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VASCULITIS (LR ESPINOZA, SECTION EDITOR)

Kawasaki Disease: Pathophysiology, Clinical Manifestations, and Management

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Abstract Kawasaki Disease, a systemic vasculitis of unknown origin with specific predilection for the coronary arteries, is the most common cause of childhood-acquired heart disease in western countries. Despite its world-wide incidence, the pathophysiology of this enigmatic disease is still under investigation. Diagnosis is made on a clinical basis, with supportive laboratory evidence and imaging. Once identified, timely initiation of treatment is imperative in order to quell the inflammatory response and decrease the incidence of long-term sequelae, specifically coronary artery aneurysms. Finally, longitudinal follow-up should be implemented based on risk stratification and individualized to each patient.

Keywords Kawasaki disease · Coronary artery · Aneurysm · Vasculitis · Immunoglobulin · Corticosteroids · IVIg resistance · Pathophysiology · Clinical manifestations · Management · Treatment · Etiology · Diagnosis

Introduction

Since the first description by Dr. Tomisaku Kawasaki in 1967 in Japan, over 4,000 articles regarding Kawasaki Disease (KD) have been published. In his original report, Kawasaki described children with febrile illnesses associated with mucocutanous involvement originally thought to be self-limited and benign [1]. However, it is now known to be a systemic vasculitis of unknown origin with specific predilection for the coronary arteries, and is the most common cause of childhood-acquired heart disease in western countries. Although originally characterized in the Japanese pediatric population, it has been found to affect children worldwide. Interestingly, the criteria established by Dr. Kawasaki in his original description are still in use today. Despite ongoing research into causes and treatment algorithms, the underlying mechanisms of this enigmatic vasculitis are still not fully understood. In this report, we aim to review the epidemiology, pathophysiology, and management of this perplexing disease.

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Epidemiology

KD is most common in young children, with 85 % of cases occurring under 5 years of age. In the US, hospitalization data showed a rate of 24.7 per 100,000 children in the year 2010 [2]. By race/ethnicity, Asian/Pacific Islander children less than 5 years of age had the highest KD hospitalization rate in 2010 (50.4 per 100,000), followed by children of black (29.8) and white (22.5) race/ethnicity [2]. This racial predilection, though poorly understood, is consistent with epidemiologic surveys done around the world; Asian populations, even when transplanted to other parts of the world, show a higher incidence of KD when compared to their non-Asian counterparts [3].

Etiology and Pathogenesis

Genetics

The racial predilection of KD to Asian populations suggests the question of a genetic predisposition towards acquiring the

disease. Additionally, there has been documentation of both increased offspring and sibling risk in KD in Japanese populations [4]. Several groups have further investigated this theory through genome-wide association studies and have found several single nucleotide polymorphisms (SNPs) associated with susceptibility of Asian populations to KD, including FCGR2A, CASP3, HLA, BLK, ITPKC, and CD40 [5•]. In European populations, FCGR2A as well as ABCC4 have also been found to confer susceptibility [6, 7]. Interestingly, there are some genes included in both of these groups which are associated with susceptibility to KD, but not coronary artery abnormalities [8]. Many of the SNPs associated with KD have also been identified in other forms of inflammatory diseases (such as ulcerative colitis, rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis) and may be indicative that these autoimmune diseases share a common pathway within the inflammatory cascade [5•].

Infections

It is generally accepted that KD may be triggered by an infectious agent which causes activation of the immune system in a genetically susceptible host. First, there is overlap of the clinical picture of KD and other infectious diseases such as adenovirus and scarlet fever. In a recent study by Jaggi et al., 10 % of their study group diagnosed with KD also showed concomitant, though low viral titer, adenoviral infection [9••]. The comparison group that exhibited some of the symptoms of KD but who did not fulfill complete criteria had higher viral loads of adenovirus and were ultimately diagnosed with adenoviral infection alone [9••]. Second, seasonal clustering of disease in the winter and spring is similar to that seen in other viral diseases [10]. Third, temporal clusters of epidemics have been reported in Japan, the US, Canada, and Finland [3]. Moreover, in Japan, outbreaks have been observed to start in one area and spread throughout the country in a period of 3 months [11]. Lastly, the peak incidence in the toddler age group, with rare cases under 3 months of age, suggest the existence of protective trans-placental antibodies to infection which wane over time [12].

