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Cardiovascular Lesions of Kawasaki Disease: From Genetic Study to Clinical Management

Ho-Chang Kuo and Wei-Chiao Chang

Additional information is available at the end of the chapter

1. Introduction

Kawasaki disease (KD) is an acute febrile systemic vasculitis that was first described by Kawasaki *et al.*(1) in 1967 in Japanese(2) and in 1974 in English. Currently, it is the leading cause of acquired heart disease in children in developed countries; however, its etiology remains unknown.(3-5) KD mainly affects children less than 5 years of age, especially those in Asian countries. In Japan, Korea, and Taiwan, the incidence ranges from 69 to 218 cases per 100,000 children less than 5 years of age.(6-9) The incidence of KD in Taiwan has increased from 66 to 69 cases per 100,000 children aged less than 5 years.(9-12) Its incidence worldwide is increasing, especially in Japan, where, in 2010, Nakamura *et al.* reported the country's highest rate of 239.6 cases per 100,000 children aged 0–4 years.(13) An epidemiologic survey of KD in Taiwan spanning 2003–2006 found that 1.5% of all cases was recurrent (having a second episode of KD and receiving intravenous immunoglobulin [IVIG] treatment).(9) In Taiwan, KD occurs most frequently in the summer (April to June) and least frequently in the winter; for unknown reasons, its seasonal occurrence varies in other countries. The most serious complication of KD is the development of coronary artery lesions (CAL), including myocardial infarction, coronary artery fistula formation,(14) coronary artery dilatation, and coronary artery aneurysm.(15)

The most commonly used definition of CAL (also known as coronary artery abnormality [CAA] or CAL) is based on the Japanese Ministry of Health criteria: maximum absolute internal diameter > 3 mm in children younger than 5 years of age or >4 mm in children 5 years and older, or a segmental diameter 1.5 times greater than that of an adjacent segment, or the presence of luminal irregularity.(16-21) Coronary arteries should be corrected relative to body surface area (if available) and expressed as standard deviation units from the mean (Z scores).(22) Several studies analyzed CAL, including aortic root dimension,(23) and transient CAL (the definition of "transient" varies among studies, from 30 days to 6–8 weeks

after diagnosis of disease). Thus, KD patients with coronary artery ectasia or dilatation that disappears within the first 8 weeks after disease onset are defined as having transient ectasia or dilatation (transient CAL). Kuo *et al.* reported the serious CAL analysis that comprised 341 KD patients;(24) 35% of KD patients had dilatation during the acute phase of admission, 17.2% still had dilatation 1 month after disease onset, 10.2% had dilatation at 2 months follow-up, and 4.1% had persistent CAL for more than 1 year.(25, 26) Ectasia or transient dilatations are somewhat considered to be a risk for a subsequent cardiovascular event or inflammation duration, rather than normal status.(27)

Although the clinical features of KD are recognizable, its underlying immunopathogenetic mechanisms are still under investigation, particularly the agent responsible for the development of CAL. KD is regarded as an autoimmune disorder rather than an infectious disease.(23) Kuo *et al.* reported that persistent monocytosis after IVIG treatment is associated with CAL formation.(28) Eosinophils in KD patients were also higher than that in age-matched febrile controls. In addition, IVIG treatment significantly increased eosinophils in KD patients. This increase of eosinophils after IVIG treatment is inversely correlated with IVIG treatment failure in KD.(29) Further studies have shown that eosinophil changes after IVIG treatment were positively correlated with changes in interleukin (IL)-5 levels. An increase in eosinophils and IL-5 levels after IVIG treatment is inversely correlated with CAL formation.(30) Recently, we found that incidence of allergic diseases (asthma and allergic rhinitis) after onset of KD were higher than that in age and sex-matched controls in a population cohort in Taiwan.

2. Allergy potential of Kawasaki disease patients

Brosius *et al.*(31) showed that the incidence of atopic dermatitis among children with KD was 9 times greater than that of controls. Burns *et al.*(32) reported associations of KD with atopic dermatitis and allergy, elevated serum IgE levels, and eosinophilia and that increased circulating numbers of monocytes/macrophages expressing the low-affinity IgE receptor (FCεR2) may be related to the effects of IL-4. Liew *et al.*(33) reported that KD may be a risk factor for subsequent allergic disease and postulated that KD occurs more frequently in children at risk of immune disequilibrium, with an initial abnormal inflammatory response, and subsequently, more allergic manifestations. Currently, Webster *et al.*(34) also reported that KD patients were more likely to have been admitted at least once with asthma/allergy than controls were. From our previous reports, we found that the T-helper (Th) type 2 immune response was elevated in the acute stage of KD, including eosinophils,(29) IL-4, IL-5,(35) and eotaxin. The eosinophil changes were correlated to changes of IL-5 levels but not to eosinophil cationic protein (ECP) levels, suggesting a Th2 immune reaction in KD. There are several lines of evidence pointing to an abnormal Th1/Th2 balance in KD patients.(28, 29, 35-39) Lin *et al.*(40) reported the comparison of eosinophils in KD and enterovirus (EV) patients with IVIG treatment and demonstrated a more significant eosinophil increase in KD patients. EV patients also had elevated eosinophil levels after IVIG therapy, but not as high as that of the KD patients after IVIG treatment. This may indicate an imbalance of the Th1/Th2 immune response, with a skewed Th2 response in KD.

