

Epidemiology and etiology of Kawasaki disease

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Abstract

Kawasaki disease was first reported in Japan in 1967 by Dr. Tomisaku Kawasaki. It has since been recognized worldwide, and in at the United States and Japan is the most important cause of acquired heart disease in children, surpassing other more recognized conditions such as rheumatic fever, endocarditis and myocarditis. It is primarily a disease of children less than 5 years of age but has been reported in older children and adults. Risk factors for the illness include Asian ancestry, male gender and certain familial predispositions. Observations such as similarity to certain exanthematous infectious diseases, temporal-geographic clustering of cases and seasonality in incidence favors an infectious etiology. Pathology and pathogenesis of the disease indicate that it is a medium-sized artery vasculitis that results from a dramatic immune activation that in most cases reversed by immune modulating agents such as intravenous immunoglobulin. Unfortunately, the etiology of the illness remains obscure, although recent studies favor a possible viral etiology.

Introduction

Doctor Tomisaku Kawasaki first described Kawasaki disease (KD) in 1967 based on 50 cases he had observed over the preceding 6 years at the Tokyo Red Cross Hospital [1]. He termed the illness mucocutaneous lymph node syndrome because of characteristic changes of the mucous membranes and skin, which seemed to characterize the illness. During the first few years following its description, it appeared to be a self-limited disease without sequelae. However, following the first nationwide survey of the illness in Japan in 1970, sudden death due to coronary artery disease was firmly linked to the illness [2]. KD was independently described in the United States in 1974 by Melish and colleagues [3], and following consultation with Dr. Kawasaki, there was agreement that the illnesses were clinically the same. Following the recognition of cardiac complications in both Japan and the United States, pathologists in both countries observed similarities

between coronary artery lesions seen in KD patients and those in patients who had died of infantile periarteritis nodosa (IPN), a rare vasculitis of infancy [3]. The question arose as to whether the two were the same disease. The issue was resolved by Landing and Larson in 1976 [4], who performed blinded evaluations of autopsy cases of children from both Japan and the United States who had died with a diagnosis of KD and IPN. They found that the two illnesses were pathologically indistinguishable.

In subsequent years KD has been recognized worldwide, and in all age groups, although 85% of cases occur in children <5 years of age. It is now recognized as the most common cause of acquired heart disease in children in the United States.

We attempt here to describe the current understanding of the epidemiology of KD and the most recent findings regarding its pathogenesis and etiology.

Diagnostic criteria and diagnostic approach

The diagnostic criteria described by Dr. Kawasaki have been used, with some modification, since the original description of the disease [5] (Tab. 1). Children with four or more principal criteria and at least 4 days of fever can be diagnosed on day 4. If fewer than four principal criteria are observed, KD may be diagnosed with the appearance of coronary artery abnormalities (CAA). With increasing experience, it became apparent that a significant minority of infants and children were not identified by the classic diagnostic criteria. This was especially true for infants <6 months of age who often presented with less than the required criteria in what became known as “atypical” or more properly “incomplete” KD. The most recent guidelines have included an algorithm for the evaluation of suspected incomplete KD that incorporates refined clinical assessment, laboratory tests and echocardiographic results into the diagnostic equation [5] (Fig. 1).

Epidemiology

While reports of the occurrence of KD have come from every continent (not including Antarctica), most epidemiological data comes from Japan and the United States and Canada with increasing reports coming from Taiwan, China and Korea in recent years (Tab. 2).

Japan

Since 1970, a total of 17 retrospective incidence surveys have been conducted in Japan (i.e., every 2 years) under the auspices of the Ministry of

Table 1. Clinical and laboratory features of Kawasaki disease

Epidemiological case definition (classic clinical criteria)*

- Fever persisting at least 5 days
- Presence of at least 4 principal features:†
 - Changes in extremities
 - Acute: Erythema of palms, soles; edema of hands, feet
 - Subacute: Periungual peeling of fingers, toes in weeks 2 and 3
 - Polymorphous exanthem
 - Bilateral bulbar conjunctival injection without exudates
 - Changes in lips and oral cavity: Erythema, lips cracking, strawberry tongue, diffuse injection of oral and pharyngeal mucosae
 - Cervical lymphadenopathy (>1.5 cm diameter), usually unilateral
- Exclusion of other diseases with similar findings

* Patients with fever at least 5 days and <4 principal criteria can be diagnosed with Kawasaki disease (KD) when coronary artery abnormalities detected by 2-D echocardiography or angiography are present.

