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REVIEW

Kawasaki disease: What is the epidemiology telling us about the etiology?

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Summary Kawasaki disease (KD) is an important and common inflammatory vasculitis of early childhood with a striking predilection for the coronary arteries. It is the predominant cause of paediatric acquired heart disease in developed countries. Despite 40 years of research, the aetiology of KD remains unknown and consequently there is no diagnostic test and treatment is non-specific and sub-optimal. The consensus is that KD is due to one or more widely distributed infectious agent(s), which evoke an abnormal immunological response in genetically susceptible individuals. The epidemiology of KD has been extensively investigated in many populations and provides much of the supporting evidence for the consensus regarding etiology. These epidemiological data are reviewed here, in the context of the etiopathogenesis. It is suggested that these data provide additional clues regarding the cause of KD and may account for some of the continuing controversies in the field.

What is Kawasaki disease?

Kawasaki disease (KD) is an acute systemic necrotising panvasculitis affecting medium-sized arteries, particularly the coronary arteries.[1] It is characterised by prolonged fever (of at least five days duration) and a collection of clinical features (rash, non-purulent conjunctivitis, oropharyngeal changes, lymphadenopathy and changes to the extremities) that together comprise the standard diagnostic criteria (Table 1).[2] As the clinical phenotype is essentially a constellation of clinical signs of unknown etiology (*vide infra*), it may be more appropriate to refer to 'Kawasaki syndrome' rather than 'Kawasaki disease'.[3] Other clinical features, such as extreme irritability and re-inflammation of a recent BCG scar may aid the diagnosis.[4,5] The full diagnostic criteria — fever $\geq$5 days, plus at least four clinical criteria — were originally derived for epidemiological studies in Japan.[3] The clinical features often appear sequentially, in

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Table 1 Diagnostic criteria for Kawasaki disease (for a detailed discussion of the clinical diagnosis and additional clinical features, see references[5,6,97]).

Fever of at least five days duration plus at least four of the following features:
Polymorphous rash
Bilateral non-purulent conjunctivitis
Changes in the peripheries
Oropharyngeal changes
Cervical lymphadenopathy

no predefined order and some may even be absent on presentation. In many children the clinical presentation is striking and KD patients are often misdiagnosed with severe sepsis. However, KD can have similar clinical features to other common childhood illnesses, such as measles, rubella and scarlet fever. These children may present a diagnostic challenge[6] and the lack of a specific diagnostic test may delay treatment and thus worsen prognosis.[7]

Moreover, to confuse the clinical picture further, there is increasing concern that the diagnostic criteria are too narrow. 'Atypical' or 'incomplete' KD is a description used for children presenting with the characteristic fever but fewer than four classical signs. A better descriptive term is 'incomplete KD' because these children do not demonstrate atypical signs, just fewer of them. Cervical lymphadenopathy is the least commonly observed of the diagnostic criteria, occurring in about three quarters of usually older children, whilst prolonged fever and peripheral desquamation have been reported as the commonest diagnostic features. Incomplete KD may be poorly recognised and occurs more often in infants.[8] Children presenting with incomplete KD are at higher risk of developing coronary artery lesions both because of their young age and their potential for not receiving timely immunoglobulin treatment.[8] Interestingly, as many as 10% of the children reported in the original report of the syndrome[2] would not fulfil the current case definition.[3] The clinical diagnostic criteria need refinement to increase their positive predictive value and recent guidelines have been developed in an attempt to increase the sensitivity of the clinical diagnosis.[5] It is unclear how these will perform in clinical practice. Although these guidelines are intended only as a clinical tool, they are likely to have an impact on the reported epidemiology of KD.

Cardiovascular sequelae

Kawasaki disease is clearly not the benign childhood exanthem initially proposed[1,2] and has significant long-term implications. Kawasaki disease is the most common cause of paediatric acquired heart disease in the world.[3] Coronary artery lesions (predominantly aneurysms) occur in up to 30% of untreated and 5–10% of treated children;[1,9,10] the poor outcome despite adequate treatment reflects an incomplete understanding of the etiopathogenesis. Acute mortality in KD is increased significantly, with deaths predominantly occurring from myocardial infarction following occlusion of giant coronary aneurysms.[11,12] Overall, myocardial infarction occurs in ~2% of those with coronary artery lesions.[13] Lifelong medical therapy, coronary artery grafting and even heart transplantation may be required.[1] Crucially, in children without coronary artery lesions who die of other causes, the coronary arteries are almost invariably markedly abnormal, with striking pro-atherosclerotic changes.[14,15] Abnormal *in vivo* function in non-coronary arteries[16] suggests that cardiovascular damage post-KD is both pervasive and persistent, even in the absence of acute coronary artery lesions. Thus, there is intense speculation that KD is pro-atherosclerotic, but definitive long-term data are lacking.

