Update on Kawasaki disease: Epidemiology, aetiology and pathogenesis

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Abstract: Kawasaki disease is an acute systemic vasculitis predominantly affecting young children. It is due to an abnormal host response to as yet unidentified infectious trigger(s). Kawasaki disease may cause coronary artery damage, long-term cardiovascular morbidity and occasionally mortality, especially if the diagnosis is missed or timely treatment is not given. This is the first of two updates on Kawasaki disease. Here we review recent advances in epidemiology, possible aetiologies, host susceptibility and pathogenesis of this fascinating condition.

Keywords: aetiology; Kawasaki disease; pathogenesis; review.

Kawasaki disease (KD) is a self-limited childhood systemic vasculitis characterised by a constellation of clinical signs and symptoms. Untreated, it results in coronary artery abnormalities in up to 25% of children.1 Although there has been significant research progress since its first description in 1967,2 the aetiology remains unknown and there is no diagnostic test. The consensus is that one or more infectious agent(s) trigger an abnormal pro-inflammatory host response that is responsible for the pathology and clinical features. Epidemiological data suggest there is widespread exposure to the infectious trigger(s) but an abnormal response occurs only in genetically susceptible individuals. The timely use of high dose intravenous immunoglobulin (IVIG) reduces the incidence of coronary artery aneurysms to 3–5%.3 The long-term cardiovascular implications – particularly whether there is an increased risk of cardiovascular disease in adulthood – remain unclear.

Key Points
• Kawasaki disease is a systemic vasculitis occurring predominantly between 6 months and 4 years of age. Cases outside this age range are more likely to have incomplete diagnostic features that may lead to a delay in diagnosis and treatment.
• The incidence of Kawasaki disease has been consistently rising in both developed and rapidly industrialising countries, with considerable variation between ethnic groups.
• The higher incidence in families of index cases suggests that host genetic factors play an important role in determining an abnormal immunological response to an infectious trigger(s).

Epidemiology
KD has been described in almost every ethnic group and the clinical and many of the epidemiological features are remarkably similar in different populations. KD predominantly affects young children; 80% of cases occur between the ages of 6 months and 4 years.4–6 Cases outside the 6-month to 4-year age range are well recognised, including in neonates,7,8 and in adults, particularly those with HIV infection.9 Diagnosis and consequently treatment are often delayed at the extremes of age, partly because of the absence of the ‘classical’ diagnostic criteria (especially in infants) and a reluctance, even among specialists, to diagnose the disease outside the typical age range.10 KD, like many childhood infections, has a male predominance (approximately 1.6 times commoner). The peak age of onset is approximately 9–11 months in the Japanese,11 Koreans12 and Taiwanese,13 and over 12 months in other populations, such as Canadians,14 Indians15 and British.16

The incidence of KD varies considerably between ethnic groups. Incidence rates in North East Asia are up to 20 times higher than in Caucasians. Australia has one of the lowest reported rates (3.7 per 100 000 <5 years of age),17 equivalent to 50–60 cases Australia-wide per year. It is likely that the current Australian incidence is higher and epidemiological studies will report soon. The incidence in New Zealand is also relatively low (8/100 000 <5 years of age).18 The highest incidence is reported in Japan (239/100 000 <5 years of age in 2010, approximately 12 755 cases per year).11 It has been estimated that up to 1 in 150 Japanese children have had KD by the age of 10 years.1 The next highest incidence rates are reported in Korea (113.1/100 000 <5 years)12 and Taiwan (69/100 000 <5 years).19 The
high incidence in Asian populations in maintained in those born and living in low incidence countries, suggesting a genetic predisposition to susceptibility. For example, the incidence in Chinese children in the UK is significantly higher than that of UK European-Caucasians.\textsuperscript{19} Japanese Americans in Hawaii have an incidence rate equivalent to Japanese children in Japan (210/100 000 <5 years of age), whereas European-Caucasian Hawaiians have a rate comparable with the overall European-Caucasian US population (13/100 000 <5 years of age).\textsuperscript{20}

The incidence of KD has been rising consistently in many developed countries such as Japan\textsuperscript{1}, Korea\textsuperscript{11} and the UK,\textsuperscript{16} where the diagnosis has been familiar to paediatricians for many years, suggesting a true increase rather than ascertainment bias.\textsuperscript{21} The first Australian case was reported in 1976,\textsuperscript{22} and the incidence has steadily increased since (Saundankar et al., unpubl. data). The incidence is also increasing in rapidly industrialising countries such as India,\textsuperscript{23} which may reflect both a genuine increase in incidence and increased recognition by physicians.

