Kawasaki Disease: 40 Years After the Original Report

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The cause of Kawasaki disease (KD) remains unknown, although a number of epidemiologic and clinical observations suggest it is triggered by one or more infectious agents, each of which can result in the clinical manifestation of the disease. Advances have been made in the management of the disease with the introduction of aspirin and intravenous immunoglobulin (IVIG), which have had a significant impact on lowering the rate of coronary artery aneurysms and death from the disease. Questions remain regarding the management of those patients who fail to respond to IVIG. It appears that some patients with severe KD who are resistant to IVIG may benefit from IV pulse steroid therapy or infliximab infusion. However, a recent multicenter, randomized, controlled trial did not support the addition of a pulsed dose of intravenous methylprednisolone to the conventional IVIG therapy for the primary treatment of KD. It remains to be seen whether other anti-inflammatory agents such as immunosuppressive therapies or new biologics will play a role in the management of patients with KD.

Introduction

Kawasaki disease (KD) is an acute vasculitis of unknown origin that predominantly involves the coronary arteries and is now the leading condition causing acquired heart disease in children in the United States [1]. It was first reported in Japan 40 years ago, and the original diagnostic clinical criteria defined by Dr. Kawasaki are still authentic. The disease, which is recognized worldwide, affects mostly infants and young children and rarely teenagers. KD is characterized by fever, polymorphic rash, conjunctivitis, mucositis, changes in the hand and feet, and unilateral cervical lymphadenopathy. However, the hallmark of this disease is the coronary artery abnormalities (mainly aneurysms) that develop in approximately 20% to 25% of untreated patients. This report aims to give an update on the epidemiology, etiology and pathogenesis, and management of this enigmatic disease.

Epidemiology

KD, which was first described by Dr. Tomisaku Kawasaki in 1967, is an acute febrile, self-limited, multisystem vasculitis that almost exclusively affects young children [2]. Although HLA association has not been identified yet, the incidence of KD is significantly increased in Japan and Korea and among Asian-American children in United States, which suggests that KD has an underlying genetic predisposition. It is an important, serious illness with annual estimated incidence in Japan between 75 and 125 cases per 100,000 in children younger than 5 years of age [3]. However, the incidence of KD among American-Indian and Alaskan native children younger than 5 years old was found to be only 4.3 per 100,000, despite the Asian ancestral origin of these children [4]. A new recent report indicated annual incidence for African American, Hispanic, and Caucasian children younger than 5 years old to be 16.9, 11.1, and 9.1 per 100,000, respectively, in the United States [5]. The figures for children of American Asian and Pacific Island origin were reported to be higher than 32.5 per 100,000. KD is most common in young children, with peak incidence between 13 and 24 months of age. It is rare in the first 6 months of life, and 80% of all cases occur before 5 years of age [6].

Etiology and Pathogenesis

Despite more than two decades of intensive research, the cause of KD remains unknown. However, several observations suggest that this disease is triggered by an unknown infectious agent. First, the clinical picture of KD overlaps with infectious diseases such as scarlet fever and adenoviral infection. In addition, KD has a seasonal occurrence: the seasonal peak of KD is in the winter/spring, similar to that seen in numerous viral diseases. Third, epidemics have a clear epicenter. Temporal clusters have been reported in the United States, Japan, and worldwide [6],

and in Japan, outbreaks have been observed to start in one area and spread throughout the country in a period of 3 months [7]. Fourth, KD has a peak incidence in toddlers; 80% of the cases are toddlers less than 5 years old, and rare cases under 3 months of age suggest protective transplacental antibodies. Despite all these observations, studies conducted so far have failed to identify viruses such as parvovirus B19, retrovirus, Epstein Barr virus, herpes, measles, and more recently human coronaviruses (NL-63) as causative agents for KD [8,9,10••]. As yet, no evidence has been found to prove causality to any particular virus.