Regressed coronary artery lesions result in abnormal coronary artery function[17] and histological changes that are pro-atherosclerotic.[15,18] The similarities between KD and adult cardiovascular pathology suggest that KD may be a useful paradigm for investigating the etiopathogenesis of atherosclerosis.[19]

Does Kawasaki disease represent an extreme phenotype of a more pervasive phenomenon?

It is possible that KD is not a distinct entity, but the more clinically obvious end of a spectrum of pathogenic processes. KD may therefore reflect an extreme clinical phenotype where childhood infections predispose to subsequent endothelial damage and cardiovascular pathology. Thus in genetically susceptible children, acute infections such as those causing fever and rash, may result in unrecognised damage to the cardiovascular system that later manifests itself as adult cardiovascular disease. Adult atherosclerotic disease (like KD) has not been reliably associated with a single infectious etiology, but correlates with overall infectious burden.[20] Furthermore, acute childhood infections are accompanied by pro-atherosclerotic phenomena and subsequent thickening of the arterial intima.[21] Understanding the etiopathogenesis of KD may therefore identify common gene–environment interactions that are involved in adult cardiovascular disease.

Why is it important to understand the etiology and pathogenesis of Kawasaki disease?

The timely diagnosis of KD is essential in maximising the prevention of overt coronary damage; treatment beyond ten days of onset is associated with a worse outcome and an increased incidence of coronary abnormalities.[22,23] The lack of a specific diagnostic test and the limited clinical utility of the current clinical diagnostic criteria mean that the diagnosis is often delayed, even in populations where the condition is well recognised.[24] The currently accepted best treatment (intravenous immunoglobulin and aspirin (Table 2)[6] fails to prevent coronary artery abnormalities (identifiable by imaging) in up to 10% of cases.[25] Specific diagnostic test(s) and rational interventions could be readily developed if the etiopathogenesis of KD was fully understood. Moreover, preventative treatments such as vaccines would be justified in populations with the highest KD incidence, where KD affects 1–2% of all children, such as Korea and Japan.[3]

The consensus view is that KD results from a widely distributed infectious agent (or possibly agents) that causes the clinical syndrome in genetically susceptible children. Much of the supporting data for this viewpoint is provided by epidemiological studies in a variety of populations. KD is described in all ethnic groups, but the incidence varies dramatically (see below). The homogeneity of the clinical phenotype and epidemiology suggest that KD arises from common disease processes, although the antigenic trigger(s) and/or the genetic determinants may differ between populations.

Epidemiological evidence for an infectious cause

Kawasaki disease shows a striking age distribution reminiscent of other childhood infections. Over 80% of cases occur between the ages of six months and four years,[26] although the condition occurs rarely both earlier[27] and later[28] in life. The low incidence of KD in both the first six months suggests that most infants are protected by passively acquired maternal antibody against the causative agent(s). A transient immunological immaturity may also account for the low incidence in the first few months postnatally.[29] The low incidence of KD beyond mid-childhood suggest a ubiquitous antigen(s) that most children encounter uneventfully in early childhood and to which they mount an appropriate and protective immune response. Kawasaki disease is more common in boys (male:female ratio ~1.6:1)[1] a feature observed in many infectious diseases[30,31] and also in coronary atherosclerosis, where sex differences in immune responses are suggested to mediate susceptibility.[32]

Seasonal variation in KD incidence is well recognised, but the predominant season varies in different countries. In the UK,[33] Australia[24] and the USA[34,35] KD is most common in winter and spring. In China, spring and summer predominate[36] and in Korea KD incidence is highest in summer months.[37] In Japan, which reports the highest KD incidence,

Table 2 Treatment of Kawasaki disease (for detailed discussion of the treatment of Kawasaki disease see references[5,6,97]).

