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Abraham Gedalia

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REVİEW ARTICLE

Kawasaki disease : A Clinical Update

Abraham Gedalia

Abstract:
The etiology of Kawasaki disease (KD) remains unknown, although a number of epidemiological and clinical observations may suggest that it is triggered by a single or more possibly multiple 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 IVIG that 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 steroids therapy or infliximab infusion. However, a recent multi-center, randomized-controlled trial do not support for the addition of a pulsed dose of intravenous methylprednisolone to the conventional IVIG therapy for the primary treatment of KD. It still remains to be seen whether other anti-inflammatory agents such as immunosuppressive therapies or new biologics play a role in the management of patients with KD.

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Introduction

KD is an acute self-limited systemic 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, but the original diagnostic clinical criteria defined by Dr. Kawasaki are still authentic. The disease that 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 are developed in approximately 20-25% of untreated patients. In this report we aim to give an update on the epidemiology, etiology and pathogenesis, and management of this disease.

Abraham Gedalia, MD
Division of Pediatric Rheumatology, Department of Pediatrics LSU Health Sciences and Children's Hospital New Orleans, LA USA

Corresponding Author: ***Abraham Gedalia, MD***
Department of Pediatrics/Rheumatology
Children's Hospital 200 Henry Clay, Ave New Orleans, LA 70118
Tel: 5048969385
Fax: 5048969410
e-mail: agedal@lsuhsc.edu

Epidemiology

KD that was first described by Dr. Tomisaku Kawasaki in 1967, is an acute febrile, self- limited, multi-system 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, Korea and among Asian-American children in US. These facts suggest that KD has an underlying genetic predisposition. It is an important serious illness with annual incidence in Japan recently estimated to 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 was

found to be only 4.3 per 100,000, despite the Asian ancestral origin of these children [4]. A new recent report indicating annual incidence for African Americans (AA), Hispanics, and Caucasians of 16.9, 11.1, and 9.1 per 100,000, respectively, in the US for children younger than 5 years of age [5]. The figures for children of American Asian and Pacific Island origin reported to be higher of 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 age 5 years [6].

Etiology and Pathogenesis

Despite more than two decades of intensive research, the cause of KD remains unknown. However, the following observations suggest that this disease is triggered by an unknown infectious agent: 1) clinical picture of KD that overlaps with infectious diseases such as scarlet fever and adenoviral infection; 2) a seasonal occurrence; In the US and other geographic areas the seasonal peak of KD is in the winter/spring, similar to that seen in numerous viral diseases; 3) epidemics with clear epicenter; temporal clusters have been reported in the US, Japan and worldwide [6]. Moreover, in Japan, outbreaks have been observed to start in one area and spread throughout the country in a period of three months; [7] 4) a peak incidence in toddler age group; 80% of the cases are toddlers less than five years old and rare cases under three months of age suggest protective trans-placental antibodies. Studies conducted throughout failed to identify viruses such as parvovirus B19, retrovirus, EBV, herpes, measles, and more recently human corona (NL-63) viruses as causative agents for KD [8-10]. So far, no evidence was 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 et al [12] reported on TSS toxin-secreting staphylococcus aureus that was isolated from a patient with KD manifested with coronary aneurysm. Others described on simultaneous presentation of KD and TSS in 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 the disease caused by viral or bacterial toxins that act as superantigens [14]. Super-antigens are proteins which bypass the conventional, highly complicated antigen presenting mechanism by binding to the Vβ2 or Vβ8 regions of the T cell receptor in conjunction with MHC class II molecule. The result is release of enormous amount of pro-inflammatory cytokines such as TNFα, IL-1β and IL-6 that mediate the disease process, which results in the clinical picture of KD or TSS [14]. In a controlled trial conducted by Leung et al, it was found that super-antigen-producing bacteria were present in 13 of 16 Kawasaki patients ($p<0.001$) [15]. However, these findings could not be confirmed by others [16]. Although data supporting the super-antigen theory is not yet conclusive, the clinical and immunological similarities between KD and TSS are striking.

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

KD is manifested by relatively prolonged fever, rash, conjunctivitis, mucous membrane changes, cervical lymph-adenopathy, 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 20-25% of untreated patients develop coronary artery aneurysms or ectasia (CAA's). In addition, KD may lead to myocardial infarction, sudden death and ischemic heart disease [18]. At 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 IgA plasma cells at the coronary arterial wall [19-21]. This is followed by production of matrix metalloproteinases (MMPs) that cause destruction of internal elastic lamina and media that 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

The diagnosis of KD is based on clinical signs and symptoms. There are no unique laboratory diagnostic tests for the disease. In 1974, Kawasaki et al [25] described the principal signs (criteria) on which the diagnosis of KD is based. The Japanese Kawasaki Disease Research Committee, and later the Centers for Disease Control (CDC) in the US adopted these criteria (Table 1) [26]. These criteria are only guidelines in order to prevent misdiagnosis or over-diagnosis. However, clinicians should be aware that there are cases of KD with incomplete signs and symptoms that do not fulfill these criteria; this refers to incomplete (atypical) KD. In these cases of insufficient clinical criteria, a proof of presence of coronary abnormalities or CAA's must be shown on echocardiogram [27].