3. Clinical phenotype and presentation of Kawasaki disease

As shown in Figures 1–8, the clinical characteristics of KD patients include fever lasting longer than 5 days, diffuse mucosal inflammation, bilateral non-purulent conjunctivitis, dysmorphic skin rashes, indurative angioedema over the hands and feet, and cervical lymphadenopathy. In addition to the diagnostic criteria, there is a broad range of non-specific clinical features, including irritability, uveitis, aseptic meningitis, cough, vomiting, diarrhea, abdominal pain, gallbladder hydrops, urethritis, arthralgia, arthritis, hypoalbuminemia,(5) liver function impairment, and heart failure.(4, 29, 41)

Figure 1. Dysmorphic skin rash of Kawasaki disease

Figure 2. Skin rash and neck lymphadenopathy (right side, >1.5 cm in diameter)
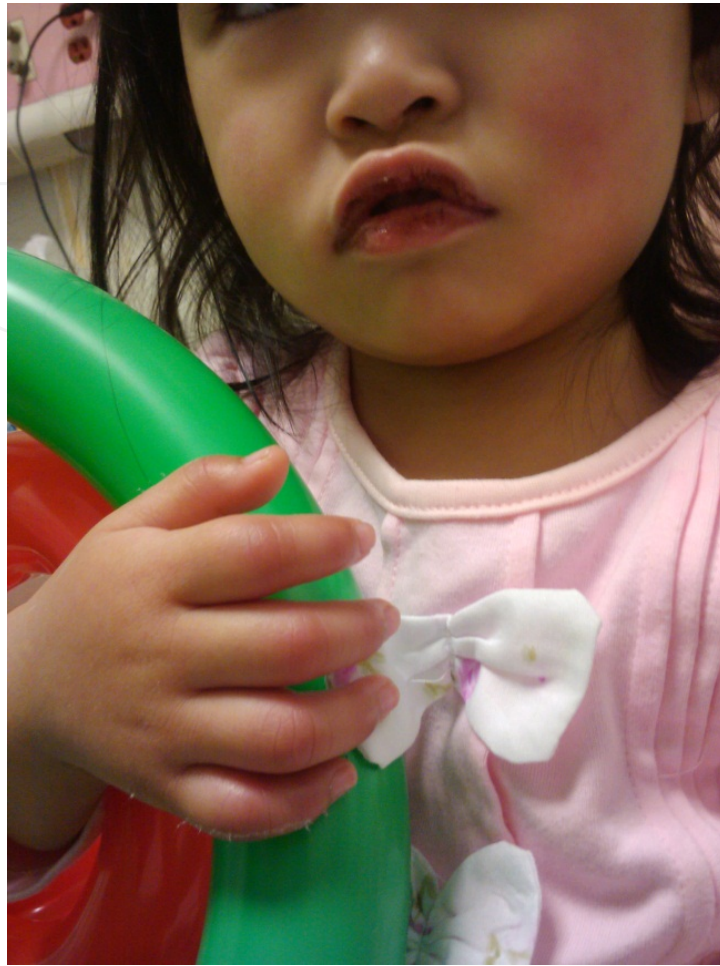
Figure 3. Strawberry tongue

Figure 4. Face of Kawasaki disease patient exhibiting conjunctivitis, fissured lips, and skin rashes