† In presence of ≥ 4 principal criteria, KD diagnosis can be made on day 4 of illness. Experienced clinicians who have treated many KD patients may establish diagnosis before day 4.

Table 2. Global distribution of KD beyond Japan and North America

Europe	England	Asia	China
	Ireland		Beijing
	Sweden		Taiwan
	Finland		Shanghai
	Germany		Hong Kong
	France		Korea
	Portugal		Thailand
	Italy		India
			Iran
			Oman
Africa	Nigeria	South America	Argentina
	South Africa		Brazil
	Egypt		Chile
	Senegal		
	Tunisia	Oceania	Australia
	Sudan		New Zealand

Health, Labor and Welfare. Questionnaires were sent to hospitals with pediatric departments and a bed capacity of at least 100, or hospitals with a bed capacity of less than 100 beds but specializing in pediatrics. The survey questions were created by the Japan Kawasaki Disease Research Committee. Response to the surveys has been about 70% [6]. The last reported surveys included the years 1999–2002 [6]. Since the inception of the epidemiological study 186 069 KD patients have been reported.

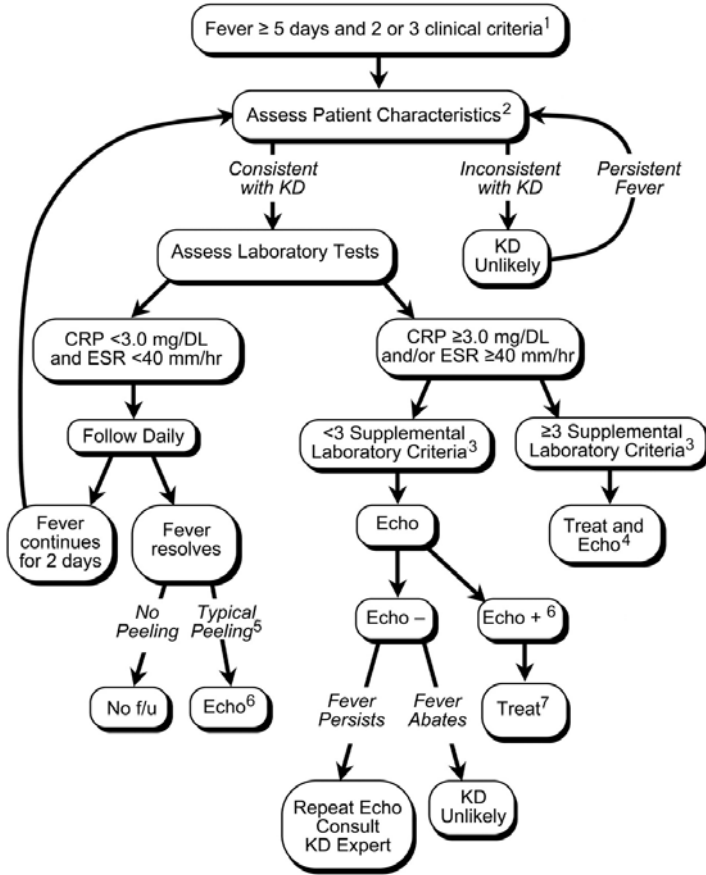


Figure 1. Evaluation of suspected incomplete Kawasaki disease (KD). In the absence of gold standard for diagnosis, this algorithm cannot be evidence-based, but rather represents the informed opinion of the expert committee. Consultation with an expert should be sought anytime assistance is needed. (1) Infants ≤ 6 months old on day ≥ 7 of fever without other explanation should undergo laboratory testing and, if evidence of systemic inflammation is found, an echocardiogram, even if the infants have no clinical criteria. (2) Patient characteristics suggesting KD are listed in Table 1. Characteristics suggesting diseases other than KD include exudative conjunctivitis, exudative pharyngitis, discrete intraoral lesions, bullous or vesicular rash, or generalized adenopathy. Consider alternative diagnoses. (3) Supplemental laboratory criteria include albumin ≤ 3.0 g/100 ml, anemia for age, elevation of alanine aminotransferase, platelets after 7 days $\geq 450\,000/\text{mm}^3$, white blood cell count $\geq 15\,000/\text{mm}^3$, and urine ≥ 10 white blood cells/high-power field. (4) Can treat before performing echocardiogram. (5) Typical peeling begins under nail bed of fingers and then toes. (6) Echocardiogram is considered positive for purposes of this algorithm if any of three conditions are met: z score of LAD or RCA ≥ 2.5 , coronary arteries meet Japanese Ministry of Health criteria for aneurysms, or ≥ 3 other suggestive features exist, including perivascular brightness, lack of tapering, decreased LV function, mitral regurgitation, pericardial effusion, or z scores in LAD or RCA of 2–2.5. (7) If the echocardiogram is positive, treatment should be given to children within 10 d of fever onset and those beyond day 10 with clinical and laboratory signs (CRP, ESR) of ongoing inflammation. Taken from [5]. Copyright © 2004 American Heart Association.

