syndrome: unique and severe subtype of Kawasaki disease. Pediatr Int. 2018;60(9):781–90.
7. Gamez-Gonzalez LB, Murata C, Munoz-Ramirez M, Yamazaki-Nakashimada M. Clinical manifestations associated with Kawasaki disease shock syndrome in Mexican children. Eur J Pediatr. 2013;172(3):337–42.
8. Natterer J, Perez MH, Di Bernardo S. Capillary leak leading to shock in Kawasaki disease without myocardial dysfunction. Cardiol Young. 2012;22(3):349–52.
9. Matsuura H, Ishikita T, Yamamoto S, et al. Gallium-67 myocardial imaging for the detection of myocarditis in the acute phase of Kawasaki disease (mucocutaneous lymph node syndrome): the usefulness of single photon emission computed tomography. Br Heart J. 1987;58(4):385–92.
10. Takahashi M. Myocarditis in Kawasaki syndrome. A minor villain? Circulation. 1989;79(6):1398–400.
11. Dahdah N. Not just coronary arteritis, Kawasaki disease is a myocarditis, too. J Am Coll Cardiol. 2010;55(14):1507; author reply 1507-1508
12. Belhadjer Z, Meot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. Circulation. 2020;142(5):429–36.
13. Tsuda E, Yashiro M, Nakamura Y. Cardiac valvular lesions due to Kawasaki disease: a Japanese Nationwide survey. J Pediatr. 2020;218(78-84):e72.
14. Liu FF, Liu HH, Qiu Z, et al. Clinical observation of noncoronary cardiac abnormalities in Chinese children with Kawasaki disease. Eur J Clin Investig. 2020;50(4):e13210.
15. Akagi T, Kato H, Inoue O, Sato N, Imamura K. Valvular heart disease in Kawasaki syndrome: incidence and natural history. Am Heart J. 1990;120(2):366–72.
16. Akagi T, Inoue O, Ohara N, et al. Valvular regurgitation in patients with Kawasaki disease and in healthy children: a pulsed doppler echocardiographic study. J Cardiol. 1989;19(3):787–96.
17. Suzuki A, Kamiya T, Tsuchiya K, et al. Tricuspid and mitral regurgitation detected by color flow doppler in the acute phase of Kawasaki disease. Am J Cardiol. 1988;61(4):386–90.
18. Takao A, Niwa K, Kondo C, et al. Mitral regurgitation in Kawasaki disease. Prog Clin Biol Res. 1987;250:311–23.
19. Gidding SS, Duffy CE, Pajcic S, Berdusis K, Shulman ST. Usefulness of echocardiographic evidence of pericardial effusion and mitral regurgitation during the acute stage in predicting development of coronary arterial aneurysms in the late stage of Kawasaki disease. Am J Cardiol. 1987;60(1):76–9.
20. Shiraishi I, Nishimura K, Sakaguchi H, et al. Acute rupture of chordae tendineae of the mitral valve in infants: a nationwide survey in Japan exploring a new syndrome. Circulation. 2014;130(13):1053–61.
21. Tsuda E, Negishi J, Miike H, Kurosaki K. Ruptured mitral valves chordae tendineae around a convalescent infant with acute Kawasaki disease. Cardiol Young. 2019;29(1):30–5.
22. Freij BJ, Gessouroun M, Fixler DE, Fink CW. Aortic and mitral regurgitation in an infant with Kawasaki disease. Pediatr Cardiol. 1985;6(2):95–8.
23. Fang LC, Shyur SD, Peng CC, et al. Unusual manifestations of Kawasaki disease with retropharyngeal edema and shock syndrome in a Taiwanese child. J Microbiol Immunol Infect. 2014;47(2):152–7.
24. Vergara A, Monda E, Mautone C, et al. Rare case of Kawasaki disease with cardiac tamponade and giant coronary artery aneurysms. Cardiol Young. 2021;31(5):865–6.
25. Kuo HC, Liang CD, Wang CL, Yu HR, Hwang KP, Yang KD. Serum albumin level predicts initial intravenous immunoglobulin treatment failure in Kawasaki disease. Acta Paediatr. 2010;99(10):1578–83.
26. Thabet F, Bafaqih H, Al-Mohaimeed S, Al-Hilali M, Al-Sewairi W, Chehab M. Shock: an unusual presentation of Kawasaki disease. Eur J Pediatr. 2011;170(7):941–3.
27. Carucci NS, Marseglia L, De Luca FL, et al. Kawasaki disease shock syndrome presenting as septic shock in a child with incomplete Kawasaki disease. J Clin Rheumatol. 2021;27(7):e274–5.
28. Song Y, Wei W, Liu L, Wang Y, Shi X, Li L. Kawasaki disease shock syndrome complicated with bilateral lung consolidation in a child: a case report. Medicine (Baltimore). 2020;99(29):e20998.
29. Lin YJ, Cheng MC, Lo MH, Chien SJ. Early differentiation of Kawasaki disease shock syndrome and toxic shock syndrome in a pediatric intensive care unit. Pediatr Infect Dis J. 2015;34(11):1163–7.
30. Power A, Runeckles K, Manlhiot C, Dragulescu A, Guerguerian AM, McCrindle BW. Kawasaki disease shock syndrome versus septic shock: early differentiating features despite overlapping clinical profiles. J Pediatr. 2021;231:162–7.

31. Nguyen E, Hershey D, Romanowski G, Tremoulet A. Intravenous immunoglobulin infusion reactions in Kawasaki disease patients who undergo sedation. J Pediatr Pharmacol Ther. 2020;25(3):251–5.
32. Kobayashi T, Inoue Y, Takeuchi K, et al. Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. Circulation. 2006;113(22):2606–12.
33. Egami K, Muta H, Ishii M, et al. Prediction of resistance to intravenous immunoglobulin treatment in patients with Kawasaki disease. J Pediatr. 2006;149(2):237–40.
34. Tai IH, Wu PL, Guo MM, et al. Prognostic nutrition index as a predictor of coronary artery aneurysm in Kawasaki disease. BMC Pediatr. 2020;20(1):203.
35. Sano T, Kurotobi S, Matsuzaki K, et al. Prediction of non-responsiveness to standard high-dose gamma-globulin therapy in patients with acute Kawasaki disease before starting initial treatment. Eur J Pediatr. 2007;166(2):131–7.
36. Lin MT, Chang CH, Sun LC, et al. Risk factors and derived Formosa score for intravenous immunoglobulin unresponsiveness in Taiwanese children with Kawasaki disease. J Formos Med Assoc. 2016;115(5):350–5.
37. Gatterre P, Oualha M, Dupic L, et al. Kawasaki disease: an unexpected etiology of shock and multiple organ dysfunction syndrome. Intensive Care Med. 2012;38(5):872–8.
38. Kuo CC, Lee YS, Lin MR, et al. Characteristics of children with Kawasaki disease requiring intensive care: 10 years' experience at a tertiary pediatric hospital. J Microbiol Immunol Infect. 2018;51(2):184–90.

Gut Microbiota in Kawasaki Disease

Cheng-Hsieh Huang and Yao-Tsung Yeh

Abstract

Although the mechanisms underlining the onset and development of Kawasaki disease (KD) remain to be underdetermined, the disease appears to be a result of multiple interactions between genetic and environmental susceptibility factors with an infectious trigger, followed by abnormal immune responses characterized by increased inflammatory cytokines in acute phase. The gut microbiota, a microbial community includes more than 1000 different interacting bacterial species in major and some other eukaryotic fungi, viruses, and bacteriophages in the gut, and has now associated with certain diseases such as immune-related disorders, metabolic diseases, and disorders of the nervous system. Mounting evidences have demonstrated that the gut microbiota participated in host immune system maturation. Intriguingly, gastrointestinal symptoms and complications are often observed in KD patients, and antibiotic administration has linked to the development of KD by changing the gut microbiota in infants and young children. Therefore, the gut microbiota may also play some roles in KD. In this chapter, we will summarize the involvement of the gut microbiota in childhood immune diseases, cardiovascular disease, and its relationship to KD as well as how gut microbiota and their associated metabolites influence KD onset and development.

Keywords

Gut microbiota · Immunity · Short chain fatty acids

Abbreviation

KD	Kawasaki diseases
SCFAs	short chain fatty acids

Introduction

Kawasaki disease (KD) was first described by Dr. Tomisaku Kawasaki on 1967. Data from Japanese KD nationwide survey reported an increase in prevalence rate from 218.6 to 100,000 in 2008 to 243.1 and 330.2 in 2011 and 2015, respectively [1–4]. Incidence rate appears more higher in

C.-H. Huang
Ph. D. Program in Environmental and Occupational Medicine, Kaohsiung Medical University National Health Research Institutes, Kaohsiung, Taiwan

Aging and Diseases Prevention Research Center, Fooyin University, Kaohsiung City, Taiwan

Y.-T. Yeh (✉)
Aging and Diseases Prevention Research Center, Fooyin University, Kaohsiung City, Taiwan

Department of Medical Laboratory Science and Biotechnology, Fooyin University, Kaohsiung City, Taiwan

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Pacific-Asia region, such as Korea, Japan, China Mainland, and Taiwan than in America or Europe [5, 6]. It is now recognized as a systemic vasculitis with a specific predilection to develop coronary artery lesions in up to 25% of children with KD who are not receiving single dose intravenous immunoglobulin (IVIG, 2 g/kg) [7, 8]. IVIG treatment might block endothelial cells proliferation and cytokines and chemokines production. Current studies have increasingly showed that KD is closely related to infectious agents, including viruses, especially DNA virus (e.g., type 2 adenovirus, parvovirus B19, and Epstein–Barr virus [9]), and "New" RNA viruses [10], but the mechanisms is still unclear. Moreover, pathogenic bacteria can modulate mucosal immunity and activate innate and adaptive immune systems [11, 12], and some of theses bacteia strains of normal flora [13, 14]. These observations indicate that Kawasaki disease seems to be a result of the interaction of genetic (e.g., *ITPKC, CASP3, CD40, and ORAI* [15]) and environmental susceptibility factors (infectious agents, climatic [16] or fungal particles in atmosphere [17]) with infectious triggers, followed by a subsequent abnormal immune response characterized by elevated levels of inflammatory cytokines and chemokines during the acute phase. However, the details of mechanisms underlying KD onset and development remain largely unknown. Intriguingly noted, antibiotic administration also contributes to the development of KD by altering the gut microbiota of infants and young children [18]. It has been clearly demonstrated that antimicrobial agents are able to cause the dysbiosis of gut microbiota [19, 20]. In addition, frequency of antibiotic administration has been shown to be positively correlated with body mass index and asthma due to gut dysbiosis [20–22]. It is noted that gut dysbiosis will destroy mucosal barrier leading to increased permeability. In KD patients, secretory immunoglobulin A (sIgA) would deposit in vascular tissue and facilitate intestinal permeability in mice, as well as "leaky gut syndrome" [23]. When mice treated with *Lactobacillus casei* cell wall extract (LCWE) would induce KD-vasculitis and increase interleukin-1β (IL-1β) production and intestinal permeability and subsequest IgA vasculitis and cardic inflammation development [23]. Together, these studies suggest that gut dysbiosis, intestinal permeability and its associated or casual immune response and pathogenesis may play some roles in the triggering and development of KD and demand further investigations.