Similar to viral illnesses, there are bacterial diseases that can be linked to KD. The fever and other clinical manifestations of KD such as mucous membrane lesions and desquamating skin rash are in overlap with other well-defined infectious toxin-mediated diseases such as staphylococcal and streptococcal toxic shock syndrome (TSS) and scarlet fever [11]. Abinum and Cant [12] reported on TSS toxin-secreting *Staphylococcus aureus* that was isolated from a patient with KD manifested with coronary artery aneurysm (CAA). Others described simultaneous presentation of KD and TSS in an adolescent male [13]. It is speculated that infection produces an immune-mediated reaction causing the signs and symptoms of the disease in an immunogenetically susceptible host. It was proposed that in both KD and TSS, disease is caused by viral or bacterial toxins that act as superantigens [14]. Superantigens are proteins that bypass the conventional, highly complicated antigen-presenting mechanism by binding to the Vβ2 or Vβ8 regions of the T-cell receptor in conjunction with major histocompatibility complex class II molecule. The result is the release of enormous amount of proinflammatory cytokines (eg, tumor necrosis factor [TNF]–α, interleukin [IL]-1β, and IL-6), which mediates the disease process and results in the clinical picture of KD or TSS [14]. In a controlled trial, Leung et al. [15] found that superantigen-producing bacteria were present in 13 of 16 KD patients ($P < 0.001$). However, these findings could not be confirmed by others [16]. Although data supporting the superantigen theory is not yet conclusive, the clinical and immunologic similarities between KD and TSS are striking.

Due to similarities between KD and acrodynia (mercury hypersensitivity), studies to link KD to drugs, toxins, chemicals, and heavy metals have revealed negative results [17••].

KD is manifested by relatively prolonged fever, rash, conjunctivitis, mucous membrane changes, cervical lymphadenopathy, and changes in hands and feet. The most serious complication of this unique illness is the development of acute coronary artery vasculitis with dilatation or aneurysm formation. Early on, the impression was that this disease was a self-limited benign condition. However, subsequent reports suggested that up to 2% of the patients die from coronary abnormalities and 20% to 25% of untreated patients develop CAAs or ectasia. In addition, KD may lead to myocardial infarction, sudden death, and ischemic heart disease [18]. At the early phase of the disease, there is development of edema and neutrophil infiltration with a rapid transition to mononuclear cells, primarily CD8 T cells, monocytes, macrophages, and immunoglobulin A plasma cells at the coronary arterial wall [19–21]. This is followed by production of matrix metalloproteinases that cause the destruction of internal elastic lamina and media, which progress to the replacement of the intima and media with fibrous connective tissue, leading to the formation of aneurysms, scarring, and stenosis [22,23]. Few reports are available from children with KD who did not develop coronary abnormalities during the acute phase of the disease and died years later due to unrelated causes. Autopsies performed on these children demonstrated coronary artery intimal thickening and medial fibrosis [24].

Diagnosis

KD diagnosis is based on clinical signs and symptoms. No unique laboratory diagnostic tests exist for the disease. In 1974, Kawasaki et al. [25] described the principal criteria on which the diagnosis of KD is based. The Japanese Kawasaki Disease Research Committee and later the US Centers for Disease Control and Prevention adopted these criteria [26]. These criteria are only guidelines to prevent misdiagnosis or overdiagnosis. However, clinicians should be aware that some cases of KD have incomplete signs and symptoms and do not fulfill these criteria (ie, incomplete or atypical KD). In these cases of insufficient clinical criteria, a proof of presence of coronary abnormalities or CAAs must be shown on echocardiogram [27••].

In the absence of a diagnostic test, the above criteria become highly important and pivotal in diagnosing a patient with KD. Some laboratory tests may be supportive such as the acute phase reactants, including the erythrocyte sedimentation rate and C-reactive protein (CRP). These are significantly elevated as seen typically in the inflammatory disorders and not to the degree found in common viral infections [28•].

Risk factors associated with coronary aneurysms

Based on a multicenter study of patients with KD treated with intravenous immunoglobulin (IVIG), Beiser et al. [29] developed a predictive instrument for the risk of CAAs. According to this study, higher counts of neutrophils, bands, and platelets, in addition to a low level of hemoglobin and a lack of defervescence within the first day of IVIG treatment are associated with higher risk. The investigators recommended that frequent cardiac testing would be unnecessary in low-risk patients with KD.

In Japan, Harada [30] treated KD patients with IVIG only if they fulfilled four of the following criteria within 9 days of

onset: 1) leukocyte count greater than 12,000/mm^3, 2) platelets greater than 350,000, 3) CRP greater than 3 mg/dL, 4) hematocrit less than 35%, 5) albumin less than 3.5 g/dL, 6) age 12 months or younger, 7) and male gender. Mori et al. [31] showed that rises in the white blood cell count and CRP after IVIG infusion are independent predictors of CAAs. More recently, Nakamura et al. [32] proposed that in KD, low sodium levels of less than 135 mEq/L at the patient's first visit to the hospital may be a predictor of giant CAAs. Fukunishi et al. [33] found that higher serum levels of CRP, lactate dehydrogenase, and bilirubin were predictive of failure to respond to IVIG.