Figure 5. BCG injection site indurations

Figure 6. Fissured lips and swelling of finger joints

Figure 7. Induration change over foot

Figure 8. Induration change over palm

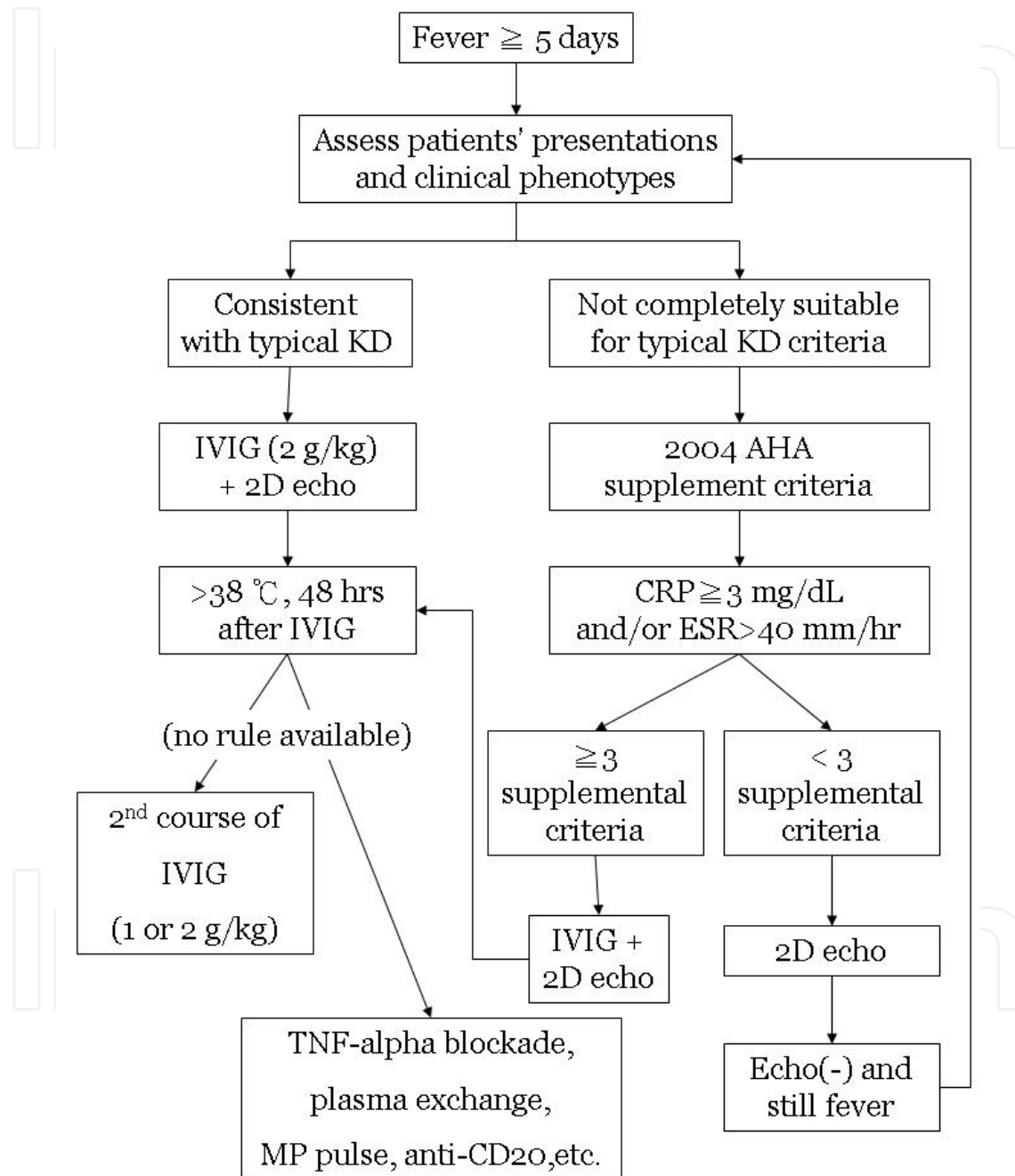## 3.1. Diagnosis of Kawasaki disease

To date, there is no specific diagnostic laboratory test for KD. Diagnosis is based on the clinical phenotype, i.e., presence of fever lasting longer than 5 days and fulfillment of 4 of 5 specific clinical criteria. In Japan, at least 5 of 6 criteria (fever and 5 other clinical criteria) should be fulfilled for a diagnosis of KD. However, patients with 4 of the principal clinical features can be diagnosed when coronary aneurysm or dilatation is identified.(42) From the Japanese Circulation Society Joint Working Groups criteria (JCS 2008, Guidelines for Diagnosis and Management of Cardiovascular Sequelae in Kawasaki Disease),(43) KD can be diagnosed even when fever lasts less than 5 days. However, according to the American Heart Association (AHA) criteria,(15) fever lasting more than 5 days is essential for the diagnosis of KD.

Some patients who do not fulfill the criteria have been diagnosed with "incomplete" or "atypical" KD, a diagnosis often based on echocardiographic identification of CAL. The term "incomplete" may be preferable to "atypical" because these patients have insufficient criteria instead of atypical presentation.(15)

In countries with a bacillus Calmette-Guérin (BCG) vaccine policy (i.e., Taiwan and Japan), KD with erythematous induration or even ulceration of the BCG scar has been observed in one-third to half of KD patients (the incidence of BCG site induration is higher than that of neck lymphadenopathy in these countries).(3) Uehara *et al.*(44) reported that redness or the formation of a crust at the BCG inoculation site is a useful diagnostic sign for KD in children aged 3–20 months. Even if patients exhibit 4 or fewer signs of the clinical criteria for KD, physicians should consider the redness or crust formation at the BCG inoculation site as a possible indicator of KD.

Incomplete cases of KD are not uncommon (up to 15–20%). The incidence of CAL in patients exhibiting 4 principal symptoms of KD is slightly higher than that in patients with 5 to 6 principal symptoms.(45) Presentation of a small number (<4) of principal symptoms does

not indicate a milder form of the disease. Patients with at least 4 principal symptoms require the same treatment as patients with complete (typical) presentation of KD, and those with 3 or fewer principal symptoms should be treated similarly when they meet the supplementary criteria. Herein, common supplementary criteria for the diagnosis of incomplete KD are introduced.

Figure 9. Flowchart of Kawasaki disease management

Incomplete KD is more common in young infants than in older children, making accurate diagnosis and timely treatment especially important in these young patients, who are at substantial risk of developing coronary abnormalities.(46, 47) The incidence of KD is

actually higher than that previously reported worldwide, partly because earlier reports did not take incomplete forms into account. The AHA criteria (2004), which incorporate suggestions for laboratory tests and early echocardiography, are helpful for diagnosing incomplete KD.(41, 48) Consultation with an expert (cardiologist, immunologist, or rheumatologist) should be sought whenever assistance in making a diagnosis is needed. Patients with fever for 5 days or more (with 2 or 3 principal clinical features for KD) without other causes 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. Likewise, infants 6 months or younger with fever for 7 days or more without other causes should undergo laboratory testing, and if evidence of systemic inflammation is found, an echocardiogram should be obtained even if the infant fulfills no clinical criteria for KD.(15)

The 2004 AHA supplemental laboratory criteria include (1) albumin ≤ 3.0 g/dL; (2) anemia for age; (3) elevation of alanine aminotransferase (ALT); (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.(15) If a patient has more than 3 supplementary criteria, incomplete KD is diagnosed and IVIG should be prescribed before performing echocardiography.(15) The flowchart for incomplete KD diagnosis and treatment are depicted in Figure 9.

4. Treatment for Kawasaki disease

The standard treatment for KD is IVIG (2 g/kg) infusion for 8–12 hours with high-dose aspirin (80–100 mg/[kg·day]).(20, 24, 29) The most serious complication of KD is the development of CAL, including myocardial infarction, coronary artery dilatation, coronary artery aneurysms, and coronary fistula formation.(25, 30, 49) Coronary artery aneurysms occur as a sequela of the vasculitis in 20–25% of untreated children. There are several risk factors for developing coronary arteritis, such as low serum albumin, age younger than 1 year, and long duration of the fever before treatment. Young patients with low albumin run a very high risk for CAL and IVIG treatment resistance.(5, 29) Although the introduction of IVIG therapy has greatly decreased the rate of coronary aneurysm to 3–10% of patients still develop some type of CAL. Durongpisitkul *et al.* showed that 11.6% patients are unresponsive to initial IVIG (2 g/kg) treatment. The worst prognosis occurs in children with so-called "giant aneurysms of the coronary arteries" (those with a maximal diameter of >8 mm), as thrombosis is promoted both by sluggish blood flow within the massively dilated vascular space and by the frequent development of stenotic lesions later. The treatment for KD are reviewed and introduced as follows.