During the most recent study period, 32 266 patients were reported with an annual incidence of 137.7 per 100 000 children <5 years old in 1999 and 151.2 per 100 000 in 2002. The male to female ratio was 1.30 [6]. The annual incidence of KD in Japan has increased progressively from 1987 to 2002 from 73.8 to 151.2 per 100 000 <5 years of age [6–10].

Over the 32-year period of surveillance, three nationwide epidemics of KD have been observed, in 1979, 1982 and 1986 [11]. The incidence rate in the last epidemic in 1986 was 176.8 per 100 000 children <5 years of age. No national epidemic outbreaks have been reported since 1987 but regional outbreaks continue to occur.

United States

Surveillance of KD in the United States is through passive reporting of cases to the Centers for Disease Control and Prevention, where a database has been maintained since 1984. Unfortunately, only a fraction of cases are identified through this system. More robust estimates of the incidence of KD has come from reports from regional investigators [12–14], surveys conducted by specialty societies and more recently through the use of administrative databases [15] of childhood hospitalizations.

Taubert [16] conducted surveys of 440 general hospitals with at least 400 beds that included a pediatric section and of 63 children's hospitals. The survey periods covered the years 1984–1987, 1988–1990 and 1991–1993. During the latter period only the children's hospitals were surveyed. The surveys yielded rates of 7.6 cases per 100 000 children <5 years of age and 9.2 cases per 100 000 for the first two periods. Following the third survey, the reported cases throughout the 10-year period were totaled and a minimum estimate of the annual rate for the period was calculated which was 8.9 cases per 100 000 children <5 years of age. This rate was similar to rates found previously reported in regional studies [13, 14].

More recently, investigators from the Centers for Disease Control and Prevention utilized data from a large inpatient database to determine incidence rates in the United States. The database was designed to generate robust national estimates of pediatric hospitalizations [15]. The rates were determined for the years 1997 and 2000, which were 17.6 per 100 000 <5 years of age and 17.1 per 100 000 <5 years, respectively. These rates were comparable to those determined from the regional studies using State health or health maintenance organization data [18–20]. Based on data from this study and others published previously during the decade, the authors concluded that incidence rate for KD in the United States had been stable.

A national epidemic of KD involving ten regions in the United States occurred between August 1984 and January 1985 [21]. Several other regional outbreaks have been reported over the years as well [16]. Similar incidence rates were reported from Canada based on a national health statistic data-

base. From 1990–1991 to 1995–1996 the mean rates for children <5 years across Canada were 13.8 per 100 000 children [22].

Global distribution

KD has been reported from every continent and several island groups across the globe (Tab. 2). While the incidence rates in Japan remain the highest in the world, several other Asian nations have posted high rates as well. Several reports from China (Beijing [23], Hong Kong [24], Shanghai [25]), Taiwan [26] and Korea [27] documented rates intermediate between those of Japan and North America (Tab. 3). All but Taiwan appeared to have increasing rates over the study periods.

Case reports or case series have been reported from many countries in Europe, Oceania, Africa and South Africa as well as other Asian countries (Tab. 2). Of those countries reporting incidence rates, only those from Ireland are comparable to those in North America [28].

To summarize the global experience with KD, the highest incidence rates are found in Japan followed by Korea, China, North America and Europe. Local or regional outbreaks have been documented in both Japan and the United States, and national epidemics have been observed in both countries as well as Finland [29]. Incidence rates have trended upward in several countries and have remained stable in others. The effect of ascertainment bias on apparent increases in incidence is not known.