Gut Microbiota in Childhood Diseases

The microbiota, a microbial community of trillions of microorganisms including more than 1000 different bacterial species, fungi, viruses, and bacteriophages, plays a critical role in certain diseases such as immune-related disorders, metabolic diseases, and nervon-related diseases [24, 25]. The intestinal mucosal immune system, such as gut-associated lymphoid tissues (GALT), is shaped after colonization with normal flora, suggesting that microbiota and host immune systems are closely linked and may be co-elevated [26]. Disruption of the mutual balance between microbiota and host, known as dysbiosis, is now associated with metabolic, gastroenteric, psychiatric, neurologic, and allergic diseases and even cancers. More intriguingly, gut dysbiosis has been observed in KD patients and juvenile idiopathic arthritis (JIA) [27, 28]. *Streptococcus* had been increased in acute phase of Kawasaki diseases patients. In JIA, moreover, also been discussed excessive bad bacteria (i.e., *Prevotella copri*) or insufficient good bacteria (i.e., *Faecalibacterium prausnitzii*) in children diseases. Although the mechanisms linking gut dysbiosis to disease remain unclear, dysbiosis-causing microbes, overproduction of toxic molecules, microbial invasion through wakened mucosal barriers, or homeostatic disruption between the microbiota and the host's immune system may be responsible for disease onset [13, 29].

The fetal microbiota composition is according to the type of delivery, caesarian section or vaginal delivery and breast milk feeding. Vaginally born infants were shown greater abundance of *Bacteroides* and *Bifidobacterium spp.* than caesarian section ones [30]. In addition, these two bacteria were significantly increased in breast-feeding infants. In formula-fed infants, however,

Streptococcus and *Enterococcus spp.* were more abundant than breastfed ones [31]. Nevertheless, a cesarean delivery delays contact with these species, producing a similar-to-skin flora, mainly *Staphylococci* [32] and high abundance in *Enterobacteriaceae* [33]. Multiple-drug-resistant *Staphylococci aureus* colonized in neonates might be transmitted from their mothers [34]. The feeding regimens and food supplements also play roles in modifying the resident flora; a greater complexity is normally seen in formula-fed infants, rather than in breastfed babies who have an "adult-like" structured microbiota with a population rich with *Bifidobacteria*, *Lactobacilli*, and *Bacteroides* [32]. These results indicated that mother's vaginal flora and breast milk are the major source of *Lactobacillus, Prevotella*, and *Bifidobacterium* in infants' microbiota composition [32].The infant gut microbiota is highly variable and dynamic in composition, especially in the first year of life, and is influenced by which a baby happens to be exposed, as shown by the similarity of infant [35]. Thereafter, the infant's intestinal tract progresses toward an extremely dense colonization, ending with a mixture of microbes that is broadly very similar to an adult's intestine. It is well-established fecal microbiota to breast milk, feces, and vaginal samples that early events of birth, environmental factors during infancy, sex hormones, diet, body weight, and antibiotics use can undoubtedly differentiate the composition of the microbiota [36, 37]. Notably, both prenatal and postnatal conditions modulate the establishment of gut microbiota in infancy. Maternal factors such as the maternal gut microbiota, vaginal infection or periodontitis as well as postnatal factors such as cesarean delivery, formula feeding, excessive antibiotic use, host genetics, and the environment can all influence the initial colonization of the gut by microbes [38]. Interestingly, formula feeding [39] and social environment factors such as higher household income, smaller family size, and urbanization lead to an increased incidence of KD, which is accompanied by gut dysbiosis [40]. The peak age of KD onset ranging from 6 months to 4 years corresponds to the critical period for establishment of the gut microbiota during the first 1000 days of life [41]. These results document the key player role of dysbiosis in contributing to KD onset and development, and the impacts of the prenatal and postnatal factors on gut microbiota should be seriously taken into concerns.

Immune-mediated diseases in children, including KD and JIA, may be associated with prevalent infections in early childhood [42]. Interestingly, the incidence rate of these two diseases is quite different among populations; the incidence of KD in East Asian countries such as Japan and Korea is over 10–20 times higher, and the incidence of JIA in North European countries is more than 10 times that of children in East Asian countries [43]. Population-specific difference in incidence have been observed in other infection-related immune-mediated diseases, including type I diabetes [44], inflammatory bowel disease [45], and Behcet's disease [46]. Although genetic or environmental factors may be responsible for this finding, it is possible that children living in higher-prevalence countries may have greater exposure to KD or JIA pathogens, since the clinical manifestations and immune function of children with KD or JIA have been nearly identical across the populations.

Gut Microbiota and Risk of Cardiovascular Diseases

Systemic vasculitis with specific coronary artery lesions has been frequently observed in KD children who are not receiving IVIG treatment [7, 8]. In regarding the association of dysbiosis in the gut with cardiovascular disease (CAD), it is presumably possible that some overlapping microbes of intestinal dysbiosis in CAD may also contribute to KD onset or development. When the intestinal flora is imbalanced (i.e., dysbiosis), the mucosal barrier is usually destroyed and become leaky, adversely increasing the risk of CVDs and other diseases. There is significant differences in the gut microbiota between healthy individuals and patients with prehypertension and hypertension. The flora of the latter two has a marked reduction of probiotics and excessive abundances of genera *Preto* and *Klebsiella*. Transplanting the fecal microbiota of hypertensive patients into sterile mice can increase blood pressure [47].

Intriguingly, treatment of ST-elevation myocardial infarction with antibiotic attenuated systemic inflammation and myocardial damage in mice [48]. Post ST-elevation myocardial infarction, had been found some gut bacteria (i.e., *Lactobacillus, Bacteroides*, and *Streptococcus*) would translocated into blood stream. These results indicated antiobiotic treatment would attenuated systemic inflammation and mycardial infarction. In patients with heart failure (HF), *Eubacterium rectale* and *Dorea longicatena* are present in lower levels in HF patients than healthy participants [49]. In KD patients, intestinal permeability and circulating secretion of immunoglobulin A (IgA) are increased [50], suggesting an antigen-driven response to pathogens with respiratory or gastrointestinal entry. It is noted that targeted correction of intestinal permeability can prevent IgA deposition and alleviate the cardiovascular pathological changes in a murine model [23].

The gut microbiome can produce hydrogen peroxide, short chain fatty acids (SCFAs), and other metabolites to protect the body from potentially harmful, invading pathogens, and modulate immune responses [51]. SCFAs are mainly produced by anaerobic gut bacteria in the cecum and the proximal colon, principally through the fermentation of dietary fibers, and to a lesser extent, proteins, and peptides [52]. Butyrate, acetate, and propionate are the major SCFAs [53], which have local effects as primary energy sources for gut mucosal cells or distal effects as an important source of calorie and energy for the organism and to act as signaling molecules. Several lines of evidence suggest a reduction in regulatory T cells (Tregs) and imbalance between T helper 17 cells (Th17s) and Tregs in acute KD [54–56]. Interestingly, Th17 and Treg differentiation are found to be regulated by SCFAs, especially butyrate, produced by the gut microbiota [57–59], while acute KD-associated gut dysbiosis has been characterized by lower abundance of butyrate-producing bacteria, *Roseburia* and *Faecalibacterium* [28, 60, 61]. On this basis, gut dysbiosis and reduced production of SCFAs lead to imbalances of Th17s/Tregs, which may be related to the etiology of KD. Simultaneous measurements of Th17s/Tregs in peripheral blood and SCFA concentrations in feces will provide valuable information on the association between dysbiosis and immune responses dysregulation in KD.

Many studies suggested that SCFAs have beneficial effects on the pathophysiological process of CVDs. For example, after treating C57BL/6J mice with antibiotics, SCFAs will be reduced, and the host immune profiles and repair capacity after the myocardial infraction will be impaired [62]. Supplementation of dietary SCFAs improved the physiological state of mice after myocardial infarction [63]. Fecal microbiota transplantation being rich in SCFAs alleviates intestinal dysbiosis and lipid metabolism disorders and can prevent obesity and ischemic stroke in mice fed with high-fat diet [64]. It is noteworthy noted that dietary fiber supplementation may serve as a therapeutic strategy for CVDs and also KD children because supplementation of dietary fiber is appeared to modulate the production of SCFAs and further provide benefits to type 2 DM, obesity, and atherosclerosis [65–67].

Proposed Infectious Causes of KD

The current pathogenesis of KD suggested that the disease may be result of a pathologically amplified immune response against infectious agents in a genetically and environmentally susceptible child [68]. There are some clinical overlaps between KD and infectious diseases such as viruses (human Adenovirus (HAdV) [69], parvovirus B19 [70], or Epstein–Barr virus (EBV) [71, 72]) and bacteria (*Staphylococcus* [73], *Streptococcal* [71, 74], *Mycoplasma* [75], or *Chlamydia* [76]) infection. Seasonal clustering of KD in the winter and spring mimics that of several viral diseases [77]. Moreover, temporal clusters of epidemics have been reported in Japan, the USA, Canada, and Finland [5] and within 6 months in Japan, outbreaks can spread nationwide [78]. The low incidence of KD in school-aged children may suggest that most children encounter indeterminate common antigens in early childhood and mount an appropriate and protective immune response against these antigens [79]. Notably, the incidence in the first 3 months of life is very low, suggesting at least partial protection from transplacental antibodies [80]. However, efforts to find a single unifying

microbiological cause of KD have so far been unsuccessful. Furthermore, the microbiological cause may not be a single microbe but an interaction between multiple microbial populations.

It has long been thought that infection with one or more widely distributed microorganisms may trigger a dysregulated immune response in genetically or environmentally susceptible children, leading to the pathogenesis of KD. Those candidate pathogens including Epstein–Barr virus [81, 82] had been detected in peripheral blood mononuclear cells (PBMCs) by polymerase chain reaction (PCR). Human herpes virus [83], human immunodeficiency virus (HIV) [84], human adenovirus [85], human coronavirus [86], retrovirus [87], human parvovirus B19 [88], and human bocavirus [89], moreover, would elevate chemokines levels, such as TNF-alpha level, and develop Kawasaki like syndrome (KLS). SARA-CoV-2 infection in children with multisystem inflammation syndrome (MIS-C) would develop Kawasaki-diseases picture [90]. In constant, S*taphylococcus aureus* [91], *Streptococcus pyogenes* [92], *Yersinia pseudotuberculosis* [93, 94], *Bacillus cereus* [95], *Mycoplasma pneumoniae* [96], *Mycobacterium spp*. [97], *Bartonella henselae* [98], *Coxiella burnetii* [99], and *Candida* spp. [100] would produce bacteria toxin, e.g., toxic shock syndrome toxin (TSST), Yersinia pseudotuberculosis derived mitogen (YPM), microbe-associated molecular pattern (MAMP), and streptococcal pyogenic exotoxin (SPE) and activate $V\beta^{2+}$ T cells in KD with heart diseases. The link of viruses to KD has been demonstrated by cytoplasmic inclusion bodies containing viral RNA in the bronchial epithelia [101] and by intracytoplasmic inclusion bodies containing viral proteins and nucleic acid aggregates [102, 103]. It is worth noting, however, it is difficult to distinguish infection caused by adenovirus from KD due to frequent incidental detection of adenovirus as well as its increased inflammatory biomarkers in KD patients [104]. In particular, adenovirus was detected in 8.8 and 25% of complete and incomplete KD patients, respectively [69]. About half of patients with KD may have one or more respiratory viruses detected by polymerase chain reaction, a positive respiratory viral test or present with respiratory symptoms [105]. Hence, those tests or symptoms for respiratory virus shall not be used to rule out the diagnosis of KD [105]. Some other studies have suggested a potential relationship between KD with coronaviruses [86, 106], and the links between KD and coronavirus disease 2019 (COVID-19) are also of concern [107–110]. Cohorts of children with KD-like symptoms have been documented in the UK, the USA, France, and Italy, some of whom were later confirmed to have COVID-19. It appears that hyperinflammation associated with COVID-19 may serve as a primer for the development of KD in individuals with genetical or suffering environmental predisposition. The underlying mechanism demands further investigations [107].