4.1. Aspirin

Aspirin has been used in the treatment of KD for many years, even before the usage of IVIG. Although aspirin has important anti-inflammatory (high dose) and anti-platelet (low dose) effects, it does not appear to reduce the frequency of CAL formation. During the acute phase of the illness, aspirin is administered in 4 doses of 80–100 mg/kg per day (30–50 mg/[kg·day]

in Japan)(50) with IVIG. High-dose aspirin and IVIG appear to possess additive anti-inflammatory effects.

Practices regarding the duration of high-dose aspirin administration vary across countries and centers, many of which reduce the aspirin dose when the patient is afebrile. When high-dose aspirin is discontinued, low-dose aspirin (3–5 mg/[kg·day]) is administered until there is no evidence of CAL and inflammatory markers (including platelets, C-reactive protein [CRP], and erythrocyte sedimentation rate [ESR]) have returned to normal levels, which usually occurs 6–8 weeks after disease onset. For children who develop CAL, low-dose aspirin (or other anti-platelet agents) is continued indefinitely until the inflammatory markers return to the normal range and the echocardiogram does not display abnormalities. Hsieh *et al.*(50) reported that regardless of timing (before or after day 5 of the illness), single-infusion, high-dose (2 g/kg) aspirin in the acute stage of KD had no effect on the response rate to IVIG therapy, duration of fever, or the incidence of CAL. This review reiterates the recommendation that exposing children to high-dose aspirin therapy in the acute phase of KD is unnecessary because available data show no appreciable benefit to IVIG therapy response, CAL formation, or fever duration.

Our recent study investigated 609 KD patients from 2 medical centers in Taiwan. The patients were divided into Group 1, receiving high-dose aspirin (N = 274), and Group 2, without high-dose aspirin (N = 335). There were no significant differences between Groups 1 and 2 in terms of gender (p = 0.51), IVIG resistance rate (34/274 vs. 26/335, p = 0.06), CAL formation rate (57/274 vs. 74/335, p = 0.64), and total hospital stay (6.3 ± 0.2 vs. 6.7 ± 0.2 days, p = 0.13). There were also no significant differences between total white blood cell counts, hemoglobin levels, platelet counts, and CRP levels before (within 1 day) and after (within 3 days) IVIG treatment of the 2 groups (p > 0.1). These results provide evidence that high-dose aspirin in the acute phase of KD does not affect the treatment results (CAL and IVIG resistance rate) or inflammatory condition. High-dose aspirin treatment in the acute phase of KD appears unnecessary, and further randomized controlled trials are needed.

However, Reye syndrome is a risk in children who receive salicylates while they are experiencing active infection with varicella or influenza and has been reported in patients receiving high-dose aspirin for a prolonged period after KD.(52) Taken together, it seems unnecessary to expose children to high-dose aspirin in acute KD, especially those with G6PD deficiency. However, as reported in the literature, due to the anti-platelet effect, low-dose aspirin has been prescribed for at least 6–8 weeks to prevent thrombocytosis in KD patients.(15) If patients are allergic or intolerant to a particular drug, clinicians must avoid using it and look for alternatives. Aspirin is used in most patients, often in conjunction with dipyridamole. Dipyridamole has been widely used to treat patients with a coronary aneurysm resulting from KD.(43, 53) The relationship between aspirin therapy and hemolytic disorder in G6PD-deficient patients is unclear. There are also no literature regarding usage of low-dose aspirin and the outcome of KD. G6PD deficiency, an X-linked disorder, is the most common enzymatic disorder of red blood cells in humans. The clinical expression of G6PD deficiency

encompasses a spectrum of hemolytic syndromes. While affected patients are usually asymptomatic, some have episodic anemia, while a few have chronic hemolysis. With the most prevalent G6PD variants (G6PD A- and G6PD Mediterranean), severe hemolysis is induced by the sudden destruction of older, more deficient erythrocytes after exposure to drugs with a high redox potential or to fava beans, selected infections, or metabolic abnormalities. The likelihood of developing hemolysis and the severity of disease are determined by the magnitude of the enzyme deficiency, which in turn is determined by the biochemical characteristics of the G6PD variant. The World Health Organization has classified the different G6PD variants according to the magnitude of the enzyme deficiency and the severity of hemolysis.(54) Class I variants have severe enzyme deficiency (less than 10% of normal) and are associated with chronic hemolytic anemia. Class II variants also have severe enzyme deficiency, but are usually only intermittently associated with hemolysis. Class III variants have moderate enzyme deficiency (10–60% of normal), with intermittent hemolysis usually associated with infection or drugs. Class IV variants have no enzyme deficiency or hemolysis. Class V variants have increased enzyme activity, and classes IV and V are of no clinical significance. The incidence of hemolysis development in a patient with G6PD deficiency after taking aspirin is dosage-related.(55) G6PD deficiency is commonly considered a contra-indication to aspirin intake. However, just few studies(56) have suggested that aspirin can be safely administered in therapeutic doses to G6PD-deficient subjects without nonspherocytic hemolytic anemia. Anti-platelet therapy is most commonly used to prevent thrombotic events for adults with atherosclerotic vascular disease, children with certain types of congenital heart disease, stroke, and KD.(57) Unfortunately, very little data on the efficacy and safety of anti-platelet therapy for pediatric patients, or even G6PD patients, are available. No prospective data exist to guide clinicians in selecting an optimal regimen. Therapeutic regimens used in patients with KD depend on the severity of CAL and include anti-platelet therapy with aspirin, with or without dipyridamole or clopidogrel; anticoagulant therapy with warfarin or low-molecular-weight heparin; or a combination of anticoagulant and anti-platelet therapy.(15)