Race

As suggest by higher incidence rates in Asian countries, KD occurs in higher frequency in Asian populations. Numerous studies from the Unites States have shown KD to be over-represented among Asian children [12, 14–16, 18, 19]. An interesting study of the epidemiology of KD in Hawaii dramatically demonstrated this predominance [30]. A retrospective analysis of the State Inpatient Database for Hawaii was performed for KD patients hospitalized during 1996 through 2001. Race classification provided by Census 2000 indicated race listed alone or in combination with other races. This race-specific numerators and denominators could be determined. The average annual incidence for KD was 45.2 per 100 000 children <5 years of age, highest in the United States. Japanese-American children <5 years had the highest incidence (197.7 per 100 000) followed by Native Hawaiian (99.1), Chinese (81.3) and Filipino (64.8). Caucasian children <5 years old had a rate of 35.3 per 100 000 children. These findings suggest there may be true differences in incidence of KD among Asian populations. Since the populations in Hawaii came from relatively similar social and physical environments and have similar access to healthcare and diagnostic practices,

Table 3. Incidence rate of KD in different areas

Location	Surveillance period	Incidence rate	
		Overall	Range
Beijing [23]	1995–1999	22.9	18.2–30.6
Taiwan [26]	1996–2002	66.0	59.0–76.0
Hong Kong [24]	1997–2000	39.0	–
Shanghai [25]	1998–2002	–	16.8–36.8
Korea [27]	2000–2002	86.4	73.7–95.5

the socioeconomic and environmental factors would not introduce bias to the ascertainment. Incidence rates among racial groups in the United States (2000) were Caucasian (non-Hispanic) 11.4 per 100 000 children <5 years, African American (non-Hispanic) 19.7 per 100 000 children, Hispanic 13.6 per 100 000 and Asian/Pacific Islander 39.0 per 100 000 [15]. In a separate study of American Indian/native Alaskan children the rate was 4.2 per 100 000 [31].

Age and gender

Most series from diverse geographic and racial populations have shown approximately 85% of children with KD are <5 years of age [2]. Thus, incidences are expressed generally as a proportion of children <5 years old. The most recent population-based study in the United States indicated 76% and 77% of patients were <5 years of age in 1997 and 2000. The median age of KD patients in the United States is 2 years. In Japan, the peak age is 9–11 months and 88.9% of KD patients were <5 years of age [6].

KD is relatively uncommon in children <6 months old and above 5 years of age [6, 15, 17–19]. Studies have suggested that CAA are more common in these two age groups possibly because the illness is less typical and thus diagnosis is delayed [6, 32–36]. While KD is overwhelmingly a disease of children, rare cases have been reported in adults [37].

KD occurs in males more frequently than females [5–16]. Males are at greater risk of developing CAA as well [33]. In the United States the male:female ratio is 1.5:1 while in Japan it is 1.3:1.

Seasonality and temporal-geographic clustering of KD

In the United States, KD hospitalizations are more frequent in the winter months [16, 38]. The seasonality in Hawaii is less obvious, although fewer cases were seen during April through June [30]. In a 5-year period of active

surveillance in San Diego County, California, KD incidence was inversely associated with average monthly temperature and positively associated with average monthly precipitation [39].

In Japan, excluding epidemic years, there appears to be a bimodal seasonal occurrence with peaks in January and early summer and a nadir in October [6, 40]. In China and Korea seasonal peaks appear to be more frequent in spring and summer [23, 26, 29].

Temporal-geographic clustering has been frequently observed in both the United States [15, 32, 38, 41] and Japan [6, 40]. The Japanese experience has been especially well described with “hot spots” occurring in various prefectures on a rotating basis [6, 40].

Familial cases

There appears to be an observable enhanced risk of KD within certain families. In Japan, there is a tenfold increased risk of the illness in siblings of an index case [42, 43]. Parents of children with KD are twice as likely to have had the disease as compared to the general population [42]. In families where parents had KD, sibling cases among children are significantly more common [44]. Similar findings have been reported from the United States [45].

Recurrence of KD

Recurrent cases of KD have been reported in both the United States and Japan [42, 46]. The estimated rate of recurrence in Japan is 3%, while that in the United States is <1 to slightly over 1% [46, 47].