Intriguingly, *Staphylococci* and *Streptococci* can secrete certain exotoxins, e.g., toxic shock syndrome toxin-1 (TSST-1), known as superantigens that can promote the activation of a large number of T helper cells (Th) leading to a robust of immunological reaction [111]. Matsubara et al. suggests that TSST-1, *Streptococcal Pyogenic* Exotoxin A or C (SPEA or SPEC), and *Staphylococcal* Enterotoxin A or B (SEA or SEB) may act as superantigens that can stimulate the immune system and subsequently result in KD [73]. Anti-streptococcal SPEC antibodies are found to be increased in the sera of KD patients at acute phase [112], and anti-SPEC and -SPEA IgM are found in the first few weeks following the illness [73]. Nevertheless, no significant differences in superantigen antibody are found in other serological studies. *Candida albicans* (*C. albicans*) has recently noted that administration of water-soluble extracellular polysaccharide from culture supernatants of *C. albicans* induces coronary arteritis in mice similar to KD symptoms [113]. The following reports further suggest that *C. albicans* may play an important role as an infectious trigger of KD [100, 114, 115]. Furthermore, studies of systemic vasculitis induced by C. albicans extracts in mice highlighted the relationship between the development of vasculitis and increased proinflammatory cytokines such as TNF-α and IL-6 [116, 117]. Additionally noted, gut dysbiosis has been also linked to aberrant levels of TNF-α and IL-6 [118, 119].

The Complex Relationship Between Gut Microbiota and Kawasaki Disease

Gut microbiota is considered as the largest organ in our body and is involved in immune regulation [120, 121]. There are several **gastrointestinal symptoms and complications** in KD patients [122]. All KD patients had abdominal pain and fever presentation, and found there were about 70% with vomiting, 50% with diarrhea, and 43% with clinical jaundice. These results indicated that gastrointestinal syndrome should be considered. In clinic, KD patients frequently have high levels of lipopolysaccharide (LPS)-binding neutrophils or plasma protein [123, 124], and of antibody against mycobacteria heat shock protein (HSP65) [97]. In convalescent, not acute phase patients with KD, shown strong antibody reactivity against in HSP65 in their sera. This results indicated that HSP65 may be the most potent factor predisposing to Kawasaki disease, and that an autoreactivity to the epitope of the human HSP65 homolog may be related to the susceptibility to the disease. In addition, different pathogens found in KD patients are involved in secondary infections such as *Streptococcus pyogenes* [125], *Staphylococcus aureus* [73, 126], *Mycoplasma pneumoniae* [75, 127], *and Chlamydia pneumoniae* [128]. Toshiaki et al. have previously found *Streptococci* and *Staphylococci* in children with KD [129]. A paired case-control study also shows that early administration of antibiotics will promote KD development in young children [18]. Furthermore, *Ruminococcus, Roseburia, Faecalibacterium, and Streptococcus* are found to be increased in KD patients [28]. Metagenomic studies were indicated that *Ruminococcus spp.* was increased in non-acute phase of KD. Moreover, *Streptococcus spp.* was enriched in acute phase of KD. This study indicated that *Streptococcus spp.* might be involved in pathogenesis of KD. These results collectively strengthen that gut microbiota may play roles in KD onset and development (Table 1).

Table 1 Perturbation in the intestinal microbiota of patients with Kawasaki syndrome

Methods	Site	No of patients	Results	References
Culture	Throat	21 patients with KD, 20 with other febrile illnesses	No difference	Horita et al. [149]
Culture	Jejunum biopsy	15 patients with KD	↑*Streptococci* ↑*Staphylococci*	Yamashiro et al. [129]
Culture	Gut	20 patients with KD, 20 patients with acute febrile diseases, 20 healthy children	↓*Lactobacillus*↑*Eubacterium*↑*Peptostreptococcus*	Takeshita et al. [139]
Culture	Gut	19 patients with KD, 15 patients with food-sensitive enteropathy in remission	↑Gram-negative producing hsp60, ↑Gram-positive cocci with superantigenic properties	Nagata et al. [140]
Metagenomic analysis on feces	Gut	28 KD patients, 28 samples during acute phase, 28 samples in non-acute phase	↑*Ruminococcus*↑*Roseburia*↑*Faecalibacterium*↑*Streptococcus*	Kinumaki et al. [28]
Metagenomic analysis on feces	Gut	5 KD patients during acute phase and receiving IVIG treatment, 13 healthy controls	↑*Fusobacterium*,↑*Neisseria*,↑*Shigella*↑*Streptococcus*	Imran Khan et al. [152]
Metagenomic analysis on feces	Gut	48 KD patients during acute phase and 46 healthy controls	↓*Alpha diversity*↓*Bacteroidetes*↓*Dorea*	Jie Shen et al. [153]
Metagenomic analysis on feces	Gut	30 KD patients during acute phase, and 30 age-matched control for 6 months follow-up	↑*Enterococcus*↑*Acinetobacter* ↑*Helicobacter* ↑*Lactococcus* ↑*Staphylococcus* ↑*Butyricimonas*	Jie Chen et al. [154]

However, all bacteria were identified by culture-based method in previous studies. With next-generation sequencing (NGS) development, gut microbiota analysis is applied in human diseases research, including gastrointestinal diseases [130, 131], metabolic syndrome [132, 133], and cancers [134, 135]. It is noted that gut microbiota also participated in several pathways such as SCFAs pathway, trimethylamine (TMA)/trimethylamine N-oxide (TMAO) pathway, phenylacetylglutamine (PAGln), and primary and secondary bile acid pathways in cardiovascular diseases progression [136–138].

Direct association between one or more pathogens with KD is limited. Even though the most frequent detected bacteria or viruses in KD have a higher prevalence in overall pediatric population, only a limited number of children will develop KD. In addition, the genetic predispositions and environmental factors associated with onset or pathogenetic process of KD are similar to other multifactorial diseases. Thus, the intestinal environment such as gut microbiota shall be taken into consideration and is supposed to one of the mechanisms underlying KD onset and development. Of note, KD patients frequently exhibit gastrointestinal symptoms and complications [122]. Mounting evidence have now revealed that the composition of the gut microbiota in KD patients differs from healthy subjects. The gut microbiomes of KD patients are lacking of *Lactobacilli* during the acute phase [139], whereas both HSP60-producing Gram-negative bacteria and Gram-positive cocci inducing Vβ2 T cell expansion are isolated from KD patients [140]. It is importantly noted that a strong link between KD and allergic diseases [141–143] in which gut dysbiosis plays a critical role [144]. These results suggest that distinct gut microbes may be involved in the pathophysiology of KD. The immune system may lose tolerance toward a part of the resident intestinal flora and those environmental factors such as Western lifestyle or improved public health systems, may convert the commensal flora into pathogenic flora, such as in different gastrointestinal or immune systems seen in different gastrointestinal or immunological disorders. However, because some of these studies were conducted using culture-based methods, those unculturable microbes that make up more than half of the gut microbiome may be overlooked.

Compared with culture-based methods, metagenomic analysis can reveal more about the composition of the gut microbiota. *Streptococcus* spp., including *S. pneumoniae, S. pseudopneumoniae, S. mitis, S. oralis, S. gordonii*, and *S. sanguinis* are found to be more abundant, while the abundance of *Ruminococcus, Roseburia,* and *Faecalibacterium* are less abundant during the acute phase of KD [28]. However, one intriguing limitation must be noted that more than half of subjects will be treated empirically with antibiotics during the early phase of KD when the fecal samples are collected [145], because clinical and laboratory findings often do not fulfill the diagnostic criteria of KD but are instead suggestive of bacterial infections [146]. As antibiotic administration rapidly perturbs the gut microbiota [147], these results may merely reflect the effects of antibiotic therapy on the gut microbiota but not dysbiosis associated with KD.

The gastrointestinal tract may be one of the main sites of entry of bacteria in children with KD. A perturbation in the gut microbiota has been increasingly linked to the KD's pathophysiology. The bacterial species isolated from jejunal biopsies is characterized by a wider variety of Gram-positive cocci including 5 kinds of streptococci (*Streptococcus salivarius, Streptococcus mitis, Streptococcus oralis, Streptococcus sanguinis*, and *Gemella haemolysans*) and 2 kinds of staphylococci (*Staphylococcus capitis* and *Staphylococcus hyicus*) from KD patients in the acute phase, suggesting that some antigens induce a delayed-type hypersensitivity reaction in the mucosa of small intestine of KD patients [129]. This speculation is also confirmed in the study by Nagata et al. [148]. The throat flora might be another microbial source that triggers KD. However, the throat flora between KD and febrile controls even in the mean mitogenic activity of bacteria isolated did not show significant difference [149]. Takeshita et al. show that the incidence of *Lactobacilli* isolated from KD patients is significantly lower than that from

patients with acute febrile diseases and healthy children, while the presence of *Eubacterium* and *Peptostreptococcus* is significantly higher in KD patients than in patients with febrile diseases [139]. The authors collected a total of 56 samples—equal samples each for both acute and non-acute phases. It was demonstrated that the genera *Ruminococcus, Roseburia*, and *Faecalibacterium* are mostly predominant during the non-acute phase, 4–6 months after the onset of KS, while a higher presence of *Streptococcus* spp., including *Streptococcus pneumoniae, pseudopneumoniae, mitis, oralis, gordonii*, and *sanguinis*, are detected in the fecal specimens during the acute phase [28]. Intriguingly, these interpretation of KD can be also shared by other situations such as liver cirrhosis and Sjögren syndrome, in which dominant changes of gut microbiota show a higher proportion of *Streptococcus* spp. [150, 151]. These findings suggest that many other immune-mediated disorders are likely to be linked to an abnormal bacterial colonization of the intestinal tract potentially through oral or respiratory route such as *Streptococcus* spp., and that alterations in the gut microflora may harvest systemic and extra-intestinal inflammation niche. It is that an imbalance of the gut microbiota may directly or indirectly interrupt with the immune system, or interplay with other genetic or environmental factors, mainly infectious agents, eventually leading to the onset and development of KD.

Conclusion

Dysbiosis is defined as alterations in gut microbiota composition, caused by prenatal and postnatal factors that are not necessarily infectious agents, that may contribute to the onset and development of KD under genetically and environmentally determined preferences. As illustrated in Fig. 1, the take home messages can be outlined as follows: (1) various prenatal and postnatal factors drive gut dysbiosis in infant and young children; (2) gut dysbiosis results in aberrant production of associated metabolites including SCFAs; (3) aberration of SCFAs in the gut cause an imbalance of Th17s/Tregs or other immune cells; and (4) individuals with Th17/Treg imbalances develop hypercytokinemia triggered by ubiquitous infectious agents(s), followed by KD (Fig. 1). In summary, gut dysbiosis may be involved in KD onset and devel-

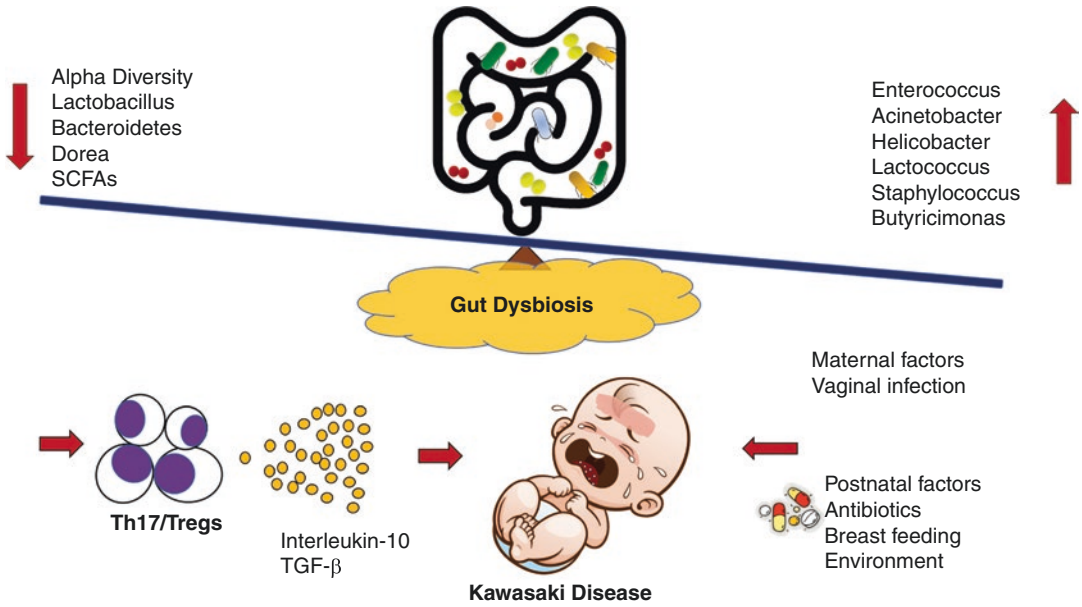

Fig. 1 Potential roles of gut dysbiosis in KD may be in relation to reducing SCFAs production and promoting TH17 and Tregs imbalance. Th17/Treg imbalances may trigger hypercytokinemia and subsequent KD development [155]

opment under genetically and environmentally determined predilections. Thus, intervention by supplying prebiotics, probiotics, symbiotic or postbiotics at birth or during IVIG treatment may reduce the risk of KD in infancy or improve the treatment response at acute phase. It is noted that supplying prebiotics, probiotics, symbiotic, or postbiotics can reshape gut microbiota and improve dysbiosis-associated disorders potentially including KD.