A few articles have reported G6PD-deficient patients with sustained KD.(58) However, the question of whether aspirin is suitable for KD patients with G6PD deficiency remains

4.2. Intravenous immunoglobulin (IVIG or IVGG) responsiveness

The efficacy of IVIG administered in the acute phase of KD for reducing the incidence of coronary artery abnormalities is well established.(59) The mechanism of IVIG action is still under investigation. IVIG appears to have a generalized anti-inflammatory effect. Possible mechanisms of action include modulation of cytokine production, neutralization of bacterial super-antigens or other etiologic agents, augmentation of regulatory T cell activity (TGF-β),(23, 26) suppression of antibody synthesis and inflammatory markers (CD40-CD40L, nitric oxide, and iNOS expression),(60-62) provision of anti-idiotypic antibodies, Fc-gamma receptor,(63) and balancing Th1/Th2 responses.(28-30)

KD patients should be treated with a single 12-hour infusion of 2 g/kg IVIG together with aspirin in the acute phase with fever or inflammation progression without fever.(3, 4, 15) This therapy should be administered within 10 days of illness onset, and if this is not possible, within 7 days of illness onset. Treatment of KD before day 5 of illness appears no more likely to prevent cardiac sequelae than treatment on days 5–9. However, it may be associated with an increased need for repeat IVIG treatment.(64, 65) In the presence of 4 of 5 classic criteria for KD, US and Japanese experts agree that only 4 days of fever are necessary before initiating treatment with IVIG.(15, 66)

The efficacy of treating patients using IVIG after 10 days of illness is unknown; therefore, early diagnosis and treatment is desired. IVIG should be administered to children presenting after day 10 of illness (i.e., children with delayed diagnosis or incomplete KD) if they have either persistent fever without explanation or aneurysms and ongoing systemic inflammation, as manifested by elevated ESR or CRP.(4, 67-69) Burns et al. also suggested that any child with KD who has evidence of persisting inflammation, including fever or high concentrations of inflammatory markers with or without coronary artery abnormalities, should be treated even if the diagnosis is made after 10 days of illness.(4)

4.3. IVIG resistance (or IVIG unresponsiveness, initial IVIG treatment failure)

The incidence of IVIG resistance varies from 9.4% to 23% between centers (but it can be as high as 38%, as reported in one US cohort).(70) Recent studies have identified demographic and laboratory characteristics as predictors of IVIG resistance, including age, illness day, platelet count, ESR, hemoglobin concentration, CRP, eosinophils, lactate dehydrogenase, albumin, and ALT.(5, 29, 71-73) As IVIG-resistant patients are at a higher risk for CAL formation, it is important to identify those who may benefit from more aggressive therapy. As shown in Figure 1 (modified from Newburger et al.(15)), there are no definite treatment principles available for the management of KD patients with initial IVIG resistance or unresponsiveness to other adjuvant therapies. A second dose of IVIG (1 or 2 g/kg),(15, 74) methylprednisolone (MP) pulse therapy,(75) tumor necrosis factor (TNF)-α blockade,(76) cytotoxic agents (cyclophosphamide, cyclosporine A [CyA], or MTX(77)), plasmapheresis,(78) and plasma exchange(79) have been reported to benefit KD patients with initial IVIG treatment failure. These other treatment modalities will be discussed.

4.4. Methylprednisolone pulse therapy

At present, the usefulness of steroids in the initial treatment of KD is not well established.(15) Newburger et al. reported that, compared to conventional IVIG therapy for routine primary treatment of KD in children, a single-pulse dose of intravenous MP (IVMP) does not improve treatment outcome.(22) However, IVMP therapy appears to benefit IVIG-resistant KD patients.(80) Miura et al. revealed the effectiveness of IVMP therapy for KD patients that were previously unresponsive to initial IVIG treatment. IVMP suppresses cytokine levels faster, and subsequently, the outcomes are similar to those of IVIG-responsive patients who receive a second dose of IVIG.(81) Furukawa et al. reported similar

findings.(82) IVMP appears to have the same effect on IVIG-resistant KD patients compared to an additional IVIG treatment.(83) The cost-benefit differences between IVMP and additional IVIG should be carefully considered, taking into account different medical conditions or health insurance policies among countries. The first dose of IVIG is well established, while IVMP or additional IVIG for IVIG-resistant KD patients requires further investigation. Ogata *et al.*(83) reported that IVMP was useful for reducing fever duration and medical costs for KD patients with initial IVIG resistance. IVMP (N = 13) and additional IVIG treatment (N = 14) were not significantly different in terms of preventing the development of coronary artery aneurysm. IVMP (30 mg/kg MP per day for 3 days) or a second dose of IVIG (2 g/kg) was prescribed to KD patients with fever and marked inflammation (i.e., non-exudative conjunctival injection, strawberry tongue, fissured lips, and erythematous change at the BCG inoculation site) 48 hours after initial IVIG treatment.(22, 82-84)

The safety of IVMP therapy in patients with KD is uncertain. Miura *et al.*(85) reported that IVMP (N = 11) incurred a higher incidence of sinus bradycardia and hyperglycemia when compared with the additional IVIG group (N = 11). Hypertension between IVMP and IVIG groups did not differ significantly. All of the adverse effects were transient. There were no convulsions, gastrointestinal symptoms, infections, malignant arrhythmias, or sudden death in any subject.(85) Taken together, IVMP is safe for KD patients as additional or adjuvant therapy of initial IVIG treatment.(22, 86, 87) After additional IVIG therapy, IVMP is considered for KD patients with persistently poor responses to the second IVIG treatment.(74, 88) Kobayashi *et al.*(89) reported that the addition of prednisolone (2 mg/[kg·day] administered over 15 days) to the standard regimen of IVIG improves coronary artery outcomes in patients with severe KD in Japan.