1. **Intravenous immunoglobulin** (IVIG)	At a dose of 2 g/kg given as a single infusion over 10–12 hours (unless cardiac status necessitates infusing the dose more slowly or in divided doses). Failure to respond to this initial IVIG dose is usually treated with a second dose (usually 2 g/kg as a single infusion). Failure to respond to the second IVIG dose is often treated with intravenous methylprednisolone under expert supervision
2. **Aspirin**	The dose of aspirin is controversial and its utility has never been proven in a randomised controlled trial. It remains, however, part of the standard management of KD. Generally 'high dose' aspirin (50–100 mg/kg/day in divided doses) is given acutely until the fever defervesces, when 'low dose' aspirin (2–5 mg/kg/day) is given until an echocardiogram at six weeks after the KD diagnosis is normal. If the six week echocardiogram is abnormal, aspirin is usually continued under cardiological supervision
3. **Adjunctive therapies**	Anti-cytokine therapies and other interventions are generally unproven but have occasionally been used. For a review see Newburger and Fullton[5]

the seasonal variation is less marked.[38] One possible explanation for these divergent data is that season is a marker for weather conditions that have a more direct role in determining the incidence. In the US, KD incidence clearly correlates negatively with average ambient temperature and positively with average rainfall in the preceding month.[39] Studies are underway investigating similar parameters in the UK.

It is unknown whether the meteorological conditions themselves predispose to KD, or, more plausibly, if they alter the epidemiology of etiological agents. The lack of consistent seasonal associations in different countries raises the possibility that various etiological agents may be involved in the etiology of KD. Geographical clustering of KD cases and epidemics have been reported from a number of countries,[40–44] although they have been much less frequently reported in the past decade, possibly suggesting a changing epidemiology. In Japan, which has provided the most comprehensive epidemiological data, epidemics of KD have been described with a clear epicentre and documented geographical spread across the whole nation within six months.[42]

These epidemiological data clearly indicate an infectious etiology for KD. The clinical features of the disease are also characteristic of a severe acute childhood infection. It seems likely that the causative agents are widely distributed and are also highly immunogenic, at least in most children, as more than one episode of KD is rare. Recurrent KD is reported in 1–3% of children,[45] although it appears less common in Caucasians.[46] It may reflect a specific immunological deficiency in these children or exposure to more than one causative agent.[3] Various environmental causes of KD have been repeatedly suggested (Table 3), but none has been consistently replicated. However, the possibility of environmental factors influencing etiology, possibly by modulating infection risk, remains a possibility.

Table 3 Proposed but unproven causes of Kawasaki disease.

Putative etiological agent/ environmental association	References
Adenovirus	98
Herpesvirus	99
Mycoplasma species	100
Toxigenic streptococci	101,102
Viridans streptococci	103
Toxigenic staphylococci	104,105
Propionibacterium acnes	106,107
Ehrlichia chaffeensis	108,109
Rickettsia species	110,111
Epstein Barr virus	112–114
Retrovirus	115–117
Human coronavirus New Haven	48
Measles virus	118,119
Chlamydia pneumoniae	120–122
Bartonella henselae	109
Coxiella burnetii	123,124
House dust mite	125
Mercury	126
Carpet shampoo	127,128
Residence near body of water	129

Which infection?

The search for a single unifying microbiological cause has been unrelenting but, to date, fruitless. Standard microbiological techniques, molecular methods and serological investigations have so far failed to identify an etiological agent. Molecular techniques fail to detect circulating conserved microbial sequences in KD,[47] indicating that the antigenic stimulus may arise from a distant site (e.g. colonising pathogens in the nasopharynx) and/or may represent host-derived factor(s) that induce or promote the pro-inflammatory cascade. The list of discarded and/or unproven etiological agents in KD is long (Table 3). A recent report of an association between the presence of genetic material from a novel coronavirus and Kawasaki disease in a handful of cases[48] remains unproven and may reflect an epiphenomenon; the putative etiological agent is a relatively common viral pathogen in young children and it is unclear how long the DNA persists. The lack of a unifying etiological agent despite a significant research effort suggests that KD can follow exposure to more than one infectious agent, or that a novel infectious agent is involved. Alternatively the clinical phenotype may reflect a stereotyped response in a genetically-susceptible host to one of a variety of infectious agents.