Two recent reports on the protective role of African American ethnicity in the development of CAAs in KD reported by Abuhammour et al. [34] and Porcalla et al. [35•] concur with yet unpublished data of a retrospective study from our center at Children's Hospital of New Orleans. Referrals to our center are drawn from a population comprised of 68% African American (according to 2003 community survey). Indeed, 55% of our KD patients were African American, and 39% were Caucasian. However, the majority (60%) of those who developed CAAs were Caucasian [36]. These findings may further support the notion that in KD, African American ethnicity background might play a protective role for the development of coronary abnormalities. More studies with larger numbers of patients are required to assess the significance of these findings.

Management

In the United States, the administration of single infusion of IVIG at 2 g/kg given early in the course of the disease (within 10 days of the onset) complemented by aspirin, 80–100 mg/kg/day in four divided doses, is considered the most current treatment regimen and has been successful in reducing the duration of fever and the prevalence of CAAs for KD [37]. High-dose aspirin is an important adjunct to IVIG therapy and is supposed to have an additive anti-inflammatory effect in KD. Two-thirds of patients will be afebrile and improve by 24 hours after completion of the IVIG infusion; 90% will be afebrile by 48 hours. This therapy regimen is effective in reducing the prevalence of coronary artery abnormalities from 20% to 25% down to 2% to 4% [38]. Approximately 10% of patients may have persistent or recrudescent fever 48 hours after a single dose of IVIG infusion. These patients are at risk of developing more coronary artery abnormalities and may benefit from a second IVIG infusion [38]. A small subset of patients (2%–3%) remain febrile despite a second dose of IVIG therapy. On the other hand, it has been shown that corticosteroids are beneficial in refractory KD [39]. Although conflicting reports exist in the literature on the use of oral and intravenous pulse steroid therapy in KD, several recent case reports and case series suggest that pulse methylprednisolone therapy, 30 mg/kg given intravenously, may be beneficial in patients with IVIG-resistant KD. These reports include a report from Harvard, which described the experience with the use of pulse methylprednisolone therapy in four IVIG-resistant KD patients [39].

An earlier report from Japan by Kato et al. [40] stated that steroids may be potentially harmful and lead to higher rates of coronary artery abnormalities. Therefore, the use of corticosteroids therapy in KD has been controversial and practically was contraindicated. Their study has shown that steroid therapy was associated with increased incidence of CAAs, and apparently formed the basis for the suggestion regarding the contraindication of corticosteroids in KD. These investigators found that 11 of 17 (65%) patients with KD in the group treated with steroids alone developed CAAs, as compared to four of 36 (11%) patients in the group that was treated with aspirin alone. Although none of the seven patients in the group treated with steroids and aspirin developed CAAs, the authors concluded that their findings did suggest that steroids might act adversely to cause a progression of coronary lesions of the disease. This study is difficult to interpret, because it is unclear if the patients were randomized for the different protocols, and there was no mention of patients' ages or other parameters that affect patient severity score.

Contrary to this report, another Japanese retrospective study conducted in 1982 by Kijima et al. [41] showed that pulsed doses of steroids in KD were beneficial in the prevention of CAAs. Furthermore, previous [42,43] and more recent [44,45•] studies on the possible role of corticosteroids in the initial treatment of the acute phase of KD have shown them to be beneficial. However, most recently [46••], a multicenter, randomized, double-blind, controlled trial for the addition of pulsed dose of methylprednisolone therapy to the conventional IVIG therapy for the primary treatment of KD 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.

The corticosteroid compounds are the most potent anti-inflammatory agents in the treatment of rheumatic diseases. Although they are the mainstay in the treatment of other more chronic and complicated forms of vasculitides (ie, polyarteritis nodosa, Wegener's granulomatosis and Takayasu's arteritis), clinicians should remember that anti-inflammatory doses of steroids can cause toxicity, including cushingoid appearance, suppression of growth, gastrointestinal irritation, hypertension, cataracts, psychosis, and more. Therefore, steroids should be used in the management of well-defined pediatric indications, in a proper way, and in the minimal amount needed to control disease activity. As with other self-limited autoimmune diseases (ie, rheumatic fever, Henoch-Schönlein purpura), epidemiologic data on KD suggest an infectious trigger(s)