4.5. Tumor necrosis factor-α blockade

TNF-α levels are elevated in children with KD,(90) and the TNF-α (–308) genetic polymorphism is associated with KD susceptibility, suggesting a role for TNF-α receptor blocking in the treatment of KD, especially for those patients/cases refractory to IVIG. The early administration of TNF-α receptor antagonists in KD may provide effective adjunctive therapy. Infliximab, which binds the pro-inflammatory cytokine TNF-α, has been evaluated in several studies and shown to have a significant effect in KD patients with IVIG resistance.(91-93) Recently, etanercept, a more suitable TNF-α receptor blocker for children with refractory juvenile idiopathic arthritis,(94, 95) was reported to benefit the treatment of IVIG-resistant KD as an adjuvant therapy to initial IVIG.(96, 97) A TNF-α receptor blocker may be administered after initial IVIG treatment failure or after a second dose of IVIG therapy.

4.6. Statins

Chronic vascular inflammation and endothelial dysfunction persists in KD patients with CAL, even long after the acute stage.(98, 99) There is currently no specific treatment for

ongoing vascular inflammation and endothelial dysfunction. Low-dose aspirin can be prescribed until CAL normalizes, but it does not have an effect on inflammation or endothelial dysfunction. Lipid abnormalities in the acute phase of KD, with decreased triglycerides and high-density lipoprotein cholesterol (HDL-C) levels have been reported in previous studies.(100, 101)

Statins, hydroxymethylglutaryl coenzyme A reductase inhibitors, have been shown to reduce cholesterol levels as well as improve surrogate markers of atherosclerosis and cardiovascular disease.(102) Huang et al.(103) reported that short-term (3 months) statin treatment (simvastatin, 10 mg/day as a single dose at bedtime) in KD patients complicated with CAL (N = 11) can significantly reduce total cholesterol and low-density lipoprotein cholesterol levels and increase HDL-C levels. Chronic vascular inflammation is also significantly improved, as is endothelial dysfunction, with no adverse effects. However, long-term and randomized control trials are needed before further conclusions can be drawn.

Recently, Blankier et al.(104) also reported that atorvastatin is able to inhibit critical steps (T cell activation and proliferation, production of the pro-inflammatory cytokine TNF-α, and upregulation of matrix metalloproteinase-9 and an elastolytic protease) known to be important in the development of coronary aneurysms in an animal model of KD (murine model with injection of *Lactobacillus casei* cell wall extract), suggesting that statins may have therapeutic benefits in KD patients. Taken together, statins may be beneficial as an adjuvant therapy in KD patients with CAL. However, the association between dyslipidemia and atherosclerosis in KD patients is not certain.

4.7. Other treatments

Acute KD can lead to the development of large coronary artery aneurysms that may persist for years. Abciximab, a platelet glycoprotein IIb/IIIa receptor inhibitor, is associated with resolution of thrombi and vascular remodeling in adults with acute coronary syndromes. Williams et al.(105) reported that KD patients who were treated with abciximab demonstrated greater regression in aneurysm diameter at early follow-up than patients who received standard therapy alone. McCandless et al.(106) also reported that abciximab treatment might be associated with vascular remodeling in patients with aneurysms. Abciximab appears to benefit KD patients, especially those who develop aneurysms.

There are still no well-defined treatments for refractory KD. Suzuki et al.(107) reported that CyA treatment is considered safe and well tolerated and may serve as a promising option for patients with refractory KD. Hyperkalemia developed in 9 of 28 (32%) patients 3–7 days after commencing CyA treatment. Adverse effects such as arrhythmias should be monitored with CyA. Kuijpers et al.(108) described a case of mortality, and a review of the literature showed that immunosuppressive medication such as CyA may not influence coronary inflammation and proliferation. Further trials are needed to clarify the optimal dose, safety, and timing of CyA treatment.

Specific changes in inflammatory markers (such as white blood cell count, neutrophil count, CRP, IL-6, soluble IL-2 receptor [sIL-2R](109), Th17/regulatory T-cell imbalance(110), and IL-1 pathway(111)) have been reported to disrupt immunological functions and result in KD with IVIG resistance and CAL formation. This indicates the possible treatment role of plasma exchange (PE) for KD with IVIG resistance. Mori *et al.*(79) studied 46 children who had not responded to the second IVIG treatment and subsequently received PE, and compared them with 59 children that received a third dose of IVIG therapy. No complications occurred with PE therapy. CAL developed in 8 of the 46 children (17.3%) who received PE and in 24 of the 59 (40.7%) who received a third course of IVIG (p < 0.001). PE is considered safe and effective in the prevention of CAL in KD that is refractory to IVIG therapy. PE can be performed at an early stage, as soon as fractional increases in inflammatory markers are found after the first or second dosage of IVIG therapy.(79)