Recent investigations into infectious causes have focused on superantigen, bacterial toxin, or viral etiologies, the last of which has been associated with intracytoplasmic inclusion (ICI) bodies in KD tissues [13]. Although no specific bacteria or superantigen has been identified in the KD scenario, there are clinical similarities between KD and toxin-mediated diseases, such as scarlet fever and toxic shock syndrome (TSS). Superantigens (viral or bacterial) act by binding to the Vβ region of the T cell receptor and induce a widespread immunologic response resulting in release of TNFα, IL-1β, IL-6, and IFN-γ. These pro-inflammatory cytokines are felt to be directly related to the clinical picture of fever, mucosal involvement, and desquamation in both TSS and KD [14]. Identification of oligoclonal IgA plasma cell infiltrate in vascular and other tissues of KD patients by Rowley et al., spurred further investigation into what was felt to be an immune response to an intracellular pathogen with a respiratory portal of entry, such as a virus. The recent detection of ICI bodies in KD patients is now hypothesized to be related to an IgA-mediated antigen response to an unknown RNA virus [15•].

Immune Dysregulation

Regardless of pathway of activation, T cells have been implicated in the inflammatory cascade of KD, with an emphasis on inositol 1,4,5-triphosphatase 3-kinase C (ITPKC), a negative regulator of T cell activation. Loss of this regulator causes an increase in T cell activation and cytokine production, and is hypothesized to confer an increased risk of developing coronary artery lesions [16]. In Yeung et al.'s mouse model of KD using *Lactobacillus casei* as a superantigen, production of IFN-γ is involved with disease induction while TNF-α production is involved in coronary disease. Furthermore, as TNF-α is involved in up-regulation of matrix metalloproteinases (MMP), any process which induces the TNF-α response also induces the enzymatic activity of MMP-9 and leads to elastin breakdown and aneurysm formation in vessel walls. Ablation of TNF-α activity via blockade or knock-out showed that, despite a robust T cell response induced by IFN-γ, there was no local inflammation or vessel wall breakdown [16].

As further evidence of T cell involvement, Th17 cells, which are also known to have pro-inflammatory properties and are associated with both autoimmune and allergic diseases, were found to be up-regulated in KD patients who had developed coronary artery lesions during the course of their disease, compared to KD patients who did not [17].

Because of the varied interactions between extrinsic (infectious) and intrinsic (inflammatory) factors, the differential diagnosis of KD is quite broad. It includes infectious causes (adenovirus, measles, parvovirus, herpesviruses, Rocky Mountain spotted fever, Leptospirosis, Streptococci, Staphylococci), immune reactions (Stevens–Johnson syndrome and serum sickness), and rheumatic diseases (systemic-onset juvenile idiopathic arthritis and polyarteritis nodosa).

Diagnosis

The diagnosis of KD is based on clinical signs and symptoms; there are no unique diagnostic laboratory tests for the disease. The US criteria requires documentation of daily fever for at least 5 days, with four of five other clinical manifestations outlined below (Table 1). These other clinical manifestations may be documented at any point in the acute and sub-acute phases of the disease. In order to help clinicians correctly diagnose the

Table 1 Diagnostic criteria for Kawasaki Disease: fever must be present, with 4 of the 5 other criteria met

Criteria	Manifestations
Fever	Present for at least 5 days, typically high spiking and remittent, lasts an average of 10 days when untreated
Conjunctivitis	Bilateral conjunctival injection, typically limbic sparing, non-exudative
Mucosal changes	• Erythema, cracking, peeling of lips • "strawberry tongue" • Diffuse erythema of oral mucosa
Lymphadenopathy	Cervical lymphadenopathy; may be single node >1.5 cm in diameter or several smaller, firm, non-fluctuant nodes bilaterally
Polymorphous rash	Commonly maculopapular, but may be erythrodermic, urticarial, or erythema multiforme-like; may show early desquamation in the perineal region as well
Extremity cchanges	Erythema and induration of hands and/or feet seen in acute phase; periungual desquamation may follow in subacute phase

evolving KD patient, a multidisciplinary committee convened by the American Heart Association (AHA) in 2004 created an algorithm to aid in identification of patients at risk [18]. The AHA statement also includes use of supportive laboratory testing and echocardiogram in order to detect those patients who do not meet the (full) criteria for KD diagnosis. These patients are considered to have "incomplete KD" and are still at risk for coronary abnormalities [19]. Corroborating laboratories include: increase in markers of inflammation, presence of anemia, hypoalbuminemia, leukocytosis and thrombocytosis, liver function abnormalities, and sterile pyuria. Early echocardiogram can also reveal coronary involvement (Table 2). The AHA algorithm was recently reviewed using a 25-year retrospective cohort of 263 patients with KD and coronary artery abnormalities. They found that, although all patients were eventually diagnosed with KD, only 70 % of them would have been treated with IVIG infusions if clinicians had relied on fulfillment of the complete case definition, whereas ≥97 % of subjects would have been treated based on the 2004 AHA recommendations, including the supporting criteria [20].