References

1. Nakamura Y, Yashiro M, Uehara R, Oki I, Watanabe M, Yanagawa H. Epidemiologic features of Kawasaki disease in Japan: results from the nationwide survey in 2005-2006. J Epidemiol. 2008;18(4):167–72. https://doi.org/10.2188/jea.je2008001.
2. Yanagawa H, Nakamura Y, Yashiro M, Ojima T, Tanihara S, Oki I, et al. Results of the nationwide epidemiologic survey of Kawasaki disease in 1995 and 1996 in Japan. Pediatrics. 1998;102(6):E65. https://doi.org/10.1542/peds.102.6.e65.
3. Yanagawa H, Yashiro M, Nakamura Y, Kawasaki T, Kato H. Epidemiologic pictures of Kawasaki disease in Japan: from the nationwide incidence survey in 1991 and 1992. Pediatrics. 1995;95(4):475–9.
4. Makino N, Nakamura Y, Yashiro M, Kosami K, Matsubara Y, Ae R, et al. Nationwide epidemiologic survey of Kawasaki disease in Japan, 2015–2016. Pediatr Int. 2019;61(4):397–403. https://doi.org/10.1111/ped.13809.
5. Uehara R, Belay ED. Epidemiology of Kawasaki disease in Asia, Europe, and the United States. J Epidemiol. 2012;22(2):79–85. https://doi.org/10.2188/jea.je20110131.
6. Lue HC, Philip S, Chen MR, Wang JK, Wu MH. Surveillance of Kawasaki disease in Taiwan and review of the literature. Acta Paediatr Taiwan. 2004;45(1):8–14.
7. Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children. Arerugi. 1967;16(3):178–222.
8. Burns JC, Glode MP. Kawasaki syndrome. Lancet. 2004;364(9433):533–44. https://doi.org/10.1016/S0140-6736(04)16814-1.
9. Embil JA, McFarlane ES, Murphy DM, Krause VW, Stewart HB. Adenovirus type 2 isolated from a patient with fatal Kawasaki disease. Can Med Assoc J. 1985;132(12):1400.
10. Rowley AH, Shulman ST. The epidemiology and pathogenesis of Kawasaki disease. Front Pediatr. 2018;6:374. https://doi.org/10.3389/fped.2018.00374.
11. Nagata S. Causes of Kawasaki disease-from past to present. Front Pediatr. 2019;7:18. https://doi.org/10.3389/fped.2019.00018.
12. Nakamura A, Ikeda K, Hamaoka K. Aetiological significance of infectious stimuli in Kawasaki disease. Front Pediatr. 2019;7:244. https://doi.org/10.3389/fped.2019.00244.
13. Esposito S, Polinori I, Rigante D. The gut microbiota-host partnership as a potential driver of Kawasaki syndrome. Front Pediatr. 2019;7:124. https://doi.org/10.3389/fped.2019.00124.
14. Rhim JW, Kang HM, Han JW, Lee KY. A presumed etiology of Kawasaki disease based on epidemiological comparison with infectious or immune-mediated diseases. Front Pediatr. 2019;7:202. https://doi.org/10.3389/fped.2019.00202.
15. Onouchi Y. The genetics of Kawasaki disease. Int J Rheum Dis. 2018;21(1):26–30. https://doi.org/10.1111/1756-185X.13218.
16. Corinaldesi E, Pavan V, Andreozzi L, Fabi M, Selvini A, Frabboni I, et al. Environmental factors and Kawasaki disease onset in Emilia-Romagna, Italy. Int J Environ Res Public Health. 2020;17(5) https://doi.org/10.3390/ijerph17051529.
17. Manlhiot C, Mueller B, O'Shea S, Majeed H, Bernknopf B, Labelle M, et al. Environmental epidemiology of Kawasaki disease: linking disease etiology, pathogenesis and global distribution. PLoS One. 2018;13(2):e0191087. https://doi.org/10.1371/journal.pone.0191087.
18. Fukazawa M Jr, Fukazawa M, Nanishi E, Nishio H, Ichihara K, Ohga S. Previous antibiotic use and the development of Kawasaki disease: a matched pair case-control study. Pediatr Int. 2020;62(9):1044–8. https://doi.org/10.1111/ped.14255.
19. Ianiro G, Tilg H, Gasbarrini A. Antibiotics as deep modulators of gut microbiota: between good and evil. Gut. 2016;65(11):1906–15. https://doi.org/10.1136/gutjnl-2016-312297.
20. Korpela K, Salonen A, Virta LJ, Kekkonen RA, Forslund K, Bork P, et al. Intestinal microbiome is related to lifetime antibiotic use in Finnish preschool children. Nat Commun. 2016;7:10410. https://doi.org/10.1038/ncomms10410.
21. Marra F, Marra CA, Richardson K, Lynd LD, Kozyrskyj A, Patrick DM, et al. Antibiotic use in children is associated with increased risk of asthma. Pediatrics. 2009;123(3):1003–10. https://doi.org/10.1542/peds.2008-1146.
22. Hoskin-Parr L, Teyhan A, Blocker A, Henderson AJ. Antibiotic exposure in the first two years of life and development of asthma and other allergic diseases by 7.5 year: a dose-dependent relationship. Pediatr Allergy Immunol. 2013;24(8):762–71. https://doi.org/10.1111/pai.12153.
23. Noval Rivas M, Wakita D, Franklin MK, Carvalho TT, Abolhesn A, Gomez AC, et al. Intestinal permeability and IgA provoke immune Vasculitis linked to cardiovascular inflammation. Immunity. 2019;51(3):508–21 e6. https://doi.org/10.1016/j.immuni.2019.05.021.

24. Robinson CM, Pfeiffer JK. Viruses and the microbiota. Annu Rev Virol. 2014;1:55–69. https://doi.org/10.1146/annurev-virology-031413-085550.
25. Sudo D, Nakamura Y. Nationwide surveys show that the incidence of recurrent Kawasaki disease in Japan has hardly changed over the last 30 years. Acta Paediatr. 2017;106(5):796–800. https://doi.org/10.1111/apa.13773.
26. Maynard CL, Elson CO, Hatton RD, Weaver CT. Reciprocal interactions of the intestinal microbiota and immune system. Nature. 2012;489(7415):231–41. https://doi.org/10.1038/nature11551.
27. Arvonen M, Berntson L, Pokka T, Karttunen TJ, Vahasalo P, Stoll ML. Gut microbiota-host interactions and juvenile idiopathic arthritis. Pediatr Rheumatol Online J. 2016;14(1):44. https://doi.org/10.1186/s12969-016-0104-6.
28. Kinumaki A, Sekizuka T, Hamada H, Kato K, Yamashita A, Kuroda M. Characterization of the gut microbiota of Kawasaki disease patients by metagenomic analysis. Front Microbiol. 2015;6:824. https://doi.org/10.3389/fmicb.2015.00824.
29. Milshteyn A, Colosimo DA, Brady SF. Accessing bioactive natural products from the human microbiome. Cell Host Microbe. 2018;23(6):725–36. https://doi.org/10.1016/j.chom.2018.05.013.
30. Nafady-Hego H, Li Y, Ohe H, Elgendy H, Zhao X, Sakaguchi S, et al. Utility of CD127 combined with FOXP3 for identification of operational tolerance after liver transplantation. Transpl Immunol. 2016;36:1–8. https://doi.org/10.1016/j.trim.2016.04.005.
31. Ma J, Li Z, Zhang W, Zhang C, Zhang Y, Mei H, et al. Comparison of gut microbiota in exclusively breast-fed and formula-fed babies: a study of 91 term infants. Sci Rep. 2020;10(1):15792. https://doi.org/10.1038/s41598-020-72635-x.
32. Buccigrossi V, Nicastro E, Guarino A. Functions of intestinal microflora in children. Curr Opin Gastroenterol. 2013;29(1):31–8. https://doi.org/10.1097/MOG.0b013e32835a3500.
33. Kim G, Bae J, Kim MJ, Kwon H, Park G, Kim SJ, et al. Delayed establishment of gut microbiota in infants delivered by cesarean section. Front Microbiol. 2020;11:2099. https://doi.org/10.3389/fmicb.2020.02099.
34. Lin J, Yao Z. Maternal-infant correlation of multidrug-resistant Staphylococcus aureus carriage: a prospective cohort study. Front Pediatr. 2018;6:384. https://doi.org/10.3389/fped.2018.00384.
35. Palmer C, Bik EM, DiGiulio DB, Relman DA, Brown PO. Development of the human infant intestinal microbiota. PLoS Biol. 2007;5(7):e177. https://doi.org/10.1371/journal.pbio.0050177.
36. Chen J, Ryu E, Hathcock M, Ballman K, Chia N, Olson JE, et al. Impact of demographics on human gut microbial diversity in a US Midwest population. PeerJ. 2016;4:e1514. https://doi.org/10.7717/peerj.1514.
37. Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE, et al. A core gut microbiome in obese and lean twins. Nature. 2009;457(7228):480–4. https://doi.org/10.1038/nature07540.
38. Tamburini S, Shen N, Wu HC, Clemente JC. The microbiome in early life: implications for health outcomes. Nat Med. 2016;22(7):713–22. https://doi.org/10.1038/nm.4142.
39. Yorifuji T, Tsukahara H, Doi H. Breastfeeding and risk of Kawasaki disease: a Nationwide longitudinal survey in Japan. Pediatrics. 2016;137(6):e20153919. https://doi.org/10.1542/peds.2015-3919.
40. Fujiwara T, Shobugawa Y, Matsumoto K, Kawachi I. Association of early social environment with the onset of pediatric Kawasaki disease. Ann Epidemiol. 2019;29:74–80. https://doi.org/10.1016/j.annepidem.2018.10.010.
41. Selma-Royo M, Tarrazo M, Garcia-Mantrana I, Gomez-Gallego C, Salminen S, Collado MC. Shaping microbiota during the first 1000 days of life. Adv Exp Med Biol. 2019;1125:3–24. https://doi.org/10.1007/5584_2018_312.
42. Lee KY, Hamada H, Arvonen M. Editorial: infection-related immune-mediated diseases and microbiota. Front Pediatr. 2020;8:108. https://doi.org/10.3389/fped.2020.00108.
43. Thierry S, Fautrel B, Lemelle I, Guillemin F. Prevalence and incidence of juvenile idiopathic arthritis: a systematic review. Joint Bone Spine. 2014;81(2):112–7. https://doi.org/10.1016/j.jbspin.2013.09.003.
44. Tuomilehto J. The emerging global epidemic of type 1 diabetes. Curr Diab Rep. 2013;13(6):795–804. https://doi.org/10.1007/s11892-013-0433-5.
45. Ahn HJ, Kim YJ, Lee HS, Park JH, Hwang SW, Yang DH, et al. High risk of fractures within 7 years of diagnosis in Asian patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol. 2021;20(5):e1022–39. https://doi.org/10.1016/j.cgh.2021.06.026.
46. Yildiz M, Haslak F, Adrovic A, Sahin S, Koker O, Barut K, et al. Pediatric Behcet's disease. Front Med (Lausanne). 2021;8:627192. https://doi.org/10.3389/fmed.2021.627192.
47. Li J, Zhao F, Wang Y, Chen J, Tao J, Tian G, et al. Gut microbiota dysbiosis contributes to the development of hypertension. Microbiome. 2017;5(1):14. https://doi.org/10.1186/s40168-016-0222-x.
48. Zhou X, Li J, Guo J, Geng B, Ji W, Zhao Q, et al. Gut-dependent microbial translocation induces inflammation and cardiovascular events after ST-elevation myocardial infarction. Microbiome. 2018;6(1):66. https://doi.org/10.1186/s40168-018-0441-4.
49. Kamo T, Akazawa H, Suda W, Saga-Kamo A, Shimizu Y, Yagi H, et al. Dysbiosis and compositional alterations with aging in the gut microbiota of patients with heart failure. PLoS One. 2017;12(3):e0174099. https://doi.org/10.1371/journal.pone.0174099.