5. Genetic association study in Kawasaki disease

The higher incidence of KD in Asia, in conjunction with a higher incidence of the disease in Asian descendants compared with other ethnic populations in the United States and Europe, suggests that genetic predisposition might play an important role in the susceptibility to this disease.(3, 4, 9, 15) There is also evidence that the incidence of KD is higher among siblings than in the general population.(112) A growing number of research reports provide evidence that genetic polymorphisms contribute to the susceptibility to KD. For example, single-nucleotide polymorphisms (SNPs) in the monocyte chemoattractant protein 1 (*MCP-1*),(113) *IL-10*,(114-116) *CD40L*,(117) *CD40*,(62) *IL-4*,(32) *CASP3*,(24) *IL-18*,(118) *IL-1B*,(119) *HLA-E*,(120) C-C chemokine receptor 5 (*CCR5*),(121-124) and *ITPKC*(20, 125, 126) and TGF-β receptors(23) have been reported to be associated with the development of KD. Although genetic association studies have been widely performed in KD, several studies have produced inconsistent results. Some genes were proposed in one population; however, the findings could not be replicated in another population. In addition, the genes that are responsible for KD susceptibility may not be involved in CAL formation. Thus, studies addressing this question are plagued with inconsistencies. Three possibilities may explain these inconsistencies. First, some studies were performed in a small sample size that may not have been able to provide sufficient power to detect minor genetic effects. Second, it is becoming clear that there are different genetic backgrounds within populations that, due to variations in allele frequencies or heterogeneity of the phenotypes, may also influence the results. Third, the incidence of KD in Asia is much higher than that in other regions. Thus, the environmental factors or infectious agents between countries should also be considered carefully.

6. Genetic polymorphisms of the ITPKC signaling pathway in Kawasaki disease

A major advancement in the genetic study of KD was made by the discovery of *ITPKC* in the RIKEN SNP center Japan. In 2008, Onouchi and colleagues first identified a functional pol-

ymorphism of *ITPKC* (rs28493229) that significantly associated with the susceptibility of KD and CAL in both Japanese and US children.(125) By using cell-based functional studies, Onouchi *et al.* further provided evidence to indicate that the risk C allele of *ITPKC* can reduce the splicing efficiency of the *ITPKC* mRNA that, in turn, contributes to the hyperactivation of Ca^{2+}-dependent NFAT pathways in T cells. Thus, in the model of Onouchi *et al.*, IT-PKC is a negative regulator of T cells, and it may function as a calcium channel modulator that is involved in controlling immune systems. Interestingly, replication studies in the Taiwanese populations are strikingly controversial. The first replication study was by Chi *et al.* A total of 385 KD patients and 1158 normal subjects were genotyped.(127) However, no significant association was observed. Lin *et al.* took similar approaches in another independent medical center in Taipei. Their results indicated that the C allele of rs28493229 is associated with KD susceptibility.(128) Recently, data by meta-analysis support the correlation between rs28493229 of *ITPKC* and susceptibility of KD in the Taiwanese population.(23) Due to the increase in genetic diversity between cities in the south or north of Taiwan, we attribute the controversial results in the Taiwanese population to population migration.
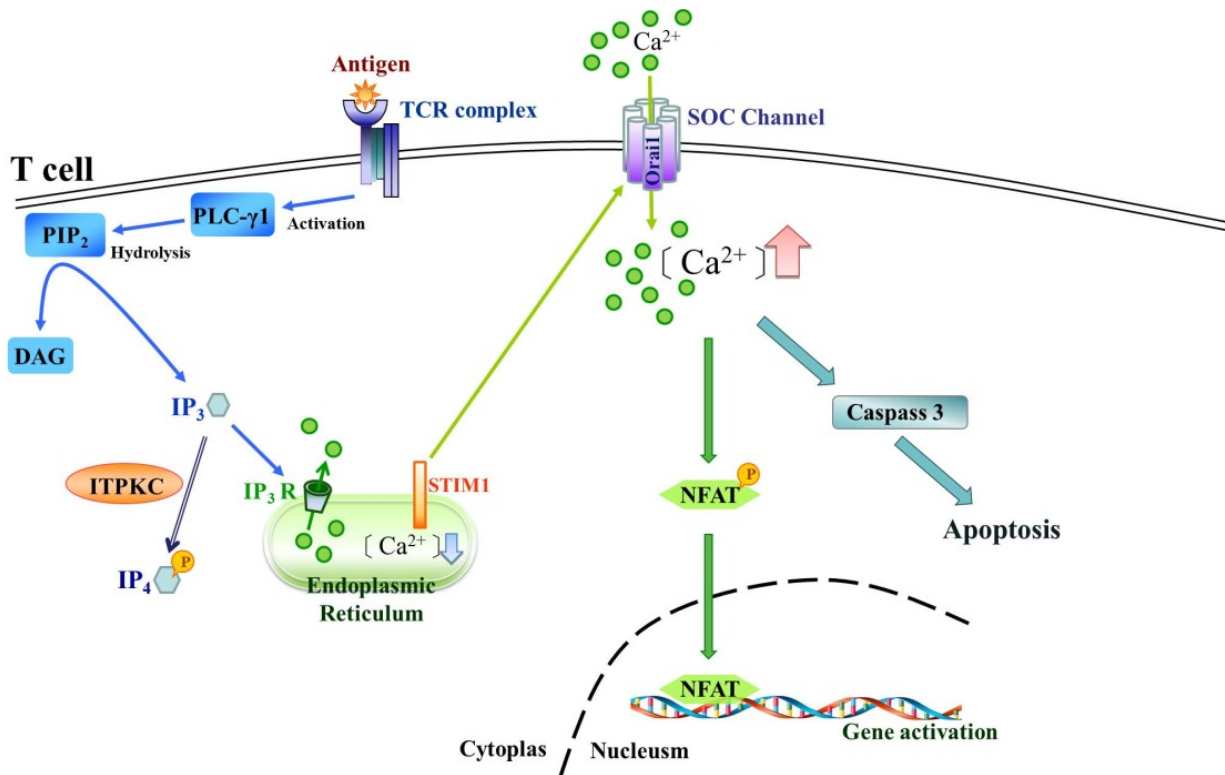
Figure 10. Model depicting the cellular pathways of ITPKC/calcium signaling in T cells.