Socioeconomic factors

KD patients in the United States come from families with a higher median household income and are more likely to have private insurance [15, 39]. An analysis of hospitalization costs for KD in the United States for children <5 years of age showed that the median cost was \$6189 [48]. The average annual total estimated cost associated with hospitalization for KD patients <18 years of age was \$38.6 million [48].

Other risk factors

Several other risk factors for KD have been reported in the past. An ante-

cedent respiratory illness has been a significant association with KD patients as compared to controls in outbreak situations in the United States [32].

Shampooing or spot-cleaning carpets within 30–45 days of onset of KD has been a risk factor in some studies but not others [49, 50]. Other factors associated with KD include use of a humidifier [49], living near a body of water [38] and having preexisting eczema [51].

Synthesis of epidemiological data

KD is an acute self-limited illness of children that is characterized epidemiologically by seasonality and occurring in geographic clusters. It shares many clinical characteristics with known infectious diseases such as scarlet fever, toxic shock syndrome, measles and adenovirus infections. It has been associated with antecedent viral-like illnesses in some epidemic situations. All of these factors suggest an infectious etiological agent or agents as a cause. The relative rarity in the first 3 months of life (possibly due to maternal antibody) and peak occurrence early in childhood is another characteristic shared by many common childhood infections.

Host factors also appear to be important in the disease. Susceptibility to the disease is clearly influenced by ethnicity, familial risk factors and possibly preexisting conditions such as atopy. A genetic predisposition is suggested by these factors.

Finally, environmental influences cannot be ruled out as suggested by apparently recent emergence of the disease in the last half of the 20th century, a socioeconomic bias toward more affluent lifestyle, possibly climatic associations and less well established associations such as rug cleaning.

The exposure of a predisposed host to an infectious pathogen or pathogens with possible environmental contributing factors is a reasonable model to propose for KD.

Pathology

Pathologically KD is a vasculitis of medium-sized vessels [52]. Studies from Japan have described four stages of pathology in the heart [53] (Tab. 4). The classification was based on the careful evaluation of 20 hearts taken from patients who had died of KD. Stages were based on the duration of illness at the time of death. The pathological description is considered unique and is distinguished from other vasculitis in the “medium-sized vasculitis” group, polyarteritis nodosa, in that the arterial inflammation does not affect vessels smaller than arteries [52]. Prior to the introduction and the availability of intravenous immunoglobulin (IVIG) for treatment of KD, 20–25% of children developed coronary artery aneurysms as a sequela [2].

Table 4. Pathology of the heart in KD [52]

Stage I (0–9 days):	<p>Acute perivasculitis and vasculitis of microvessels (arterioles, capillaries and vessels) and small arteries</p> <p>Acute perivasculitis and end-arteritis of the three major coronary arteries (MCAs)</p> <p>Pericarditis myocarditis</p> <p>Inflammation of the atrioventricular conductor system</p> <p>Endocarditis with valvulitis</p>
Stage II (12–25 days):	<p>Panvasculitis of the MCAs and aneurysm with thrombus in the stems</p> <p>Myocarditis, coagulation necrosis, lesions of the conduction system</p> <p>Pericarditis</p> <p>Endocarditis with valvulitis</p>
Stage III (28–31 days):	<p>Disappearance of inflammation in the microvessels</p> <p>Granulation of the MCAs</p> <p>Myointimal proliferation in the coronary and other medium-sized arteries</p>
Stage IV (40 days to 4 years):	<p>Scarring with severe stenosis in the MCAs</p> <p>Fibrosis of the myocardium</p> <p>Coagulation necrosis</p> <p>Lesions of the conduction system</p> <p>Endocardial fibroelastosis</p>

Pathogenesis

The vasculitis of KD is clearly immunologically mediated and a wide variety of immunoregulatory abnormalities have been documented during the acute phase [54]. In a study of 21 children in the acute phase of KD, Leung and colleagues [54, 55] demonstrated a significant reduction in circulatory T8-positive (T8⁺) suppressor-cytotoxic T cells, increased activated T4⁺ helper cells and a proliferation of circulating activated B cells spontaneously secreting IgG and IgM. Furukawa et al. [56], in Japan, demonstrated activation of CD23⁺ monocytes/macrophages in the peripheral blood of patients with acute KD.

