Kawasaki Disease: Still an Enigma - But We Know So Much More
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Kawasaki Disease (KD) is the most common cause of acquired heart disease in children in the developed world. It is more common than rheumatic fever, viral myocarditis and endocarditis of native heart valves combined. We have come to understand the pathology, pathogenesis, epidemiology of KD and we have effective ways of treating the disease and preventing the most serious consequences, coronary artery aneurysms. We now appreciate that genetics play an important role in the acquisition of KD and the occurrence of the cardiac consequences but we still do not know the etiology of the disease and do not have a diagnostic "gold standard" for KD. The following is a brief summary of KD as we understand it today.

History

Dr. Tomisaku Kawasaki saw his first case of the illness that would come to bear his name in 1961. He observed 49 additional cases over the next 5 years and published his findings in the *Japanese Journal of Allergy* in 1967 (1). The main clinical symptoms described were fever lasting over 6 days, swollen cervical lymph node(s), hyperemia of both bulbar conjunctivae, erythematous eruption of the skin, angioneurotic-like condition of the hands and feet, erosive cracked lips and diffuse hyperemia of the oral mucosa and strawberry tongue, and membranous desquamation of the fingers and toes. The name given the illness was "Acute Febrile Mucocutaneous Lymph Node Syndrome". From these observations came the "classical criteria" for KD. (See Table 1) The etiology, criteria and even existence of MCLNS, subsequently known as KD, were initially hotly debated in Japan. It was first asserted that KD was a self-limited disease with no sequelae but in 1970, following the first nation-wide survey in Japan, 10 cases of sudden death were described due to coronary artery thrombosis. The importance of KD was firmly established and children with KD were thereafter assessed for coronary artery disease (2).

In the early 1970s, a similar illness was recognized in Hawaii by Drs. Marian Melish and Raquel Hicks, and their findings were published in 1974 (3). Dr. Eunice Larson a pathologist at Kauikeolani Children's Hospital in Honolulu described the autopsy findings of a 10-month-old infant who died of coronary artery thrombosis in 1971. At the time it was speculated in both
Japan and the U.S. that MCLNS or KD was really "infantile periarteritis nodosa" (IPN). Dr. Larson and Dr. Benjamin Landing from Children's Hospital Los Angeles blindly reviewed pathologic material from cases submitted as KD and IPN and concluded that the illnesses were pathologically and, to a large extent, clinically identical (4).

**Diagnosis and Clinical Manifestations**

The criteria established by Dr. Kawasaki remained the primary mode of diagnosis of KD for several decades but it was recognized that as many as 20% of children diagnosed with KD failed to fulfill all the necessary criteria for the diagnosis and were termed "atypical" and later more properly "incomplete" KD. An algorithm was developed and published by the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease and Council of Cardiovascular Disease in the Young of the American Heart Association (5a) to more accurately capture these incomplete cases of KD. It incorporated both laboratory tests and echocardiographic findings that supplemented the clinical findings previously sued. (See Figure 1). This algorithm was subsequently validated and demonstrated that application of the algorithm would have referred 97% of the study patients for treatment with Intravenous immune globulin. (5b)

In addition to the classic clinical criteria, KD is known for presentation with extreme irritability, hypotensive crisis and shock, inflammation at a prior BCG site, arthritis and definitely arthralgia, aseptic meningitis, hydrops of the gall bladder, pancreatitis, and myocarditis. The latter probably occurs in 100% of patients (6) and may explain the persistent tachycardia seen in the early phases of the illness. Prodromal symptoms such as upper respiratory tract infection symptoms and acute gastroenteritis are frequently seen.

**Epidemiology**

KD has a worldwide distribution and has been described in all racial and ethnic groups. It occurs from infancy to adulthood but is most prevalent in children between 1 and 5 years of age, with 75%-85% of cases reported in this age group. The diagnosis should not be excluded based on patient age however. (7) In most of the U.S. it is a winter-spring disease, in Japan it is bimodal with peaks in January and June-July. (8) The incidence in the U.S. has remained stable for several years at about 17-20 cases/ 100,000 children < 5 years of age (9) while in Japan it has continues to increase, > 200/100,000 in 2008. (8) Incidence is highest in Asian countries, which was an early suggestion of a genetic predisposition. Recurrence is about 3% in Japan and 1% in the U.S.

**Etiology**

Many features of KD favor infectious involvement. Among these are the seasonal occurrence of
the illness, many of the clinical features suggestive of an infectious disease (rash, enanthemas, occasional epidemics of KD documented in Japan and the U.S., and association with certain weather patterns) (10). Many infectious disease agents have been associated with cases of KD but as yet none have been shown to have a causal association. Recent studies have suggested possible infection with a viral agent, possibly an as yet to be identified RNA virus, that triggers an immune response in genetically predisposed individuals leading to KD. (11)

**Pathology**

The understanding of the pathology of KD is in transition. Early studies suggested the pathology of vasculitis was characterized by proliferative granulomatous inflammation with monocytes and macrophages, starting with the onset of illness then peaking rapidly and then remitting and healing by scarring, i.e. a synchronous process. (12,13) A more recent study (14a), using molecular and electron microscopy techniques, suggests 3 distinct processes: necrotizing arteritis, sub-acute/chronic vasculitis, and luminal myofibroblastic proliferation. Differences in these descriptions may have profound implications for monitoring and management of KD patients in the future(14b).