There is a well-recognised seasonal variation in incidence rates.\textsuperscript{21} Australia\textsuperscript{17}, UK\textsuperscript{16} and the USA\textsuperscript{24} report increased incidence in winter and spring, whereas spring/summer peaks are seen in China.\textsuperscript{25} Seasonal variation is less marked in Japan.\textsuperscript{26} An intriguing association between recent meteorological conditions (higher average rainfall, lower average ambient temperature) and KD activity has been reported.\textsuperscript{27}

The epidemiology of KD strongly suggests that at least one infectious trigger is involved in precipitating the abnormal immune response. Two major epidemics of KD occurred in Japan (in 1982 and 1986), with ‘waves’ of disease activity spreading over a period of months.\textsuperscript{28} A fascinating association between wind patterns and increased incidence in Japan and the western USA has recently been reported, raising the possibility that a wind-borne trigger may contribute to seasonal fluctuations and epidemics.\textsuperscript{29} Such large epidemics have not been observed recently, but clustering of cases and smaller outbreaks are regularly seen,\textsuperscript{30} even in lower incidence countries such as Australia.\textsuperscript{31} The low incidence in the first three months of life suggests at least partial protection from trans-placental antibodies.\textsuperscript{32} The relative low incidence after the age of 4 years suggests a widespread trigger(s) to which most school-age children have previously mounted an immune response, without developing clinical KD.\textsuperscript{21} Recurrence of KD occurs in 3–5% of cases in Japan,\textsuperscript{33} although it appears much less frequent in other populations.\textsuperscript{17} This suggests that a small proportion of children do not develop a protective immune response and/or that more than one infectious agent, which does not induce cross-protective immunity, may trigger a similar clinical syndrome.

### Aetiology

There is ongoing debate as to the importance of conventional antigens (which stimulate about one in a million T cells) and/or superantigens (which are not major histocompatibility complex (MHC)-restricted and which stimulate 20–30% of T cells)\textsuperscript{34} in triggering KD. There is evidence to support involvement of both mechanisms, which are not necessarily mutually exclusive, especially if two infectious triggers are involved.\textsuperscript{18} Both conventional and superantigens may lead to common pathways of immune activation and inflammation that result in the clinical features and vascular damage observed in KD. Analysis of autopsy specimens of children who have died of KD (which are limited in number as the mortality rate is low and may not be typical of KD in general) have identified immunoglobulin A (IgA)-producing plasma cells in the walls of coronary arteries. The IgA recognises cytoplasmic inclusion bodies, which may be viral in origin.\textsuperscript{36} Within the bronchial wall, there is increased expression of genes involved in the interferon pathways, which are particularly important in anti-viral responses. These findings suggest that an as yet identified respiratory virus may contribute to KD.\textsuperscript{19}

The clinical similarities between KD and toxic shock syndrome have led to investigation of the possible role of bacterial superantigen toxins.\textsuperscript{18} In addition, the occurrence of cases with apparent simultaneous toxic shock syndrome and KD (with coronary artery aneurysms) strongly suggests a shared aetiology,\textsuperscript{19} Individual superantigens cause a skewed expansion of cells bearing specific V-beta regions of T-cell receptors (to which superantigens bind) and such cells have been reported infiltrating the coronary arteries in fatal KD.\textsuperscript{30} However, there have been inconsistent results from studies of peripheral T-cell receptor skewing in patients.\textsuperscript{41,42} This suggests that the involvement of superantigens is likely to be more complex (and hence difficult to assay)\textsuperscript{43} and/or that more than one superantigen can trigger KD. Immunoglobulin M antibody levels are significantly elevated against a variety of superantigens following KD,\textsuperscript{44} and one or more superantigen-producing bacteria are detected in gastrointestinal flora specimens more frequently in KD cases than controls.\textsuperscript{45–47} In a murine model of KD, a superantigen from a lactobacillus cell wall induces a coronary arthritis. This model provides evidence that co-stimulation by both conventional antigens and superantigens may be important.\textsuperscript{15} If human studies confirm this phenomenon, this may partly reconcile some of the discrepant findings on the infectious trigger(s) of KD.

### Pathogenesis

The infectious trigger(s) of KD precipitate a complex and incompletely understood cascade of host inflammation in susceptible children.\textsuperscript{5,17} Initial systemic inflammation leads to the clinical and laboratory features, and local subclinical vascular inflammation may result in vessel damage and remodeling. Initially, activated inflammatory cells, particularly monocytes, macrophages, T cells and, later in the disease, platelets adhere to the endothelial cells that line medium-sized elastic arteries. The endothelium expresses surface molecules that allow leucocytes and platelets to adhere and some of the adherent inflammatory cells penetrate the vessel wall. Local expression of mediators attracts further inflammatory cells and increase vessel permeability. Other mediators contribute to destruction of the extra-cellular matrix, leading to vessel dilatation, and subsequent smooth muscle proliferation in the media contributes to later pathology. The predilection for the coronary artery damage is not understood, but it may partly reflect local flow dynamics\textsuperscript{48} Understanding the proclivity for the coronary arteries would provide important clues to the pathogenesis.
**Host Factors for Susceptibility**