Much of the continuing debate in the literature concerns whether KD is caused by a superantigen[49] or a conventional antigen.[50] KD shares many clinical features with superantigen-mediated diseases (for example, rash, conjunctivitis and skin peeling) and KD has occasionally been reported concurrently in children with toxic–shock syndrome, which is caused by superantigens.[51] However, unequivocal epidemiological and laboratory support for a role for superantigens in KD is lacking. In one small study, maternal antibodies against toxic shock syndrome toxin-1 appeared protective against early-onset KD.[52] However, the carriage rates of superantigen-producing bacteria by children with KD are not consistently increased,[53,54] although these data may reflect the involvement of as yet unidentified

superantigens, with more than one superantigen capable of causing KD. Superantigens bind to the Vβ region of the T-cell receptor and clonal expansion of Vβ2-expressing T-cells has been reported in some studies of KD,[55] but again the finding is inconsistent.[56] Other studies have reported oligoclonal IgA-producing plasma cells infiltrating bronchial and intestinal tissues in fatal KD,[57] which suggests the involvement of a conventional antigen.

How many infections?

Much of the controversy and inconsistency surrounding the nature of the infectious trigger in KD might reflect multiple etiological agents resulting in the same clinical phenotype. It is possible, for example, that a viral upper respiratory tract infection may alter local immunity and allow elaboration of superantigens by colonising bacteria in the nasopharynx. Certainly the epidemiology of KD, with rapid changes in incidence, seasonal variation and the relationship between incidence and weather conditions is more redolent of acute viral infections[58,59] than bacterial colonisation, which alters more slowly.[60] In meningococcal disease, influenza infection acts in an analogous way, and meningococcal epidemics often follow influenza outbreaks.[61,62] This hypothesis could be addressed through large detailed prospective epidemiological studies.

Another possibility is that either pathogen or host factors modulate the behaviour of an antigen, so that it behaves both as a conventional antigen and as a superantigen. Heat shock proteins are increased in acute inflammatory conditions, including KD[63] and cross-reactivity with certain heat shock proteins is thought to be responsible for the inflammation of the BCG scar in KD.[64] Heat shock proteins have been reported to alter the behaviour of superantigens, so that the immune system recognises them as conventional antigens[65] and also can greatly up-regulate pro-inflammatory responses to conventional antigens.[66] The possibility of endogenous stimuli that profoundly suppress or enhance antigenic effects has not previously been considered in KD, but might account for much of the controversy surrounding the roles of conventional or superantigens.

Epidemiological evidence for genetic determinants of Kawasaki disease susceptibility and outcome

Whatever the etiological trigger(s) for KD, there is clear evidence that host genetic determinants play a major role in both susceptibility and probably outcome in KD. Genetic studies of KD are therefore likely to be highly informative about etiology and pathogenesis. Although KD is reported in all ethnic groups, the variation in incidence of KD between (and to a lesser extent within) countries is striking. The annual incidence varies from approximately three (per 100,000 children <5 years of age) in South America, to four in Australia,[24] eight in the UK,[33] 4–15 in the US,[1] 20–30 in China[36] and Hong Kong[67] 50 in Taiwan,[68] 90 in Korea[37] and >130 in Japan[69] The reported incidence is probably underestimated in many countries as atypical cases are not included. Australian data (Burgner et al., unpublished) suggest an incidence ~50% higher than that recorded through active surveillance.[24] In a number of countries the incidence of KD appears to be increasing.[33,68,69] Whilst this may be partly attributable to increased awareness, the increasing incidence is reported in countries where the disease has been widely recognised for several years and where a standard case definition is employed and may therefore reflect changing epidemiology.

The incidence of KD is therefore greatest in north-east Asians, especially in Koreans and Japanese. It is estimated that 1–2% of all hospitalised Korean children have KD (Park YW, personal communication) and that KD affects one in 150 Japanese children.[3] This indicates genetic factors may be central in determining susceptibility, especially as the incidence rate remains high in those migrating to lower incidence countries. For example, the incidence of KD in Japanese Americans in Hawaii (135/100,000 <5 years) is identical to the highest rates reported from Japanese living in Japan.[67]