Table 1: CDC Diagnostic criteria for Kawasaki Disease [26].

Fever lasting five or more days without other more reasonable explanation and at least four of the following criteria:

(1) **Bilateral conjunctival injection**

(2) **At least one of the following mucous-membrane changes:**

a. injected or fissured lips
b. injected pharynx
c. strawberry tongue

(3) **At least one of the following extremity changes:**

a. erythema of the palms or soles
b. edema of the hands or feet
c. generalized or periungual desquamation

(4) **Polymorphous rash**

(5) Cervical lymphadenopathy (at least one lymph node 1.5 cm or greater in diameter)

In the absence of a diagnostic test, the above criteria become highly important and pivotal in diagnosing a patient with KD. There are no unique laboratory diagnostic tests for KD but some laboratory tests may be supportive such as the acute phase reactants, including the ESR and 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

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

Based on a multi-center study of patients with KD treated with IVIG, Beiser et al [29] developed a predictive instrument for the risk of coronary aneurysms. According to this study the following are associated with higher risk including 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 the IVIG treatment. They recommended that in low risk patients with KD, frequent cardiac testing would be unnecessary. In Japan, Harada et al [30] treated KD patients with IVIG only if they fulfill 4 of the following criteria found within 9 days of onset: 1) WBC > 12,000/mm^3; 2) Platelets > 350,000; 3) CRP > 3; 4) Hematocrit < 35%; 5) Albumin < 3.5 g/dl; 6) Age ≤ 12 months; 7) Male sex. Mori et al [31] showed that a rise in the white blood cell count as well as C-reactive protein after IVIG infusion is independent predictors of CAA's. More recently Nakamura et al [34] proposed that in KD low sodium levels of <135 mEq/L at the

patient's first visit to the hospital may be a predictor of giant coronary aneurysms. Fukunishi et al [33] found that higher serum levels of C-reactive-protein, lactate dehydrogenase, and bilirubin to be predictive of failure to respond to IVIG. In the recent guidelines published by the American Heart Association (AHA), a stratification system to categorize patients by their risk level has been proposed [37]. The risk of CAA's is the highest in: 1) children with KD that 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 ESR, CRP or both); 4) young children (< 6 months) or older (> 8 years-old) and the male sex are also among the high risk. More recently, a susceptibility gene was identified on chromosome 19. This gene codes inositol 1,4,5-triphosphate 3-kinase C (ITPKC). It was shown that ITPKC gene is significantly more predominant in IVIG-resistant KD patients and in those with coronary artery lesions [38]. Finally, although it is not very well established, the plasma levels of brain natriuretic peptide (BNP) and its N-terminal moiety taken at the acute phase of KD correlate with severe cardiac outcome [39].

Management

In the US, the administration of single infusion of intravenous immunoglobulin (IVIG) at 2g/kg that is given early in the course of the disease (within 10 days of the onset) complemented by aspirin (80-100 mg/kg per 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 coronary artery aneurysms for KD [40]. 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 20-25% to 2-4% [41]. 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 [41]. A small subset of patients (2-3%) that remain febrile despite a second dose of IVIG therapy are regarded as IVIG resistant patients and may respond to intravenous pulse steroid therapy. Although conflicting reports exist in the literature on the use of steroids in KD, there are several recent case reports and case-series suggesting that pulse methylprednisolone therapy, 30 mg/kg/dose 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 [42].

Earlier reports from Japan, by Kato, et al [42] have 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. Kato et al [43] found that 11/17 (65%) of patients with KD, in the group treated with steroids alone, developed CAAs as compared to 4/36 (11%) of patients in the group that were treated with aspirin alone. Although none of the seven patients in the group treated with steroids and aspirin developed CAA's, 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, since it is unclear if the patients were randomized for the different protocols, and the fact that there were no mention of patient's age and other parameters that affect patient's severity score. Contrary to this report, another Japanese retrospective study conducted in 1982 by Kijima et al [44], showed that pulsed doses of steroids in KD were beneficial in the prevention of CAA's. Furthermore, previous [45-46] and more recent [47-48] studies on the possible role of corticosteroids in the initial treatment of the acute phase of KD have shown to be beneficial. However, most recently [49], a well designed multi center randomized, double-blind-controlled trial in the US 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 [49]. In addition, adding a pulse of methylprednisolone did not improve the coronary-artery outcomes [49].