**Pathogenesis**

KD is a systemic inflammatory illness that has been classified as a medium-sized artery vasculitis particularly but not exclusively involving the coronary arteries. It is associated with a marked up-regulation of cytokines in the peripheral blood including TNF, IL-1 and IL-6. Other immunopotent cells such as macrophages, T lymphocytes, and myofibroblasts secrete VEGF, matrix metalloproteinases, and other inflammatory products into the arterial wall leading to tissue damage and arterial wall weakness and dilatation.

**Genetic Influences in KD**

As noted above a genetic predisposition was suggested by higher incidence in certain racial and ethnic groups and higher incidence in families with a history of cases of KD. Whole genome analysis studies have suggested specific gene loci may be involved in the susceptibility to KD and the tendency to develop coronary artery aneurysms and resistance to IVIG therapy of KD. (See table 3).

**Management**

IVIG remains the treatment of choice for acute KD. Randomized and blinded controlled trials have shown that IVIG of 2 g/kg has an immediate effect on the clinical symptoms in most patients and has reduced the incidence of persistent coronary artery aneurysms (CAA) from 20-25% to <4% and limited the occurrence of giant CAA to <1% (5). In Japan the mortality from KD
Aspirin has also been employed as an antipyretic and analgesic. Initially, high dose aspirin was continued for 14 days but was subsequently shortened to duration of fever following IVIG &/or discharge from the hospital. This was done to minimize the occurrence of toxicity from aspirin ant the realization that aspirin has no effect on CAA.

As many as 10-30% of patients may have persistent or recrudescent fever following IVIG. The use of a second dose of IVIG and/or alternative anti-inflammatory agents have been recommended in these patients. Steroid treatment has been variable. A meta-analysis of 9 studies using prednisone or methylprednisolone was performed: 6/9 were prospective randomized controlled trials (RCT), 2 were non-randomized trials and one was retrospective observational study (20). Seven of the 9 studies were done in Japan. The rate of CAA was lower in the steroid treated patients. Another RCT from Japan use 2 mg/kg of IV prednisolone for 5 days followed by a 15 day tapering of the dose if fever abated. Patients were selected for therapy with steroids based on high risk suggested by the Kobayashi score, a system used in Japan to determine risk of development of CAA. The rate of CAA was less in the steroid group. Another prospective RTC study from the U.S. compared primary therapy with IVIG alone to IVIG and 30 mg/kg of methyprednisolone given IV. There was no difference in the CAA outcomes in the two groups (21). The latter 2 studies may not be comparable due to the difference in locations of the studies. Japanese patients may not respond to IVIG or steroids in the same way as children in the U.S. Risk assessment scores used in the U.S. are not effective in determining the risk of CAA in patients here (22) so there may be differences in both prediction and response rates in the two populations (23).

Other therapies gaining traction include anti-TNF-α therapy including infliximab 5 mg/kg given once or soluble TNF-α receptor (Etanercept®) have been used but, in the case of infliximab, in a prospective study it did not reduce the incidence of CAA (24). Other therapies that have been applied to KD are ciclosporin, cyclophosphamide, methotrexate or plasma exchange but are recommended on a case-by-case basis only for patients after consultation with KD centers.

Primary empiric therapy in the U.S. includes aspirin in high dose (80-100 mg/kg/day in 4 divided doses) until fever has abated following IVIG treatment then conversion to 3-5 mg/kg/day given until 6 to eight weeks following onset of the disease as an antiplatelet aggregation therapy. The low dose therapy in continues indefinitely in patients with persisting CAA.

**Cardiovascular Complications**

In the U.S. echocardiography is the primary tool used to identify cardiovascular abnormalities due to KD. Pericardial effusion, decreased myocardial function, perivascular echo brightness of coronary arteries, and lack of coronary artery tapering can all suggest early effects of inflammation within the heart. The most serious outcome is dilatation of the coronary arteries
in the form of ectasia (dilatation of a tubular structure), fusiform or saccular aneurysms. Dilatation or change in configuration of arteries creates more sluggish and turbulent flow within arteries which, coupled with inflamed endothelial cells, thrombocytosis and increased “stickiness” of vessels, can result in formation of thrombi and occlusion of coronary arteries. Rarely CAA may also rupture. Either event can lead to myocardial obstruction and/or ischemia and death. Risk factors identified for the development of CAA in KD (25) include delay in initiation of IVIG therapy beyond 10 days of illness, age < one year and > 9-17 years, male sex, Asian and Pacific Islander race, and Hispanic ethnicity especially when treatment is delayed. The role of genetic predisposition has been discussed.

The formation of giant coronary artery aneurysms (>8 mm internal diameter) is the most dangerous outcome due to the tendency of obstructive clot formation and the inadequacy of aspirin alone to prevent thrombosis. In these patients, the addition of heparin and/or warfarin to prevent thrombosis is indicated.