50. Rowley AH, Eckerley CA, Jack HM, Shulman ST, Baker SC. IgA plasma cells in vascular tissue of patients with Kawasaki syndrome. J Immunol. 1997;159(12):5946–55.
51. Benakis C, Brea D, Caballero S, Faraco G, Moore J, Murphy M, et al. Commensal microbiota affects ischemic stroke outcome by regulating intestinal gammadelta T cells. Nat Med. 2016;22(5):516–23. https://doi.org/10.1038/nm.4068.
52. Backhed F, Ley RE, Sonnenburg JL, Peterson DA, Gordon JI. Host-bacterial mutualism in the human intestine. Science. 2005;307(5717):1915–20. https://doi.org/10.1126/science.1104816.
53. LeBlanc JG, Chain F, Martin R, Bermudez-Humaran LG, Courau S, Langella P. Beneficial effects on host energy metabolism of short-chain fatty acids and vitamins produced by commensal and probiotic bacteria. Microb Cell Factories. 2017;16(1):79. https://doi.org/10.1186/s12934-017-0691-z.
54. Guo MM, Tseng WN, Ko CH, Pan HM, Hsieh KS, Kuo HC. Th17- and Treg-related cytokine and mRNA expression are associated with acute and resolving Kawasaki disease. Allergy. 2015;70(3):310–8. https://doi.org/10.1111/all.12558.
55. Jia S, Li C, Wang G, Yang J, Zu Y. The T helper type 17/regulatory T cell imbalance in patients with acute Kawasaki disease. Clin Exp Immunol. 2010;162(1):131–7. https://doi.org/10.1111/j.1365-2249.2010.04236.x.
56. Furuno K, Yuge T, Kusuhara K, Takada H, Nishio H, Khajoee V, et al. CD25+CD4+ regulatory T cells in patients with Kawasaki disease. J Pediatr. 2004;145(3):385–90. https://doi.org/10.1016/j.jpeds.2004.05.048.
57. Arpaia N, Campbell C, Fan X, Dikiy S, van der Veeken J, deRoos P, et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. Nature. 2013;504(7480):451–5. https://doi.org/10.1038/nature12726.
58. Asarat M, Apostolopoulos V, Vasiljevic T, Donkor O. Short-Chain fatty acids regulate cytokines and Th17/Treg cells in human peripheral blood mononuclear cells in vitro. Immunol Investig. 2016;45(3):205–22. https://doi.org/10.3109/08820139.2015.1122613.
59. Lee JR, Huang J, Magruder M, Zhang LT, Gong C, Sholi AN, et al. Butyrate-producing gut bacteria and viral infections in kidney transplant recipients: a pilot study. Transpl Infect Dis. 2019;21(6):e13180. https://doi.org/10.1111/tid.13180.
60. Haak BW, Littmann ER, Chaubard JL, Pickard AJ, Fontana E, Adhi F, et al. Impact of gut colonization with butyrate-producing microbiota on respiratory viral infection following Allo-HCT. Blood. 2018;131(26):2978–86. https://doi.org/10.1182/blood-2018-01-828996.
61. Louis P, Flint HJ. Diversity, metabolism and microbial ecology of butyrate-producing bacteria from the human large intestine. FEMS Microbiol Lett. 2009;294(1):1–8. https://doi.org/10.1111/j.1574-6968.2009.01514.x.
62. Tang TWH, Chen HC, Chen CY, Yen CYT, Lin CJ, Prajnamitra RP, et al. Loss of gut microbiota alters immune system composition and cripples postinfarction cardiac repair. Circulation. 2019;139(5):647–59. https://doi.org/10.1161/CIRCULATIONAHA.118.035235.
63. Organ CL, Otsuka H, Bhushan S, Wang Z, Bradley J, Trivedi R, et al. Choline diet and its gut microbe-derived metabolite, trimethylamine N-oxide, exacerbate pressure overload-induced heart failure. Circ Heart Fail. 2016;9(1):e002314. https://doi.org/10.1161/CIRCHEARTFAILURE.115.002314.
64. Chen R, Xu Y, Wu P, Zhou H, Lasanajak Y, Fang Y, et al. Transplantation of fecal microbiota rich in short chain fatty acids and butyric acid treat cerebral ischemic stroke by regulating gut microbiota. Pharmacol Res. 2019;148:104403. https://doi.org/10.1016/j.phrs.2019.104403.
65. Farr S, Stankovic B, Hoffman S, Masoudpoor H, Baker C, Taher J, et al. Bile acid treatment and FXR agonism lower postprandial lipemia in mice. Am J Physiol Gastrointest Liver Physiol. 2020;318(4):G682–G93. https://doi.org/10.1152/ajpgi.00386.2018.
66. Zhai X, Lin D, Zhao Y, Li W, Yang X. Effects of dietary fiber supplementation on fatty acid metabolism and intestinal microbiota diversity in C57BL/6J mice fed with a high-fat diet. J Agric Food Chem. 2018;66(48):12706–18. https://doi.org/10.1021/acs.jafc.8b05036.
67. Zhao L, Zhang F, Ding X, Wu G, Lam YY, Wang X, et al. Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. Science. 2018;359(6380):1151–6. https://doi.org/10.1126/science.aao5774.
68. Greco A, De Virgilio A, Rizzo MI, Tombolini M, Gallo A, Fusconi M, et al. Kawasaki disease: an evolving paradigm. Autoimmun Rev. 2015;14(8):703–9. https://doi.org/10.1016/j.autrev.2015.04.002.
69. Jaggi P, Kajon AE, Mejias A, Ramilo O, Leber A. Human adenovirus infection in Kawasaki disease: a confounding bystander? Clin Infect Dis. 2013;56(1):58–64. https://doi.org/10.1093/cid/cis807.
70. Holm JM, Hansen LK, Oxhoj H. Kawasaki disease associated with parvovirus B19 infection. Eur J Pediatr. 1995;154(8):633–4. https://doi.org/10.1007/BF02079066.
71. Barton M, Melbourne R, Morais P, Christie C. Kawasaki syndrome associated with group a streptococcal and Epstein-Barr virus co-infections. Ann Trop Paediatr. 2002;22(3):257–60. https://doi.org/10.1179/027249302125001543.
72. Kanegane H, Tsuji T, Seki H, Yachie A, Yokoi T, Miyawaki T, et al. Kawasaki disease with a concomitant primary Epstein-Barr virus infection.

Acta Paediatr Jpn. 1994;36(6):713–6. https://doi.org/10.1111/j.1442-200x.1994.tb03277.x.
73. Matsubara K, Fukaya T, Miwa K, Shibayama N, Nigami H, Harigaya H, et al. Development of serum IgM antibodies against superantigens of Staphylococcus aureus and streptococcus pyogenes in Kawasaki disease. Clin Exp Immunol. 2006;143(3):427–34. https://doi.org/10.1111/j.1365-2249.2006.03015.x.
74. Anderson DG, Warner G, Barlow E. Kawasaki disease associated with streptococcal infection within a family. J Paediatr Child Health. 1995;31(4):355–7. https://doi.org/10.1111/j.1440-1754.1995.tb00827.x.
75. Wang JN, Wang SM, Liu CC, Wu JM. Mycoplasma pneumoniae infection associated with Kawasaki disease. Acta Paediatr. 2001;90(5):594–5. https://doi.org/10.1111/j.1651-2227.2001.tb00810.x.
76. Normann E, Naas J, Gnarpe J, Backman H, Gnarpe H. Demonstration of chlamydia pneumoniae in cardiovascular tissues from children with Kawasaki disease. Pediatr Infect Dis J. 1999;18(1):72–3. https://doi.org/10.1097/00006454-199901000-00020.
77. Burns JC, Herzog L, Fabri O, Tremoulet AH, Rodo X, Uehara R, et al. Seasonality of Kawasaki disease: a global perspective. PLoS One. 2013;8(9):e74529. https://doi.org/10.1371/journal.pone.0074529.
78. Yanagawa H, Nakamura Y, Kawasaki T, Shigematsu I. Nationwide epidemic of Kawasaki disease in Japan during winter of 1985-86. Lancet. 1986;2(8516):1138–9. https://doi.org/10.1016/s0140-6736(86)90541-6.
79. Burgner D, Harnden A. Kawasaki disease: what is the epidemiology telling us about the etiology? Int J Infect Dis. 2005;9(4):185–94. https://doi.org/10.1016/j.ijid.2005.03.002.
80. Nomura Y, Yoshinaga M, Masuda K, Takei S, Miyata K. Maternal antibody against toxic shock syndrome toxin-1 may protect infants younger than 6 months of age from developing Kawasaki syndrome. J Infect Dis. 2002;185(11):1677–80. https://doi.org/10.1086/340513.
81. Muso E, Fujiwara H, Yoshida H, Hosokawa R, Yashiro M, Hongo Y, et al. Epstein-Barr virus genome-positive tubulointerstitial nephritis associated with Kawasaki disease-like coronary aneurysms. Clin Nephrol. 1993;40(1):7–15.
82. Kikuta H, Matsumoto S, Osato T. Kawasaki disease and Epstein-Barr virus. Acta Paediatr Jpn. 1991;33(6):765–70. https://doi.org/10.1111/j.1442-200x.1991.tb02606.x.
83. Shingadia D, Bose A, Booy R. Could a herpesvirus be the cause of Kawasaki disease? Lancet Infect Dis. 2002;2(5):310–3. https://doi.org/10.1016/s1473-3099(02)00265-7.
84. Johnson RM, Bergmann KR, Manaloor JJ, Yu X, Slaven JE, Kharbanda AB. Pediatric Kawasaki disease and adult human immunodeficiency virus Kawasaki-like syndrome are likely the same malady. Open forum. Infect Dis. 2016;3(3):ofw160. https://doi.org/10.1093/ofid/ofw160.
85. Okano M, Thiele GM, Sakiyama Y, Matsumoto S, Purtilo DT. Adenovirus infection in patients with Kawasaki disease. J Med Virol. 1990;32(1):53–7. https://doi.org/10.1002/jmv.1890320109.
86. Esper F, Shapiro ED, Weibel C, Ferguson D, Landry ML, Kahn JS. Association between a novel human coronavirus and Kawasaki disease. J Infect Dis. 2005;191(4):499–502. https://doi.org/10.1086/428291.
87. Shulman ST, Rowley AH, Fresco R, Morrison DC. The etiology of Kawasaki disease: retrovirus? Prog Clin Biol Res. 1987;250:117–24.
88. Nigro G, Zerbini M, Krzysztofiak A, Gentilomi G, Porcaro MA, Mango T, et al. Active or recent parvovirus B19 infection in children with Kawasaki disease. Lancet. 1994;343(8908):1260–1. https://doi.org/10.1016/s0140-6736(94)92154-7.
89. Santos RA, Nogueira CS, Granja S, Baptista JB, Ribeiro ML, Rocha MG. Kawasaki disease and human bocavirus--potential association? J Microbiol Immunol Infect. 2011;44(3):235–7. https://doi.org/10.1016/j.jmii.2011.01.016.
90. Magboul S, Khalil A, Hassan M, Habra B, Alshami A, Khan S, et al. Multisystem inflammatory syndrome in children (MIS-C) related to COVID-19 infection in the state of Qatar: association with Kawasaki-like illness. Acta Biomed. 2022;92(6):e2021543. https://doi.org/10.23750/abm.v92i6.11991.
91. Leung DY, Meissner HC, Fulton DR, Murray DL, Kotzin BL, Schlievert PM. Toxic shock syndrome toxin-secreting Staphylococcus aureus in Kawasaki syndrome. Lancet. 1993;342(8884):1385–8. https://doi.org/10.1016/0140-6736(93)92752-f.
92. Yoshioka T, Matsutani T, Iwagami S, Toyosaki-Maeda T, Yutsudo T, Tsuruta Y, et al. Polyclonal expansion of TCRBV2- and TCRBV6-bearing T cells in patients with Kawasaki disease. Immunology. 1999;96(3):465–72. https://doi.org/10.1046/j.1365-2567.1999.00695.x.
93. Vollmer-Conna U, Piraino BF, Cameron B, Davenport T, Hickie I, Wakefield D, et al. Cytokine polymorphisms have a synergistic effect on severity of the acute sickness response to infection. Clin Infect Dis. 2008;47(11):1418–25. https://doi.org/10.1086/592967.
94. Horinouchi T, Nozu K, Hamahira K, Inaguma Y, Abe J, Nakajima H, et al. Yersinia pseudotuberculosis infection in Kawasaki disease and its clinical characteristics. BMC Pediatr. 2015;15:177. https://doi.org/10.1186/s12887-015-0497-2.
95. Kusuda T, Nakashima Y, Murata K, Kanno S, Nishio H, Saito M, et al. Kawasaki disease-specific molecules in the sera are linked to microbe-associated molecular patterns in the biofilms. PLoS One. 2014;9(11):e113054. https://doi.org/10.1371/journal.pone.0113054.