The corticosteroids 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 (polyarteritis nodosa, Wegener granulomatosis and Takayasu arteritis), clinicians should remember that anti-inflammatory doses of steroids can cause toxicity. These include cushingoid appearance, suppression of growth, gastro-intestinal 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. KD, like any other self-limited autoimmune diseases (rheumatic fever, Henoch-Schonlein purpura), epidemilogic data so far suggests an infectious trigger(s) in genetically susceptible hosts. The fact that an infection played a role as a trigger in these conditions does not make steroids to be contraindicated. Nevertheless, steroids are indicated in subsets of patients in both rheumatic fever and Henoch-Sconlein purpura. However, their role in the treatment of KD is still unclear, and not yet defined. To date, no data of any kind is available to suggest that steroids have a primary role in the management of KD, but some data (uncontrolled) exists to suggest a secondary or partial role. Therefore, until more data is available, the small subset of patients with KD that show IVIG resistance and/or with life threatening complications should be given the option of pulsed steroid therapy. Further prospective, multi-center, 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 of pro-inflammatory cytokines, mainly tumor necrosis factor-α, and others that play a pivotal role in the pathogenesis of inflammatory disorders including rheumatoid arthritis, spondyloarthropathies and vasculitis, made it possible to block not only TNFα but also other important cytokines such as IL-1 and IL-6. This has opened a window of opportunity to use these new biologics in the management of KD. More recently, anti-tumor necrosis factor-α (infliximab) was shown to be effective therapy for IVIG resistant KD [50], although a conflicting study from Japan revealed that infliximab reduces the cytokine mediated inflammation but does not suppress cellular infiltratration in the vessel wall of patients with refractory KD [51]. In addition, due to cost issues, infliximab could be a cheaper alternative to IVIG in the primary treatment of KD [52].

In KD patients without detectable CAA, long-term follow-up (10-20 years) after onset showed that their morbidity and mortality are similar to those in normal pediatric population. Therefore, 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 [53]. In those KD patients with regressed CAA, low-dose ASA (3-5 mg/kg/day) is needed at least until aneurysm regression is complete. These patients need a yearly Cardiology follow-up with EKG and echocardiogram. Angiography would be needed if evidence of ischemia is present. In addition, in these patients high impact physical activity should be limited and guided. In high risk patients that show angiographic evidence of large or giant aneurysms (8 mm or larger), or coronary obstruction, twice yearly cardiology follow-up with EKG and echocardiogram may be needed. Stress test with myocardial perfusion scan and angiography will be performed upon cardiology recommendation. In this group of KD patients a long-term antiplatelet therapy and warfarin (to keep INR 2-3) or low-molecular weight heparin (to keep antifactor Xa level 0.5-1.0 U/ml) is necessary. β-blockers are needed to reduce myocardial O_2 consumption. In these patients, contact or high-impact sports should be avoided to reduce the risk of bleeding [27].

Natural History and Long Term Sequele

In the recent guidelines published by the American Heart Association (AHA) [53], a stratification system to categorize patients by their risk level has been proposed.

The risk of CAA's is the highest in 1) children with KD that 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 ESR, CRP or both); 4) young children (< 6 months) or older (> 8 years-old) and male sex are also among the high risk.

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 compare with those with regressed aneurysms or without aneurysms. In this group of patients with KD a long-term antiplatelet therapy and warfarin (to keep INR 2-3) or low-molecular weight heparin (to keep antifactor Xa level 0.5-1.0 U/ml) is necessary. β-blockers are needed to reduce myocardial O_2 consumption. Contact or high-impact sports should be avoided to reduce the risk of bleeding. Cardiology follow-up with EKG and echocardiogram, and stress test with myocardial perfusion scan that are performed twice a year are highly recommended, and would be followed by angiography if ischemia is present.

Moderate Risk Level: Patients with regressed CAA

In this group of patients with KD are individuals who have 50% angiographic regression of their CAA's to the level of normal lumen diameter within 2 years of onset. The rate of CAA's 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 ASA (3-5 mg/kg/day) at least until aneurysm regression was proven. Cardiology follow-up should be performed annually with EKG and echocardiogram. Stress test and myocardial perfusion studies twice a year are highly recommended. Angiography is neede 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 3-5 years is recommended to determine the future risk of ischemic heart disease.

Low Risk Level: Patients without detectable CAA

Long-term follow-up (10-20 years) after onset on these patients with KD showed that their morbidity and mortality 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.

Conclusion

Although an infectious etiology seems more likely, KD remains a puzzle. The immediate outcome of KD has improved significantly with the decrease in the frequency of coronary artery aneurysms three to five fold follow the introduction of aspirin and intravenous immunoglobulin. A significantly small subgroup of patients with severe KD who are resistant to IVIG therapy and at risk for subsequent development of coronary aneurysms and long term sequelae appear to benefit from intravenous pulse steroids 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.

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