Other manifestations which are not included in the criteria but often noted include: irritability, gastrointestinal complaints, urethritis, arthritis, arthralgia, aseptic meningitis, uveitis, and otitis [21]. In patients who present with criteria-based KD but who also have an unusual concomitant clinical features (such as hydrops of the gallbladder, renal involvement, or other neurologic sequelae), we use the term "atypical KD" in order to clarify their rare situation. It is also important to note that there are frequent concomitant respiratory viral infections which can be documented in patients with KD, as were noted recently in one center to be up to 10 % [22].

Table 2 Laboratory and echocardiographic evidence to support Kawasaki Disease diagnosis

ESR	>40 mm/h
CRP	>3.0 g/dL
Albumin	<3.0 g/dL
Hgb	Anemia for age
ALT	Elevation above normal range
Platelets	>450,000/ mm^3 after 7 days
WBC	> 15,000/mm^3
Urine WBCs	>10 WBCs per high powered field
Echocardiogram	Coronary artery dilatation with *z* score >2.5

The disease course of KD is triphasic. The *acute* phase is characterized by fever and other clinical manifestations described above. If untreated, these symptoms will subside on an average of 3–4 weeks. During the second *subacute* phase, the patient may become asymptomatic after treatment, but will often manifest with desquamation of the skin on the digits. It is during the subacute phase where the patients are most at risk for developing coronary artery aneurysm. Finally, most children are asymptomatic during the *convalescent phase*, though some may still maintain a risk of aneurysm formation.

Risk Factors Associated with Coronary Artery Aneurysm

In 1998, Beiser et al. [23] developed a predictive instrument to identify the risk of coronary artery aneurysms (CAA) in patients diagnosed with KD in the United States. This included higher neutrophils, bands. and platelet counts, along with low hemoglobin and continued fever after the first IVIg treatment. Risk factors discussed by other expert groups included male gender, extremes of age, delay in diagnosis, increased WBC count, persistently elevated inflammatory markers, and low albumin as part of their risk stratification [21]. Three risk scoring systems developed in Japan include resistance to first-line treatment as a key component to coronary artery development [24–26]. These scoring systems were validated exclusively in a Japanese population and looked at markers such as days of illness, liver function enzyme elevations, thrombocytosis, elevation of inflammatory markers, and age as part of their criteria. With a sensitivity of 77–86 % and specificity of 67–86 %, they categorized KD patients into groups based on the likelihood of non-responsiveness or resistance to a single dose of IVIg, which also predicted an increased risk of CAA. The Japanese scoring systems, when tested in the US in non-Japanese patients, showed a similar specificity for predicting IVIg non-responsiveness, but with a low sensitivity. This implies that a "high risk" score would be helpful in predicting IVIg resistance, but a "low risk" score would not exclude it [27]. Based on these findings, some experts have begun to identify specific "high risk" groups

within the US (such as those with coronary abnormalities noted early in disease) who might benefit from 2nd line therapy from the beginning in order to circumvent treatment failures and ongoing inflammation [28•].

Management

IVIg

In the US, the administration of a single infusion of intravenous immunoglobulin (IVIg) at 2 g/kg given early in the course of the disease (within 10 days of onset) is considered the most current or standard treatment regimen and has been successful in reducing both duration of fever and prevalence of CAAs for KD [29]. However, approximately 10–20 % of patients will develop recrudescent or persistent fever 48 h after the initial treatment. These patients have a higher risk of developing CAAs and therefore, a second dose of IVIg has been recommended [18]. Because of this relatively high risk in refractory KD patients, there has been renewed interest in more effective second- and even third-line therapies; in some cases, these therapies are used as first-line adjunctive therapy in an effort to diminish the inflammatory response.

Aspirin

In the US, aspirin is initially given to patients with KD in high-dose (80–100 mg/kg) divided 4 times a day during the acute phase of the illness, and then decreased to low-dose of 3–5 mg/kg/day for antiplatelet affect. Due to the risk of developing coronary artery aneurysm during the convalescent phase, low-dose aspirin is usually continued until the follow up echocardiogram at 8 weeks. The decision then to continue the antiplatelet dose of aspirin is determined by the presence of aneurysms.