In the non-excitable cells such as T and B cells, calcium entry is mainly through store-operated calcium channels (SOC). The activation of SOC can be controlled by the expression level of IP3, which is the substrate of ITPKC protein. As ITPKC is involved in the Ca^{2+}-dependent NFAT signaling in T cells, genetic association studies between calcium pathways and susceptibility of KD were performed. The calcium-dependent downstream gene CASP3 is a good example. Onouchi *et al.* reported that a G-to-A substitution in the

5′-untranslated region of *CASP3* (rs72689236) is associated with susceptibility to KD in Japanese and in Americans of European descent.(129) In the sample year, *CASP3* (rs72689236) was replicated in the KD children in the Taiwanese population.(24) Kuo *et al.* confirmed that the A allele of rs72689236 is very likely a risk allele in the development of aneurysms in patients with KD. Another 2 important molecules in the SOC are *ORAI1* (also known as *CRACM1*) and *STIM1*. Feske *et al.* identified *ORAI1* in 2006. Modified linkage analysis completed on data generated by SNP arrays and RNA interference screening led to an important finding. A single missense mutation in *ORAI1* was found in patients with severe combined immune deficiency syndrome. In 2011, genetic polymorphisms of *ORAI1* were reported to associate with the risk and recurrence of calcium nephrolithiasis(130) and HLA-B27-positive AS(131). In the KD study, no significant association between OARI1 genotypes *ORAI1* and KD clinical parameters (such as CAL formation or IVIG treatment responses) was found. However, a novel genetic polymorphism in the STIM1 gene was detected that associated with CAL formation in KD patients (data not shown). As STIM1 is a key initiator of SOC, DNA sequencing for the STIM1 gene family in a larger population may be helpful to identify novel polymorphisms. Future studies are needed to address the mechanism by which calcium signaling contributes to the development of KD. (Figure 10)

7. Genetic polymorphisms of the TGF-β signaling pathway in Kawasaki disease

TGF-β is an important molecule that is involved in the regulation of cytokine expression and immune response. It has been shown that TGF-β-mediated signaling pathways are mainly via transcription factors, Smads, which include at least 3 common proteins: Smad2, Smad3, and Smad4. The binding of TGF-β to its receptor results in the phosphorylation of Smad2 or Smad3, which heterodimerizes with Smad4. The formation of the Smad complex further translocates to the nulclus to regulate activation of the target genes. In the cardiovascular system, which is an important target of KD, TGF-β signaling is involved in the pathogenesis of multiple cardiovascular diseases via aberrant vascular remodeling. Low expression levels of endogenous TGF-β activity in the blood may contribute to the development of atherosclerotic cardiovascular disease. In 2011, a large genetic study revealed a significant association between the polymorphisms in TGF-β pathways and KD susceptibility or CAL formation in the European and US populations. In this study, Shimizu *et al.*(23) were the first to identify 16 SNPs in 6 genes (*TGFB2*, *TGFBR2*, *SMAD1*, *ENG*, *ACVRL1*, and *SMAD3*) associated with the susceptibility to KD. The significance of genetic variation in 3 genes (*SMAD3*, *TGFB2*, and *TGFBR2*) could be replicated in the multiethnic TDT analysis from the independent United States/United Kingdom/Australia subjects.

Kuo *et al.*(26) performed a replication study of 12 polymorphisms in 950 Taiwanese children. It was confirmed that genetic polymorphisms of *SMAD* as well as *TGFB2* contribute to the susceptibility of KD. These observations, in combination with those of the recent study, support the importance of TGF-β pathways for the susceptibility or severity of KD.

8. Genome-wide association study (GWAS) in Kawasaki disease

In 2009, Burgner *et al.* were the first to perform a genome-wide association study (GWAS) on 119 Caucasian KD cases and 135 matched controls. Forty SNPs and 6 haplotypes were confirmed in an independent cohort of KD families.(132) This insightful work led to the identification of an SNP within the N-acetylated alpha-linked acidic dipeptidase-like 2 gene (*NAALADL2*; rs17531088), which was significantly associated with the susceptibility to KD. Although the function of *NAALADL2* remains unclear, mutations in the gene may be involved in the development of Cornelia de Lange syndrome. In 2010, Kim *et al.* conducted another GWAS in a Korean population.(133) In total, 786 subjects (186 KD patients and 600 controls) were recruited. A locus in the 1p31 region was identified as a susceptibility locus for KD. Furthermore, the PELI1 gene locus in the 2p13.3 region was confirmed to associate with the development of CAL in KD patients. In 2012, two independent research groups by Lee *et al.*(62) and Onouchi *et al.*(134) published GWAS data from Taiwanese and Japanese populations, respectively. The results suggested that *BLK* (encoding B-lymphoid tyrosine kinase) and *CD40* are novel susceptibility genes for KD. Consistent with this findings, Kuo *et al.* conducted a case–control genetic association study and identified another polymorphism in the CD40 gene that associated with susceptibility to KD. Hence, the results from independent groups support a significant role of immune-related genes such as *CD40* for KD and CAL formation.(135)

9. Conclusion

Several major advances have been made in understanding the genetic effects of the susceptibility and clinical status of KD over the past decade. Very recently, genome-wide association led 2 groups (Lee *et al.* and Onouchi *et al.*) to identify the same novel susceptibility loci as being important for KD in the Asian population. Although the exact functional role of these genes in KD is still unclear, at present, these loci could provide a new direction for future studies. We can expect to see more insightful research beginning to elucidate the genes responsible for KD susceptibility.

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