96. Vitale EA, La Torre F, Calcagno G, Infricciori G, Fede C, Conti G, et al. Mycoplasma pneumoniae: a possible trigger of Kawasaki disease or a mere coincidental association? Report of the first four Italian cases. Minerva Pediatr. 2010;62(6):605–7.
97. Yokota S, Tsubaki K, Kuriyama T, Shimizu H, Ibe M, Mitsuda T, et al. Presence in Kawasaki disease of antibodies to mycobacterial heat-shock protein HSP65 and autoantibodies to epitopes of human HSP65 cognate antigen. Clin Immunol Immunopathol. 1993;67(2):163–70. https://doi.org/10.1006/clin.1993.1060.
98. Rathore MH, Barton LL, Dawson JE, Regnery RL, Ayoub EM. Ehrlichia chaffeensis and Rochalimaea antibodies in Kawasaki disease. J Clin Microbiol. 1993;31(11):3058–9. https://doi.org/10.1128/jcm.31.11.3058-3059.1993.
99. Weir WR, Bouchet VA, Mitford E, Taylor RF, Smith H. Kawasaki disease in European adult associated with serological response to Coxiella burneti. Lancet. 1985;2(8453):504. https://doi.org/10.1016/s0140-6736(85)90440-4.
100. Rodo X, Curcoll R, Robinson M, Ballester J, Burns JC, Cayan DR, et al. Tropospheric winds from northeastern China carry the etiologic agent of Kawasaki disease from its source to Japan. Proc Natl Acad Sci U S A. 2014;111(22):7952–7. https://doi.org/10.1073/pnas.1400380111.
101. Rowley AH, Baker SC, Shulman ST, Rand KH, Tretiakova MS, Perlman EJ, et al. Ultrastructural, immunofluorescence, and RNA evidence support the hypothesis of a "new" virus associated with Kawasaki disease. J Infect Dis. 2011;203(7):1021–30. https://doi.org/10.1093/infdis/jiq136.
102. Rowley AH, Baker SC, Shulman ST, Garcia FL, Fox LM, Kos IM, et al. RNA-containing cytoplasmic inclusion bodies in ciliated bronchial epithelium months to years after acute Kawasaki disease. PLoS One. 2008;3(2):e1582. https://doi.org/10.1371/journal.pone.0001582.
103. Rowley AH, Baker SC, Shulman ST, Fox LM, Takahashi K, Garcia FL, et al. Cytoplasmic inclusion bodies are detected by synthetic antibody in ciliated bronchial epithelium during acute Kawasaki disease. J Infect Dis. 2005;192(10):1757–66. https://doi.org/10.1086/497171.
104. Song E, Kajon AE, Wang H, Salamon D, Texter K, Ramilo O, et al. Clinical and virologic characteristics may aid distinction of acute adenovirus disease from Kawasaki disease with incidental adenovirus detection. J Pediatr. 2016;170:325–30. https://doi.org/10.1016/j.jpeds.2015.11.021.
105. Turnier JL, Anderson MS, Heizer HR, Jone PN, Glode MP, Dominguez SR. Concurrent respiratory viruses and Kawasaki disease. Pediatrics. 2015;136(3):e609–14. https://doi.org/10.1542/peds.2015-0950.
106. Shimizu C, Shike H, Baker SC, Garcia F, van der Hoek L, Kuijpers TW, et al. Human coronavirus NL63 is not detected in the respiratory tracts of children with acute Kawasaki disease. J Infect Dis. 2005;192(10):1767–71. https://doi.org/10.1086/497170.
107. Xu S, Chen M, Weng J. COVID-19 and Kawasaki disease in children. Pharmacol Res. 2020;159:104951. https://doi.org/10.1016/j.phrs.2020.104951.
108. Viner RM, Whittaker E. Kawasaki-like disease: emerging complication during the COVID-19 pandemic. Lancet. 2020;395(10239):1741–3. https://doi.org/10.1016/S0140-6736(20)31129-6.
109. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet. 2020;395(10239):1771–8. https://doi.org/10.1016/S0140-6736(20)31103-X.
110. Moreira A. Kawasaki disease linked to COVID-19 in children. Nat Rev Immunol. 2020;20(7):407. https://doi.org/10.1038/s41577-020-0350-1.
111. Proft T, Fraser JD. Bacterial superantigens. Clin Exp Immunol. 2003;133(3):299–306. https://doi.org/10.1046/j.1365-2249.2003.02203.x.
112. Yoshioka T, Matsutani T, Toyosaki-Maeda T, Suzuki H, Uemura S, Suzuki R, et al. Relation of streptococcal pyrogenic exotoxin C as a causative superantigen for Kawasaki disease. Pediatr Res. 2003;53(3):403–10. https://doi.org/10.1203/01.PDR.0000049668.54870.50.
113. Ohno N. Murine model of Kawasaki disease induced by mannoprotein-beta-glucan complex, CAWS, obtained from Candida albicans. Jpn J Infect Dis. 2004;57(5):S9–10.
114. Ishida-Okawara A, Nagi-Miura N, Oharaseki T, Takahashi K, Okumura A, Tachikawa H, et al. Neutrophil activation and arteritis induced by C. albicans water-soluble mannoprotein-beta-glucan complex (CAWS). Exp Mol Pathol. 2007;82(2):220–6. https://doi.org/10.1016/j.yexmp.2006.05.006.
115. Nagi-Miura N, Okuzaki D, Torigata K, Sakurai MA, Ito A, Ohno N, et al. CAWS administration increases the expression of interferon gamma and complement factors that lead to severe vasculitis in DBA/2 mice. BMC Immunol. 2013;14:44. https://doi.org/10.1186/1471-2172-14-44.
116. Takahashi K, Oharaseki T, Wakayama M, Yokouchi Y, Naoe S, Murata H. Histopathological features of murine systemic vasculitis caused by Candida albicans extract--an animal model of Kawasaki disease. Inflamm Res. 2004;53(2):72–7. https://doi.org/10.1007/s00011-003-1225-1.
117. Miura NN, Komai M, Adachi Y, Osada N, Kameoka Y, Suzuki K, et al. IL-10 is a negative regulatory factor of CAWS-vasculitis in CBA/J mice as assessed by comparison with Bruton's tyrosine kinase-deficient CBA/N mice. J Immunol. 2009;183(5):3417–24. https://doi.org/10.4049/jimmunol.0802484.
118. Guan Z, Jia J, Zhang C, Sun T, Zhang W, Yuan W, et al. Gut microbiome dysbiosis alleviates the progression of osteoarthritis in mice. Clin Sci (Lond).