The incidence rate in siblings of affected children is 10–15 fold higher than the population incidence in Japan.[70] The ratio of sibling to population incidence is termed the 'heritability' or 'λ_s'. Sibling rates outside Japan are unknown, but reports from Caucasians support this trend[71] and sibling rates in Korea[37] (Burgner, unpublished observations) also support this high heritability. This figure is slightly less than the heritability for insulin-dependent diabetes ($\lambda_s \sim 15$) and ~4 times higher than that of asthma,[72] suggesting a striking genetic predisposition to develop the disease in a minority of children across different ethnic groups. In addition, the incidence of previous KD in parents of Japanese children with KD is significantly increased and these families are much more likely to have other affected children and children with recurrent disease.[73] Taken together, these epidemiological data provide convincing evidence for a major role for host genetics in KD susceptibility.

Whilst there are concerns that cardiovascular damage may be pervasive in KD, overt coronary

artery lesions only develop in a minority of children. In acute KD all arms of the innate and adaptive immune response are activated, but lymphocytes, macrophages and neutrophils are central.[74] The extent and kinetics of host inflammation strongly correlates with the risk of coronary damage. The duration of fever prior to treatment,[75–77] the maximal erythrocyte sedimentation rate,[78] the extent of pro-inflammatory cytokine production[79,80] and the degree of neutrophil activation[81] have all been shown to be risk factors for coronary damage. The extent of the host inflammatory response is partly genetically determined.[82] Genetic factors are therefore likely to be important in determining outcome in KD and genetic studies may identify key pathogenic mediators and ultimately guide the development of new interventions.

Genetic epidemiological studies of KD

Kawasaki disease is likely to be a genetically 'complex disease', with contributions from a number of genetic loci to susceptibility and outcome. Associations between genetic variants at candidate loci and KD susceptibility and outcome may be extremely informative about the role of specific mediators in etiopathogenesis, allowing investigation of hypotheses suggested by the clinical data, but untestable by conventional clinical or laboratory studies. The consensus view supports the concept of a genetically-susceptible host in KD[6,83] and there is growing realisation that immunogenetic studies may reveal much about the disease and improve diagnosis, treatment and prognosis. Immunogenetic data suggest a number of plausible associations. Many studies focus on putative downstream outcome determinants and suggest a role for mediators of innate inflammation,[84] endothelial activation[85] and cardiovascular homeostasis.[86] Studies of susceptibility determinants are more limited. There are associations with class I regions of the Human Leucocyte Antigen (HLA) in Japanese,[87] with different alleles associated in Caucasians.[88] However, these HLA studies are largely historical and further work using modern HLA typing techniques are warranted.

Unfortunately, genetic studies of KD have often been undermined by methodological problems[89] that dog many such studies of human complex disease. Thus some of the reported associations are likely to be false positive results. In particular, the studies often lack statistical power, employ multiple uncorrected statistical comparisons and many do not replicate findings in an independent population.[87,88,90–92] Case-control methodology in a multi-ethnic disease may yield spurious disease associations (type I errors) due to population admixture,[93] unless this is actively identified.[94] Inadequate marker density in candidate loci, where the functional variants are unknown, may increase type II errors.[89]

Conclusions and future directions

Kawasaki disease is a fascinating and important paediatric illness, which presents a significant diagnostic challenge. It is the most common cause of heart disease acquired in childhood and an important paradigm for understanding the determinants of adult cardiovascular pathology. The epidemiology is well characterised and clearly supports the view that the disease results from an inappropriate immunological response to one or more infectious triggers in genetically-susceptible individuals. The search for the microbial etiology has been disappointing and unsuccessful and all that remains of over three decades of such studies is a 'long list of discarded pathogens'.[3] Understanding the genetic determinants of susceptibility to KD and those involved in mediating coronary artery damage may be a more profitable approach. The methodological issues that have undermined genetic analyses can be largely overcome by international collaborative studies that employ standardised phenotypic definitions and large sample sizes derived from different ethnic groups. The use of family-based genetic association analyses[95] circumvents the problems of population stratification and the use of trans-racial mapping (i.e. investigating genetic determinants in different ethnic groups)[96] may prove important to defining the critical genetic determinants, particularly in regions of high linkage disequilibrium. Newer molecular techniques, particularly gene expression profiling and proteomics may identify novel molecular 'fingerprints' that differentiate KD from other febrile and inflammatory illnesses.[3] The mystery of KD may ultimately be solved by looking within the host.

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