in genetically susceptible hosts. However, the fact that an infection played a role as a trigger in these conditions does not contraindicate steroid therapy. Steroids are indicated in subsets of patients in both rheumatic fever and Henoch-Schönlein purpura; however, their role in the treatment of KD is still unclear. To date, no data are available to suggest that steroids have a primary role in the management of KD, but some data (uncontrolled) suggest a secondary or partial role. Therefore, until more data are available, the small subset of patients with KD that show IVIG resistance and/or have life-threatening complications should be given the option of pulsed steroid therapy. Further prospective, multicenter, and randomized controlled trials are needed to determine the efficacy of pulsed or oral doses of corticosteroids in the treatment of IVIG-resistant KD. The discovery that proinflammatory cytokines, mainly TNF-α, play a pivotal role in the pathogenesis of rheumatoid arthritis, spondyloarthropathies, and other inflammatory conditions including vasculitis, encouraged the widespread use of anticytokine therapy [47]. Now, it may be possible to block not only TNF-α but also other important cytokines such as IL-1 and IL-6. This finding has opened a window of opportunity to use these new biologics in the management of KD. More recently, anti–TNF-α (infliximab) was shown to be as a novel therapy for a refractory KD [48,49].

Natural History and Long-term Sequelae

In their recent guidelines, the American Heart Association experts proposed a stratification system to categorize patients by their risk level [50••]. The risk of CAAs is highest in: 1) children with KD who missed their opportunity to receive IVIG within the recommended time period from the onset of fever (< 10 days); 2) patients who have persistent fever despite IVIG treatment; 3) patients with laboratory findings suggesting persistent inflammation (increased erythrocyte sedimentation rate, CRP, or both); 4) young (< 6 months) or older (> 8 years old) children; and 5) male gender.

High risk level: patients with angiographic evidence of large or giant aneurysms or coronary obstruction

The likelihood of progression to coronary artery stenosis is directly related to aneurysm size and is especially high with giant aneurysms (8 mm or larger). Patients with persistent aneurysms tend to have significantly higher levels of CRP compared to those with regressed aneurysms or without aneurysms. In this group of patients with KD, a long-term antiplatelet therapy and warfarin (to keep International Normalized Ratio 2–3) or low-molecular weight heparin (to keep antifactor Xa level 0.5–1 U/mL) is necessary. To reduce myocardial O_2 consumption, β-blockers are needed. Contact or high-impact sports should be avoided to reduce the risk of bleeding. Cardiology follow-up twice a year with electrocardiogram and echocardiogram and stress test with myocardial perfusion scan are highly recommended, and should be followed by angiography if ischemia is present.

Moderate risk level: patients with regressed CAA

This group of KD patients includes individuals who have 50% angiographic regression of their CAAs to the level of normal lumen diameter within 2 years of onset. The rate of CAA resolution is inversely related to its size. Studies have revealed that although regression had occurred it was through intimal thickening and endothelial dysfunction. These patients need to be treated with low-dose aspirin (3–5 mg/kg/day), at least until aneurysm regression was proven. Cardiology follow-up should be performed annually with electrocardiogram and echocardiogram. Stress test and myocardial perfusion studies twice a year are highly recommended. Angiography is needed if evidence of ischemia is present. High-impact physical activity should be limited and guided. If regression of aneurysms occurred by 8 weeks from onset, no restrictions beyond the first 8 weeks are needed. Careful assessment with counseling every 3 to 5 years is recommended to determine the future risk of ischemic heart disease.

Low risk level: patients without detectable coronary artery aneurysms

Long-term follow-up (10–20 years) after onset, the morbidity and mortality of these patients with KD are similar to those in normal pediatric population. Angiography is not necessary in these patients, and they do not need antiplatelet therapy beyond the recommended 8 weeks after onset. Careful assessment with counseling every 5 years is recommended to determine the future risk of ischemic heart disease. No restriction of physical activity beyond 8 weeks is necessary.

Conclusions

Although an infectious etiology seems likely, KD remains a puzzle. The immediate outcome of KD has improved significantly with the decrease in the frequency of CAAs three- to fivefold following the introduction of aspirin and IVIG. A significantly small subgroup of patients with severe KD who are resistant to IVIG therapy and who are at risk for subsequent development of CAAs and long-term sequelae appear to benefit from intravenous pulse steroid therapy or infliximab infusion. At this stage, corticosteroids have no role in the primary treatment of KD. Finally, the future outcome of KD patients without coronary artery changes is unknown. Long-term follow-up into their second, third, and forth decades with monitoring for late cardiovascular sequelae would be useful to determine the role of KD in adult coronary heart disease.

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