2020;134(23):3159–74. https://doi.org/10.1042/CS20201224.
119. Larabi A, Barnich N, Nguyen HTT. New insights into the interplay between autophagy, gut microbiota and inflammatory responses in IBD. Autophagy. 2020;16(1):38–51. https://doi.org/10.1080/15548627.2019.1635384.
120. Amoroso C, Perillo F, Strati F, Fantini MC, Caprioli F, Facciotti F. The role of gut microbiota biomodulators on mucosal immunity and intestinal inflammation. Cell. 2020;9(5):1234. https://doi.org/10.3390/cells9051234.
121. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. Cell. 2014;157(1):121–41. https://doi.org/10.1016/j.cell.2014.03.011.
122. Eladawy M, Dominguez SR, Anderson MS, Glode MP. Kawasaki disease and the pediatric gastroenterologist: a diagnostic challenge. J Pediatr Gastroenterol Nutr. 2013;56(3):297–9. https://doi.org/10.1097/MPG.0b013e3182794432.
123. Takeshita S, Nakatani K, Kawase H, Seki S, Yamamoto M, Sekine I, et al. The role of bacterial lipopolysaccharide-bound neutrophils in the pathogenesis of Kawasaki disease. J Infect Dis. 1999;179(2):508–12. https://doi.org/10.1086/314600.
124. Takeshita S, Tsujimoto H, Kawase H, Kawamura Y, Sekine I. Increased levels of lipopolysaccharide binding protein in plasma in children with Kawasaki disease. Clin Diagn Lab Immunol. 2002;9(1):205–6. https://doi.org/10.1128/cdli.9.1.205-206.2002.
125. Akiyama T, Yashiro K. Probable role of streptococcus pyogenes in Kawasaki disease. Eur J Pediatr. 1993;152(2):82–92. https://doi.org/10.1007/BF02072479.
126. Hall M, Hoyt L, Ferrieri P, Schlievert PM, Jenson HB. Kawasaki syndrome-like illness associated with infection caused by enterotoxin B-secreting Staphylococcus aureus. Clin Infect Dis. 1999;29(3):586–9. https://doi.org/10.1086/598638.
127. Ferwerda A, Moll HA, de Groot R. Respiratory tract infections by mycoplasma pneumoniae in children: a review of diagnostic and therapeutic measures. Eur J Pediatr. 2001;160(8):483–91. https://doi.org/10.1007/s004310100775.
128. Principi N, Rigante D, Esposito S. The role of infection in Kawasaki syndrome. J Infect. 2013;67(1):1–10. https://doi.org/10.1016/j.jinf.2013.04.004.
129. Yamashiro Y, Nagata S, Ohtsuka Y, Oguchi S, Shimizu T. Microbiologic studies on the small intestine in Kawasaki disease. Pediatr Res. 1996;39(4 Pt 1):622–4. https://doi.org/10.1203/00006450-199604000-00010.
130. Blaabjerg S, Artzi DM, Aabenhus R. Probiotics for the prevention of antibiotic-associated diarrhea in outpatients-a systematic review and meta-analysis. Antibiotics (Basel). 2017;6(4):21. https://doi.org/10.3390/antibiotics6040021.
131. Vanderhoof JA, Whitney DB, Antonson DL, Hanner TL, Lupo JV, Young RJ. Lactobacillus GG in the prevention of antibiotic-associated diarrhea in children. J Pediatr. 1999;135(5):564–8. https://doi.org/10.1016/s0022-3476(99)70053-3.
132. Singer-Englar T, Barlow G, Mathur R. Obesity, diabetes, and the gut microbiome: an updated review. Expert Rev Gastroenterol Hepatol. 2019;13(1):3–15. https://doi.org/10.1080/17474124.2019.1543023.
133. Brunkwall L, Orho-Melander M. The gut microbiome as a target for prevention and treatment of hyperglycaemia in type 2 diabetes: from current human evidence to future possibilities. Diabetologia. 2017;60(6):943–51. https://doi.org/10.1007/s00125-017-4278-3.
134. Fedorak RN, Feagan BG, Hotte N, Leddin D, Dieleman LA, Petrunia DM, et al. The probiotic VSL#3 has anti-inflammatory effects and could reduce endoscopic recurrence after surgery for Crohn's disease. Clin Gastroenterol Hepatol. 2015;13(5):928–35 e2. https://doi.org/10.1016/j.cgh.2014.10.031.
135. Liong MT. Roles of probiotics and prebiotics in colon cancer prevention: postulated mechanisms and in-vivo evidence. Int J Mol Sci. 2008;9(5):854–63. https://doi.org/10.3390/ijms9050854.
136. Wang Z, Klipfell E, Bennett BJ, Koeth R, Levison BS, Dugar B, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature. 2011;472(7341):57–63. https://doi.org/10.1038/nature09922.
137. Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, Sheehy BT, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med. 2013;19(5):576–85. https://doi.org/10.1038/nm.3145.
138. Nemet I, Saha PP, Gupta N, Zhu W, Romano KA, Skye SM, et al. A cardiovascular disease-linked gut microbial metabolite acts via adrenergic receptors. Cell. 2020;180(5):862–77 e22. https://doi.org/10.1016/j.cell.2020.02.016.
139. Takeshita S, Kobayashi I, Kawamura Y, Tokutomi T, Sekine I. Characteristic profile of intestinal microflora in Kawasaki disease. Acta Paediatr. 2002;91(7):783–8. https://doi.org/10.1080/08035250213221.
140. Nagata S, Yamashiro Y, Ohtsuka Y, Shimizu T, Sakurai Y, Misawa S, et al. Heat shock proteins and superantigenic properties of bacteria from the gastrointestinal tract of patients with Kawasaki disease. Immunology. 2009;128(4):511–20. https://doi.org/10.1111/j.1365-2567.2009.03135.x.
141. Hassidim A, Merdler I, Chorin O, Merdler-Rabinowicz R, Dallal I, Perlman M, et al. Atopic predilection among Kawasaki disease patients: a cross-sectional study of 1,187,757 teenagers. Int Arch Allergy Immunol. 2016;170(2):92–6. https://doi.org/10.1159/000447639.
142. Woon PY, Chang WC, Liang CC, Hsu CH, Klahan S, Huang YH, et al. Increased risk of atopic dermatitis in preschool children with Kawasaki disease: a population-based study in Taiwan. Evid Based

Complement Alternat Med. 2013;2013:605123. https://doi.org/10.1155/2013/605123.
143. Hwang CY, Hwang YY, Chen YJ, Chen CC, Lin MW, Chen TJ, et al. Atopic diathesis in patients with Kawasaki disease. J Pediatr. 2013;163(3):811–5. https://doi.org/10.1016/j.jpeds.2013.03.068.
144. Salameh M, Burney Z, Mhaimeed N, Laswi I, Yousri NA, Bendriss G, et al. The role of gut microbiota in atopic asthma and allergy, implications in the understanding of disease pathogenesis. Scand J Immunol. 2020;91(3):e12855. https://doi.org/10.1111/sji.12855.
145. Singh S, Jindal AK, Pilania RK. Diagnosis of Kawasaki disease. Int J Rheum Dis. 2018;21(1):36–44. https://doi.org/10.1111/1756-185X.13224.
146. Han SB, Lee SY. Antibiotic use in children with Kawasaki disease. World J Pediatr. 2018;14(6):621–2. https://doi.org/10.1007/s12519-018-0157-3.
147. Panda S, El Khader I, Casellas F, Lopez Vivancos J, Garcia Cors M, Santiago A, et al. Short-term effect of antibiotics on human gut microbiota. PLoS One. 2014;9(4):e95476. https://doi.org/10.1371/journal.pone.0095476.
148. Nagata S, Yamashiro Y, Maeda M, Ohtsuka Y, Yabuta K. Immunohistochemical studies on small intestinal mucosa in Kawasaki disease. Pediatr Res. 1993;33(6):557–63. https://doi.org/10.1203/00006450-199306000-00004.
149. Horita N, Yokota S, Fuse S, Takamuro M, Tomita H, Sato K, et al. The throat flora and its mitogenic activity in patients with Kawasaki disease. Microbiol Immunol. 2004;48(11):899–903. https://doi.org/10.1111/j.1348-0421.2004.tb03609.x.
150. de Paiva CS, Jones DB, Stern ME, Bian F, Moore QL, Corbiere S, et al. Altered mucosal microbiome diversity and disease severity in Sjogren syndrome. Sci Rep. 2016;6:23561. https://doi.org/10.1038/srep23561.
151. Qin N, Yang F, Li A, Prifti E, Chen Y, Shao L, et al. Alterations of the human gut microbiome in liver cirrhosis. Nature. 2014;513(7516):59–64. https://doi.org/10.1038/nature13568.
152. Khan I, Li XA, Law B, KI U, Pan BQ, Lei C, et al. Correlation of gut microbial compositions to the development of Kawasaki disease vasculitis in children. Future Microbiol. 2020;15:591–600. https://doi.org/10.2217/fmb-2019-0301.
153. Shen J, Ding Y, Yang Z, Zhang X, Zhao M. Effects of changes on gut microbiota in children with acute Kawasaki disease. PeerJ. 2020;8:e9698. https://doi.org/10.7717/peerj.9698.
154. Chen J, Yue Y, Wang L, Deng Z, Yuan Y, Zhao M, et al. Altered gut microbiota correlated with systemic inflammation in children with Kawasaki disease. Sci Rep. 2020;10(1):14525. https://doi.org/10.1038/s41598-020-71371-6.
155. Kaneko K, Akagawa S, Akagawa Y, Kimata T, Tsuji S. Our evolving understanding of Kawasaki disease pathogenesis: role of the gut microbiota. Front Immunol. 2020;11:1616. https://doi.org/10.3389/fimmu.2020.01616.

Allergic Diseases and Association with Kawasaki Disease

Ling-Sai Chang

Abstract

Kawasaki disease (KD) is an acute inflammatory disease. Numerous studies over the last several years have well described that KD has been related to allergic diseases such as allergic rhinitis, asthma, and atopic dermatitis. Aberrant basophils, eosinophils, and mediators of type 2 inflammation and immunologic imbalance related to uncertain pathologic stimulation in KD are associated with the development of allergic diseases. KD and allergic diseases, which share common pathways and interrelate reciprocally, are a great concern. In the process of inflammation, immunologic changes in combination with increased permeability may result in more allergen sensitization. In this chapter, we reviewed pieces of evidence that suggest KD is associated with allergic diseases. Early detection and prevention of allergic diseases are important for KD patients. Investigation of atopy including total and specific immunoglobulin E in patients with KD can facilitate better care of KD during follow-up.

Keywords

Allergic diseases · Allergic rhinitis · Atopic dermatitis · Asthma · Immunoglobulin E Kawasaki disease

The manifestation of allergic diseases is chronic inflammation and all of allergic diseases have several sub-forms. Therefore, the importance of regular follow-up visits is particularly emphasized in the treatment guidelines [1]. Childhood-onset diseases are more often associated with genetic predisposition. This situation is no exception in inflammatory diseases [2–4]. In terms of family history, it was found that 39.8% children with Kawasaki disease (KD) less than one year old had a mother with a history of at least one allergic disease [5]. In a retrospective study lacking a control group, atopic dermatitis and asthma were the most common allergic diseases in KD patients after hospitalization [5].

Allergy-Related Biomarkers in Kawasaki Disease

Patients with KD experience allergic diseases both before and after KD [6, 7]. Among 512 Japanese patients hospitalized with KD, 37.9% had at least one allergic disease [5]. The development of allergic diseases associated with KD remains poorly understood. Patients with KD

L.-S. Chang (✉)
Kawasaki Disease Center and Department of Pediatrics, Kaohsiung Chang Gung, Memorial Hospital, Kaohsiung, Taiwan
e-mail: 8702034@cgmh.org.tw

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undergo type 2 inflammation [6]. In a study using plasma samples from patients with KD, patients with KD demonstrated high immunoglobulin (Ig) E levels from acute phase to convalescent phase to normal phase [8]. Significantly more intravenous immunoglobulin (IVIG) resistance was observed in the low eosinophil (peripheral eosinophils <4%) group than in the eosinophilia group three days after IVIG treatment [9]. Higher eosinophils, eosinophil-related mediators: interleukin (IL)-4, IL-5, eotaxin, and eosinophil cationic protein levels were also found in patients with KD than controls [10]. In particular, Kuo et al. observed higher eosinophil and IL-5 levels in KD patients without CAL group three days after IVIG. In the process of regulating the cytokine of allergic inflammation, CD40, which controlled the activation of T cells, also rose [11]. Patients with KD also showed that T cells were activated [12, 13]. Medications including IVIG are also suspected to increase eosinophils in children with enterovirus infection after IVIG treatment [14]. The mechanism of the correlation between type 2 inflammation and clinical prognosis warrants further clarification. Although elevated total IgE levels in patients with KD were not associated with clinical outcomes, it is still unclear whether the occurrence of allergic diseases is related to the prognosis of KD [8].

Several pilot studies have reported alterations of gut microbiota and metabolites in KD patients [15]. Gut microbiota producing short chain fatty acids, especially butyrate, affect Th17s/Tregs balance [16]. A growing body of literature suggests butyrate regulates type 2 inflammation through epigenetic changes [11, 12]. Butyrate inhibited eosinophil migration and promoted eosinophil apoptosis [16]. A pilot study enrolled four individuals with KD and four healthy children, finding significantly reduced butyrate in the fecal samples of KD patients. Aberrant Th17s/Tregs balance in patients with KD has been well studied [17]. The important roles dysbiosis play would provide valuable information regarding the strong association between KD and allergic diseases [18]. Figure 1 showed the effects of microbiota-associated butyrate on immunopathogenesis in KD.