The timing of switching from high-dose to low-dose aspirin is controversial. Some centers will continue high-dose aspirin until inflammatory markers such as c-reactive protein (CRP) have normalized, while others may switch to low-dose therapy once the patient is afebrile.

Corticosteroids

Earlier studies have shown conflicting results regarding corticosteroids efficacy in KD, and some of them have even been reported to be either non-beneficial or even harmful for the treatment of KD [30]. Steroids are powerful anti-inflammatory agents and are indicated in subsets of patients of other self-limited inflammatory conditions (such as rheumatic fever and Henoch–Schonlein purpura). However, their role in the treatment of KD is still unclear, and has yet to be defined. Until recently, no reliable data were available to suggest that steroids have a role in the primary management of KD, although some retrospective studies from Japan supported the use of corticosteroids in the initial treatment of the acute phase [31]. Contrary to these reports, a multi-center, randomized, double-blind, controlled trial in the US by Newburger et al. evaluated the addition of a pulsed dose of methylprednisolone (30 mg/kg) to the conventional IVIG therapy for the primary treatment of KD [32]. This study revealed that the length of hospital stay, numbers of days with fever, rates of retreatment with IVIG, and numbers of adverse events were similar in both the methylprednisolone and the placebo groups. Additionally, this group showed no benefit to coronary outcomes when adding methylprednisolone to IVIg when compared to IVIg treatment alone. However, this study was done in patients who were not stratified in terms of risk. In two other recent studies from Japan conducted in "high risk" KD patients (the first using the same steroid protocol as Newburger's group and the second using a steroid dosing of 2 mg/kg over 5 days with a 2-week taper), the incidence of IVIg retreatment as well as CAAs were decreased [33, 34••]. Interestingly, a post-hoc sub-analysis of Newburger et al.'s original patients did show some benefit to the use of IVIg plus steroids when analyzed in the high risk patient group only [35]. However, since the Kawasaki disease risk scores used to predict IVIG failure (or resistance) in these studies were developed in Japan and other parts of Asia, it is important to note the reliability issues in these classifications for predictions in the US population. These newer trials have renewed interest in intensification of primary IVIg therapy with corticosteroids in selected patients who are deemed higher risk, though this definition will still need further elucidation in the USA [28•]. Therefore, experts suggest that until these high-risk scores are successfully defined and tested worldwide, IVIG alone (without the addition of corticosteroids) will remain the gold standard initial treatment of Kawasaki disease outside Japan [35].

Tumor Necrosis Factor (TNF) Inhibition

The successful modulation of pro-inflammatory cytokines, such as TNF-α, has impacted the treatment of juvenile idiopathic arthritis, rheumatoid arthritis, spondyloarthropathies, and other inflammatory conditions, including vasculitis. This has opened a window of opportunity to also use these new biologics in the management of KD. The TNF-α antagonist infliximab has been used in KD patients refractory to IVIg and methylprednisolone [36, 37]. In the US, 2.3 % of KD patients received infliximab for IVIG-resistance between 2001 and 2006 [38]. Given the known involvement of elevated TNF-α in development of CAAs in KD patients [39], TNF pathway inhibitors, including infliximab [40•] and etanercept [41], have been studied more recently for use in Kawasaki disease as primary adjunctive therapy. A recent randomized,

double-blind, placebo-controlled trial assessed the benefit of adding infliximab to the primary standard therapy of KD. This study showed that adding a dose of infliximab prior to the IVIG treatment did not reduce the IVIG treatment resistance as measured by coronary artery *z* scores at 5 weeks, although reduction of fever and inflammatory markers were significantly more pronounced in the infliximab group [40•]. Currently, there is also a study underway which is investigating use of etanercept along with IVIg as a first-line treatment to reduce need for retreatment [42].

Other Therapies

Many other immunosuppressive agents, such as cyclosporine, cyclophosphamide, methotrexate, plasma exchange, and rituximab have also been reported to be effective in patients with KD [43–45]. A recent study from Japan was designed to assess the benefit of adding plasma exchange rescue (PER) to KD patients who were IVIG and infliximab non-responders. The study showed that the addition of PER resulted in disappearance of fever and other acute symptoms and improvement of laboratory data and coronary outcomes. This study has its limitations, by being retrospective, and therefore its results should be confirmed through future randomized trials [46]. It is also important to note that, given the toxicity of some of these regimens, use of these medications cannot be recommended routinely, but should be considered on a case-by-case basis after consultation with a specialist [47].

In our center, we have had very good results using IVIg and aspirin as first-line therapy, with use of a 2nd dose of IVIg and then steroids as second- and third-line therapies, respectively. In patients whom we deem higher risk, or who fail to respond to initial therapy, we have also successfully used infliximab .