Immunopotent cellular activation is associated with a broad array of proinflammatory cytokines including TNF- α [57, 58], IL-1 [59], IFN- γ [60] and IL-6 [61]. These mediators undoubtedly contribute to the high fever, discomfort and inflammatory changes during the acute phase but also facilitate the vascular injury.

Vascular endothelial cells become activated by cytokine stimulation and may induce or increase expression of endothelial cell surface antigens that promote functional changes such as leukocyte adhesion and antigen presentation. These changes may make endothelial cells more vulnerable to attack by cytotoxic IgM antibodies present in acute phase serum of KD [62]. Further evidence of immunological injury to coronary arteries derives from immunohistochemical studies demonstrating transmural infiltration of artery walls with CD45RO T lymphocytes (activated/memory T cells) with CD8 lymphocytes predominating over CD4 T cells [63]. Remarkably, T cell activation, cytokine excretion and other immunological perturbations are reversed by IVIG [64].

Numerous other immunoregulatory abnormalities have been observed during KD or have been suggested as possible contributors to the pathogenesis of the disease. Macrophage activation syndrome has been observed with KD [65]. CD25⁺ CD4⁺ regulatory T cells, which maintain immunological self tolerance and control immune responses to microbial invasion, have been shown to be reduced in acute KD patients more than normal controls, suggesting this might play a role in the disease [66].

Wang et al. [67] proposed that CD40 ligand (CD40L) might play a role in the pathogenesis of KD because they found CD40L expression on CD4⁺ T lymphocytes in patients with the acute disease. CD40L is a potent activator of the immune system and might enhance endothelial cell inflammation and vascular damage [67].

Several recent reports implicate vascular endothelial growth factor (VEGF) in the pathological findings associated with KD. VEGF is the primary growth factor for formation of blood vessels and is a vascular permeability factor. It may also be a driver of inflammation as it enhances monocyte chemotaxis in humans and increased the production of B cells in mice [68]. Several reports have documented significantly elevated levels of VEGF in the acute and subacute phases of KD [69–71]. VEGF induces expression of matrix metalloproteinases (MMP), which degrade extracellular matrix and basement membrane proteins such as collagen and elastin [68]. Gavin et al. [72] demonstrated MMP-2 and MMP-9 in the damaged arterial walls of children who died of KD. The same group subsequently demonstrated angiogenesis in acute KD aneurysms much earlier than previously reported, probably related to several angiogenesis factors including VEGF.

Thus, through such highly complex and intricate interactions of immunopotent cells, cytokines and other mediators, the inflammatory process results in vascular damage in KD.

Genetic influence of the pathogenesis of KD

Racial differences in incidence, families with multiple cases, and the apparent greater tendency for CAA to occur in some children but not in others

Table 5. Gene polymorphisms and single nucleotide polymorphisms (SNPs) in KD

Polymorphism or SNP	Susceptibility or risk factor	Reference
HLA Bw22J	Associated with KD in Japanese children	74, 75
HLABw51	Associated with KD in United States and Israel population	76, 77
HLABw44	Associated with KD during Boston epidemic	78
IFN- γ gene	Over production of TNF- α	79
Monocyte chemoattractant protein 1 gene (MCP-1)	Over production of MCP-1	80
TNF- α gene A/A at LT-x + 250	Over production of TNF- α	81
SLC11A1 gene 5 ¹ -promoter (GT) _n	Possible dysregulation of IL-1B or TNF- α	82
Genotype 1/11 fa IL1-Ra	Higher susceptibility of KD	83
Angiotensin converting enzyme genotype ID	Associated with KD	84
Vascular endothelial growth factor (VEGF) CGCC	Associated with KD	85
Angiotensin/converting enzyme genotype I/I	Associated with development of CAA	86
MHC-class-1-chain related gene A (MICA) allele 4A	Protective for development of CAA	87
Methylenetetrahydrofolate reductase (MTHFR) TT genotype	Protective for females and risk factor for males for CAA	88
CD14/-159 TT genotype	Associated with CAA	89
CD40 ligand (CD40L) SNP in intron 4	Associated with CAA in males	90
VEGF G allele	Associated with CAA	91
Matrix metalloproteinase-3 gene 6A/6A genotype	Associated with CAA	92
Fc x RIIa HR and RR alleles	May predict failure of IVIG therapy	93
Mannose-binding lectin (MBL)gene MBL2 genotype	May predict failure of IVIG therapy in < 1 year olds	94

are all observations that suggest there may be a genetic influence in the pathogenesis of KD. Many investigators are attempting to identify genetic factors that predispose to acquiring KD or its complications.