Allergic Diseases and Association with Kawasaki Disease

Sometimes we may think that after IVIG treatment, KD will be cured and ignore the importance of clinical follow-up. According to the evidence provided by the National Health Insurance database in Taiwan and several publications, the three

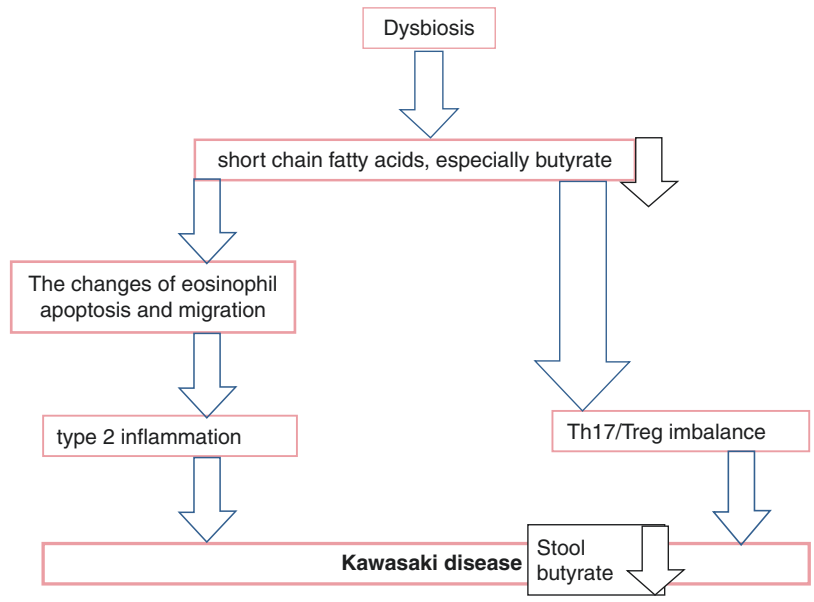

Fig. 1 Involvement of altered gut microbiota associated with butyrate in systemic inflammation of Kawasaki disease. Reg, regulatory, T helper type (Th)17

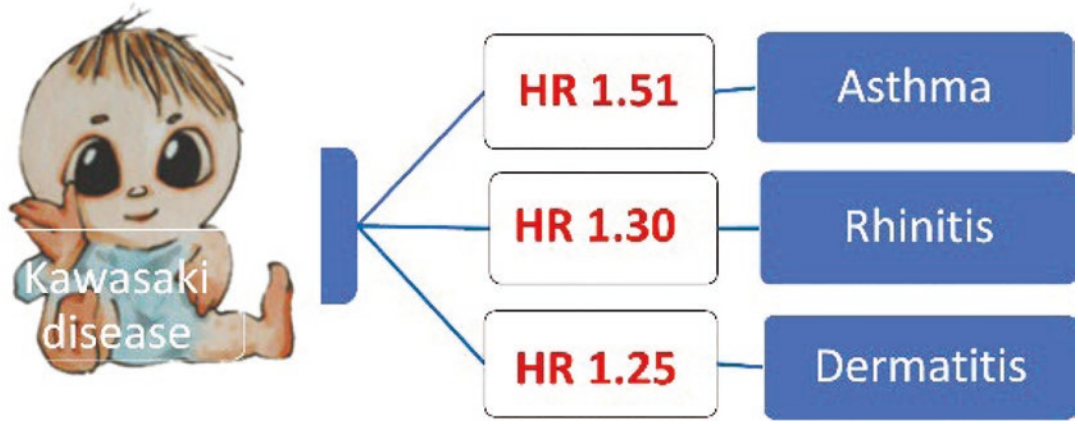

Fig. 2 Population-based matched cohort studies revealed subsequent risks of allergic diseases after Kawasaki disease in Taiwan. HR, adjusted hazard ratio

most common allergic diseases after KD are allergic rhinitis, asthma, and atopic dermatitis [19–21]. The incidence of KD in Taiwan has almost doubled significantly [22]. In the year of 2013, four studies using the Taiwan National Health Insurance Database were published in international journals, all on topics related to research on allergic diseases and KD [19–21, 23]. As a research tool, big data provided us with many research findings for understanding the relationship between KD and other diseases. Population-based matched cohort studies revealed subsequent risks of allergic diseases after KD in Taiwan shown in Fig. 2 [19, 21]. Starting from the age of one, children with KD begin to have a higher rate of allergic diseases [20]. Allergic tendency continues into school age [20]. Between one and five years of age, male patients have an increased risk of atopic dermatitis (odds ratio 3.02, 95% confidence interval, CI: 1.22–7.50) [23]. More than 60% of children developed allergic diseases after KD was diagnosed [23]. Most allergic diseases occur after the onset of KD [23].

Allergic Diseases Before Kawasaki Disease

Children with a single allergic disease are at increased risk of KD, 1.82 times risk in urticaria [7], 1.44 times risk (95% CI, 1.23–1.70) in allergic rhinitis, and 1.22 times risk (95% CI, 1.06–1.39) in atopic dermatitis. The risk of KD increases with the number of concurrent allergic diseases [7]. Children with only one allergic disease has a 1.61 times risk (95% CI, 1.43–1.82) of KD. At least two allergic diseases have a 1.71 times risk (95% CI, 1.48–1.98) of KD. Children who have two or more visits to related allergic diseases each year also have an increased risk of KD [7]. As the prevalence of allergic diseases is significantly increased in the past two decades so as the increase of KD, whether they cause the increase in the incidence of KD is also a very important issue and still needs further investigation to reach a conclusion [22].

Asthma and Kawasaki Disease

Recent meta-analysis focused on asthma and KD summarized that asthma before KD did not increase the incidence of KD, which is consistent with the Wei's report by Taiwan Health Insurance Database [7, 24]. On the contrary, asthma after KD had an increasing trend [24]. Some investigators considered it was only a temporary mild asthma, some considered it would increase the hospitalization rate compared with the control group [25].

It has been over 60 years after Dr. Kawasaki discovered the first KD patient in 1961, Dr.

Kawasaki passed away in 2020, but we have accumulated more and more experience in treating and following up KD patients, including allergic diseases in KD patients. Especially the increase in asthma, rhinitis, and atopic dermatitis in KD patients is particularly noteworthy. Allergic laboratory data and related symptoms survey may be suggested for the regular followed up schedule of KD patients.

References

1. Bousquet JJ, Schünemann HJ, Togias A, Erhola M, Hellings PW, Zuberbier T, et al. Next-generation ARIA care pathways for rhinitis and asthma: a model for multimorbid chronic diseases. Clin Transl Allergy. 2019;9:44.
2. Yang KD, Chang JC, Chuang H, Liang HM, Kuo HC, Lee YS, et al. Gene-gene and gene-environment interactions on IgE production in prenatal stage. Allergy. 2010;65(6):731–9.
3. Chang JC, Kuo HC, Hsu TY, Ou CY, Liu CA, Chuang H, et al. Different genetic associations of the IgE production among fetus, infancy and childhood. PLoS One. 2013;8(8):e70362.
4. Xie X, Shi X, Liu M. The roles of genetic factors in Kawasaki disease: a systematic review and meta-analysis of genetic association studies. Pediatr Cardiol. 2018;39(2):207–25.
5. Matsubara T, Fujita Y, Sato T, Sasai K, Furukawa S. The prevalence of allergy in Kawasaki disease. Allergy. 1998;53(8):815–6.
6. Huang PY, Huang YH, Guo MM, Chang LS, Kuo HC. Kawasaki disease and allergic diseases. Front Pediatr. 2020;8:614386.
7. Wei CC, Lin CL, Kao CH, Liao YH, Shen TC, Tsai JD, et al. Increased risk of Kawasaki disease in children with common allergic diseases. Ann Epidemiol. 2014;24(5):340–3.
8. Kim JJ, Kim HJ, Yu JJ, Yun SW, Lee KY, Yoon KL, et al. IgA levels are associated with coronary artery lesions in Kawasaki disease. Korean Circ J. 2021;51(3):267–78.
9. Kuo HC, Yang KD, Liang CD, Bong CN, Yu HR, Wang L, et al. The relationship of eosinophilia to intravenous immunoglobulin treatment failure in Kawasaki disease. Pediatr Allergy Immunol. 2007;18(4):354–9.
10. Kuo HC, Wang CL, Liang CD, Yu HR, Huang CF, Wang L, et al. Association of lower eosinophil-related T helper 2 (Th2) cytokines with coronary artery lesions in Kawasaki disease. Pediatr Allergy Immunol. 2009;20(3):266–72.
11. Lee T, Nair P, Corrigan CJ. Review of monoclonal antibody therapies in asthma and allergic diseases - a new paradigm for precision medicine. Asian Pac J Allergy Immunol. 2020;38(2):78–90.
12. Lee YC, Kuo HC, Chang JS, Chang LY, Huang LM, Chen MR, et al. Two new susceptibility loci for Kawasaki disease identified through genome-wide association analysis. Nat Genet. 2012;44(5):522–5.
13. Chang LS, Yan JH, Li JY, Yeter DD, Huang YH, Guo MM, et al. Blood mercury levels in children with kawasaki disease and disease outcome. Int J Environ Res Public Health. 2020;17(10):3726.
14. Lin LY, Yang TH, Lin YJ, Yu HR, Yang KD, Huang YC, et al. Comparison of the laboratory data between Kawasaki disease and enterovirus after intravenous immunoglobulin treatment. Pediatr Cardiol. 2012;33(8):1269–74.
15. Kaneko K, Akagawa S, Akagawa Y, Kimata T, Tsuji S. Our evolving understanding of Kawasaki disease pathogenesis: role of the gut microbiota. Front Immunol. 2020;11:1616.
16. Yip W, Hughes MR, Li Y, Cait A, Hirst M, Mohn WW, et al. Butyrate shapes immune cell fate and function in allergic asthma. Front Immunol. 2021;12:628453.
17. Jia S, Li C, Wang G, Yang J, Zu Y. The T helper type 17/regulatory T cell imbalance in patients with acute Kawasaki disease. Clin Exp Immunol. 2010;162(1):131–7.
18. Chen J, Yue Y, Wang L, Deng Z, Yuan Y, Zhao M, et al. Altered gut microbiota correlated with systemic inflammation in children with Kawasaki disease. Sci Rep. 2020;10(1):14525.
19. Woon PY, Chang WC, Liang CC, Hsu CH, Klahan S, Huang YH, et al. Increased risk of atopic dermatitis in preschool children with Kawasaki disease: a population-based study in Taiwan. Evid Based Complement Alternat Med. 2013;2013:605123.
20. Tsai YJ, Lin CH, Fu LS, Fu YC, Lin MC, Jan SL. The association between Kawasaki disease and allergic diseases, from infancy to school age. Allergy Asthma Proc. 2013;34(5):467–72.
21. Kuo HC, Chang WC, Yang KD, Yu HR, Wang CL, Ho SC, et al. Kawasaki disease and subsequent risk of allergic diseases: a population-based matched cohort study. BMC Pediatr. 2013;13:38.
22. Huang YH, Lin KM, Ho SC, Yan JH, Lo MH, Kuo HC. Increased incidence of Kawasaki disease in Taiwan in recent years: a 15 years Nationwide population-based cohort study. Front Pediatr. 2019;7:121.
23. Hwang CY, Hwang YY, Chen YJ, Chen CC, Lin MW, Chen TJ, et al. Atopic diathesis in patients with Kawasaki disease. J Pediatr. 2013;163(3):811–5.
24. Wang Z, Zhang J, Dong L. Is there any association between asthma and Kawasaki disease? A systematic review and meta-analysis. Pediatr Pulmonol. 2021;56(8):2503–11.
25. Webster RJ, Carter KW, Warrington NM, Loh AM, Zaloumis S, Kuijpers TW, et al. Hospitalisation with infection, asthma and allergy in Kawasaki disease patients and their families: genealogical analysis using linked population data. PLoS One. 2011;6(11):e28004.