**Long-term Outcomes and Management**

Long term follow-up of KD patients with CAA has demonstrated there is a strong tendency for CAA to regress. In one U.S. study, 67% of patients showed partial or complete regression (26) and in a longer follow-up trial from Japan 50% regressed (27). Giant CAA rarely, if ever, return to normal or even show significant regression.

The long term prognosis of patients who have had KD is generally very good. A recent study from the U.S compared 586 KD patients with 2218 control patients who did not have KD (28). Patients who were followed for about 15 years were assessed for specific cardiac adverse events. About 80% of the KD patients had been treated with IVIG and only 5% of patients had persistent CAA. Outcome was measured in adverse event/1000 person years. There was no significant difference between outcomes of the two patient groups. There were 5 events among the whole cohort of KD patients (546 patients followed for > 1 year. Of these there were 2 deaths, one from “coronary artery disease” without other information and one who died while on aspirin, warfarin and persantine but who had no thrombosis or infarct on autopsy. Three other patients had acute coronary syndrome. Patients with giant CAA also have a fairly good prognosis but with significantly more interventions that include bypass grafting, often using internal thoracic arteries, percutaneous interventions, or heart transplantation. Survival rates of 95%, 88%, and 88% at 10, 20, and 30 years have been reported (29). Another long term outcome that remains controversial is the enhanced risk of atherosclerotic heart disease as adults. Studies are ongoing to answer this question.

**Areas of Current Interest and Research**

At the recent 11th International Symposium on Kawasaki Disease held in Honolulu Hawaii
several areas of research were reported:

1. Epidemiology: Why is the incidence of KD continuing to increase in Japan and remain fairly stable in North America and Europe?

2. Diagnosis: Failing to determine the etiology of KD has led investigators to look for biologic markers that alone or in combination represent the “gold standard” for diagnosis.

3. Illnesses or complications associated with KD such as macrophage activation syndrome/hemophagocytic lymphohistiocytosis and KD shock syndrome.

4. New studies using steroids, cyclosporin A, or IL-1 antagonists. Newly recognized complication of IVIG-associated hemolysis in KD.

Summary

While we have made great progress in the diagnosis and management of KD and improved our understanding of the pathology, pathogenesis, and genetics of the illness we still do not know the etiology nor do we have a “gold standard” diagnosis. Hopefully answers to these unknowns will be forthcoming in the near future.

TABLE 1.

Diagnostic Criteria for Kawasaki Disease

Fever for at least 5 days and four of the 5 following criteria:

a. Changes of the mucous membranes of the mouth including red, cracked lips &/or, diffusely red buccal mucosa &/or strawberry tongue
b. Polymorphous rash
c. Bilateral conjunctival injection without discharge
d. Changes of the peripheral extremities: erythema of the palms and soles; swelling of the hands/feet; periungual peeling of the fingers and toes IN THE 2\textsuperscript{ND} OR 3\textsuperscript{RD} WEEK OF THE ILLNESS
e. Cervical lymphadenopathy >1.5 cm in diameter, usually unilateral

Exclusion of other diseases with similar findings. (Infections: e.g. measles, scarlet fever, staphylococcal toxic shock syndrome, adenovirus, enterovirus, EBV, bacterial cervical lymphadenitis; drug hypersensitivity reactions; Stevens-Johnson syndrome; juvenile rheumatoid arthritis; Rocky Mountain spotted fever; leptospirosis; acrodynia)
In patients with fever for at least 5 days and < 4 of the 5 other criteria, the diagnosis can be made by demonstration of coronary artery abnormalities on echocardiogram.

Figure 1.

Evaluation of Suspected Incomplete Kawasaki Disease (KD)\(^1\)

Algorithm for diagnosis of incomplete Kawasaki disease from AHA in Pediatrics 2004; 114:1708

Supplemental laboratory criteria include: albumin $< 3.0 \text{ g/dL}$, elevation of ALT, anemia for age, platelets after 7 days of illness $\geq 450,000 \text{mm}^3$, WBC count $\geq 15,000 /\text{mm}^3$, urine WBCs on micro $\geq 10$ WBCs/HPF
Echocardiographic criteria positive if any of 3 conditions are met:

- Z score of either LAD or RCA $> 2.5$

Or

- Greater than or equal to 3 other suggestive features exist: perivascular echo brightness, lack of tapering, decreased left ventricular function, mitral regurgitation, pericardial effusion, or
  - z scores in LAD or RCA of 2-2.5.

Table 2.

Genetic associations with susceptibility to KD, susceptibility to development of CAA and resistance to IVIG therapy.

**Susceptibility to Kawasaki disease**

- **FCGR2A** (15)
- **ITPKC** (16, 17, 19)
- **CASP-3** (16, 17)

**Susceptibility to CAA**

- **SRC-1** (18)
- **CASP-3** (16, 17)
- **ITPKC** (16, 17)

**IVIG unresponsiveness**

- **ITPKC** (17)
- **CASP-3** (17)

References