Imaging

After baseline echocardiography during the acute phase of illness, the 2004 AHA recommendations advise repeat echocardiography at 2 weeks and at 6–8 weeks after illness [18]. However, if patients have abnormalities noted early or show other evidence of risk (such as continued fever), the frequency of imaging should be increased. This should ideally also be monitored with a cardiovascular specialist in consultation.

Long-Term Follow-Up

Long-term management is guided by stratification of patients according to the severity of their CAD and consequent risk of myocardial ischemia. According to the AHA statement in 2006 regarding cardiovascular risk in KD, the risk of coronary aneurysms is highest among children (1) who do not receive timely treatment with high-dose intravenous immunoglobulin (≤10 days and ideally 7 days from the onset of fever), (2) who have persistent fever despite treatment with intravenous immunoglobulin, (3) those who have laboratory test results that reflect severe, persistent inflammation, (4) those at extremes of age, and (5) those of male sex [48]. A recent study of Japanese patients with KD demonstrated that, although the mortality rate for young adults without cardiac sequelae was the same as the general population, young adults *with* cardiac sequelae did have a higher mortality rate [49]. The guidelines for Kawasaki diagnosis and treatment divide risk into five categories [18]:

Low Risk (Risk Level I): Patients without detectable coronary artery abnormalities

Patients should be followed for 10–20 years after a diagnosis of KD, even without documented abnormalities. After the first 6–8 weeks, no anti-platelet therapy or restriction of physical activity is needed. Counseling on lifestyle factors affecting cardiovascular health, including dyslipidemia, hypertension, smoking, and obesity, is an important aspect of long-term risk management in all patients with a previous history of KD. The guidelines recommend healthy lifestyle counseling and cardiovascular risk assessment through primary health care for all KD patients every 5 years as minimal follow-up [50••].

Moderate Risk (Risk Levels II-III): Patients with regressed CAAs

If the regression of aneurysms occurs in the first 6–8 weeks from onset (*Risk level II*), the patients should be treated as low-risk patients and no restrictions beyond the first 8 weeks are necessary; however, cardiovascular risk assessment should occur every 3–5 years. If 50 % of angiographic regression occurs within the first 2 years after KD diagnosis, the patient would be considered *Risk Level III* and would have a different level of observation and ongoing prophylaxis. The rate of resolution of CAA is inversely related to size and is associated with intimal thickening as well as endothelial dysfunction. For this reason, these patients should be treated with low dose aspirin (3–5 mg/kg/day) until regression of aneurysm is documented. Cardiology evaluation should occur yearly with an electrocardiogram (EKG) and echocardiogram (ECHO). Although there is no limitation of physical activity beyond the first 6–8 weeks in the first decade of life, in the second decade, recommendations for physical activity and sports may be guided by stress testing with myocardial perfusion studies. If evidence of ischemia is present, angiography is also recommended.

High Risk (Risk Levels IV-V): Patients with angiographic evidence of large and giant aneurysms or coronary obstruction

In patients at the highest risk levels, the likelihood of progression to coronary artery stenosis is directly related to

aneurysm size and is especially high among arterial segments with giant aneurysms (8 mm in diameter or larger). For these patients, use of long-term anti-platelet therapy with adjunctive use of warfarin or heparin is recommended. In patients with coronary obstruction, beta blockers may be used to decrease myocardial oxygen consumption. Cardiology evaluation with EKG and ECHO should be performed twice per year with stress testing and perfusion studies done yearly. Physical activity recommendations should be based on monitoring, though contact or high-impact sports should be avoided because of the risk of bleeding. Finally, need for catheterization with angiography, magnetic resonance imaging (MRI), or magnetic resonance angiography (MRA) can be determined on an as-needed basis after initial screening examination during the first 6–12 months after KD diagnosis.

Conclusions

Kawasaki Disease remains a complicated and poorly understood disease process. However, through collaborative and world-wide efforts, the characterization and treatment of this disease continues to evolve and improve. Because of the importance of quelling the inflammatory process in these patients, a timely diagnosis with a robust treatment protocol is imperative to decrease the incidence of coronary artery sequelae. The recent addition of biologics into the treatment arena, along with close long-term follow-up, shows good promise to allow us to make a significant impact on both the acute disease course as well as future prognosis.

Compliance with Ethics Guidelines

Conflict of Interest Victoria R. Dimitriades, Amanda G. Brown, and Abraham Gedalia declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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