The high incidence of KD in Japanese-Americans, as well as the increased risk (approximately 6–8 times the population risk) in siblings of cases, suggests that host genetic factors are important in determining the abnormal immunological response to the infectious trigger(s). KD also segregates in families; parents of Japanese children who have KD are more likely than the general population to have had KD themselves, and these families have more severe disease. KD is genetically complex, with many genes contributing modestly to the overall genetic risk. Given the relatively low incidence, many genetic studies have been under-powered and positive findings have not been replicated, so it has been difficult to be confident about many of the marginal genetic associations reported. Candidate gene approaches, where the loci are chosen on their biological plausibility, have provided some insights into pathogenesis, particularly in studies where genes have been analysed with reference to their biological pathways. There are also functional data suggesting that the genetic associations may be biologically important. For example, regulation of apoptosis (programmed cell death) is abnormal in KD, with abnormal persistence of activated leukocytes, which may contribute to sustained inflammation. In keeping with these observations, there is evidence of significant differences in both gene expression, and of sequence variation, in genes involved in apoptotic pathways in KD. In animal models and in human autopsy cases, matrix metalloproteinas (MMPs) are involved in damage to the arterial wall and coronary aneurysm formation. Abnormal circulating levels of MMPs and their endogenous inhibitors are abnormal in some studies of acute KD, and variation in MMP genes have been associated with KD and coronary artery formation in different populations.

An alternative approach to identify genetic determinants is to interrogate the whole genome, rather than to focus on specific (and usually somewhat predictable) candidate genes. Linkage studies, which require affected sibling pairs or multiply-affected pedigrees, are logistically difficult, given the relative low incidence, but two have been successfully performed to date. A Japanese linkage study identified a region of chromosome 19 that was subsequently fine-mapped to an important regulator of T-cell function, **ITPKC**. Functional variants in this gene (which may affect gene splicing) have been associated with overall susceptibility and coronary artery damage in Japanese, US, Caucasian and Taiwanese populations, highlighting the importance of T cells in KD pathogenesis.

To date, four genome-wide association studies (GWAS) of modest size have been published in KD. A number of biologically plausible loci involved in inflammation, immune responses and cardiovascular status have been identified. In the largest study to date, involving 2173 individuals with KD and 9383 controls from five independent sample collections, two variants exceeded genome-wide significance (\(P < 5 \times 10^{-8}\)), the usual statistical benchmark for GWAS. The most significantly associated variants were a non-synonymous polymorphism in a high affinity receptor for immunoglobulin G (FCGR2A) and variants in the region of the T-cell regulator **ITPKC**, originally reported in the Japanese.

**Summary**

There have been important research advances highlighted in this review that have broadened our knowledge and understanding into the observed epidemiology, genetic susceptibility and pathogenesis in KD. However, the precise aetiology and genetic determinants of susceptibility and outcome remain incompletely understood. Increased understanding is crucial to developing a diagnostic test, biologically based treatments and possibly preventative interventions in high incidence populations. The second review focuses on the diagnosis, treatment, follow-up recommendations and cardiovascular outcomes of KD.

**Review Questions**

1. With regard to the epidemiology of KD, which of these statements is false?

   A) Highest rates of KD are reported in Japan, Korea and Taiwan
   B) Clustering of cases and small outbreaks have been observed in Australia
   C) An estimated 1 in 150 Japanese children have had KD by the age of 10 years
   D) Recurrence of KD occurs in 10% of cases in Japan
   E) Australia reports an increased incidence in winter and spring months

   Answer: D is false. Recurrence of KD occurs in 3–5% of cases in Japan.

2. What is the reported risk of KD for siblings of index cases?

   A) 2–4 times the population risk
   B) 4–6 times the population risk
   C) 6–8 times the population risk
   D) 8–10 times the population risk
   E) 10–12 times the population risk

   Answer: The increased incidence of KD in siblings of cases is approximately 6–8 times the population risk in Japanese. There are no data from other populations.

3. Regarding the aetiology of KD, which of these statements is false?

   A) Shock is occasionally seen as a manifestation of KD
   B) KD has clinical similarities to toxic shock syndrome, leading to research into a shared aetiologic basis
   C) Superantigens stimulate T cells that bear specific V-beta receptors to which superantigens can bind
   D) Autopsy studies have identified IgA producing plasma cells in the walls of coronary arteries
   E) A murine model of KD supported involvement only of conventional antigens

   Answer: E is false. In a murine model of KD, a superantigen, derived from a lactobacillus cell wall, was shown to induce coronary arteritis. The murine model provides evidence that both conventional antigens and superantigens are important in immune activation.

**References**