Many single-nucleotide polymorphisms (SNPs) have been identified that seem to be associated with susceptibility to KD or a risk factor for developing CAA. Table 5 lists 21 studies that identify polymorphisms or SNPs possibly associated with these or other risks.

Table 6. Proposed etiological agents of KD

Infections	Human herpes virus 6 & 8
	Epstein-Barr virus
	Human parvovirus B-19
	Retrovirus
	Adenovirus
	TT virus
	<i>Propionibacterium acnes</i>
	<i>Streptococcus mitis</i>
	Leptospira
	<i>Erlichia</i> species
	<i>Staphylococcus aureus</i> (TSST-1 positive)
	<i>Chlamydia pneumoniae</i>

The numerous known or candidate SNPs identified on multiple separate gene locations suggest that the genetic influence on pathogenesis, like the inflammatory process itself is highly complex [68]. New genetic markers will undoubtedly be identified in the future.

Etiology

After almost 40 years of investigation following description of KD, we know a great deal about the epidemiology, pathology, pathogenesis of the disease and there is a fairly effective, although less than elegant, therapy available in the form of IVIG. The etiology of KD, however, remains an enigma.

As discussed previously, clinical and epidemiological factors favor an infectious etiology, but, as yet, a single microbial pathogen has not been consistently associated with the disease. A very abridged list of microbial and environmental agents that have been proposed as causes for KD is found in Table 6.

The two most heavily investigated areas in the last 10–15 years have been a bacterial toxin-mediated cause *versus* a viral pathogen etiology.

Superantigen-mediated etiology

The possibility of a superantigen (SA) being implicated in the cause of KD was prompted by the observation that the illness is associated with marked activation of T lymphocytes and monocytes/macrophages. The differences between SA and conventional antigen are compared in Table 7. Early studies showed significantly elevated levels of V β 2⁺ and V β 8.1⁺ T cells in patients with KD [95, 96]. Subsequently, Leung et al. [97] published a case

Table 7. Comparison of the Effect of Conventional and Superantigens

Conventional antigen	Superantigen
Processed by antigen presenting all (APC). Presented as a peptide on the APC surface in association with MHC II molecule.	Directly bind to class II MHC molecules on the APC and TCR.
Interacts with the variable (V), joining (J) and diversity (D) portions of the α and β chains of the T cell receptor (TCR).	Binding restricted to the specificity of the variable regions of the β chain (V β) of TCR.
Recognized by the few sensitized T-cells with receptors for the antigen resulting in a limited more specific immune response.	Activates a specific set of V β families resulting in activation of a large portion of T-cells causing a much more intense immune response.

Adapted from: Curtis et al. [95].

control study on the presence of bacterial colonization with *Staphylococcus aureus* organisms capable of producing toxic shock syndrome toxin (TSST). They found a significant association between colonization with toxin secreting *S. aureus* and the KD patients. Subsequent studies seemed to confirm the association [95, 98, 99]. A prospective multicenter trial assessing KD patients and controls for SA-producing staphylococcal and streptococcal bacteria (TSST-1, staphylococcal enterotoxins B and C, and streptococcal pyrogenic exotoxins A and C) were undertaken. Overall, isolation rates of SA-producing bacteria between KD patients and controls were not different statistically. A subset of patients with organisms expressing superantigens that stimulate V β 2⁺ T cell receptor families of T cells were found significantly more often in the KD group [100]. Other investigations have not confirmed the SA hypothesis, however [101–104]. More recent serological studies suggest a role in the pathogenesis of KD for TSST-1 staphylococcal enterotoxin B and streptococcal pyrogenic exotoxins A and C [105–107].

The role of SA in the etiology of KD remains controversial [108].

Conventional antigen/viral etiology

An alternative hypothesis to the superantigen theory is that KD results from infection with an as yet unidentified viral pathogen. Central to this idea is that the immunological response is oligoclonal in response to a conventional antigen rather than a polyclonal response as seen with a challenge by SA. A series of studies have compiled evidence to support this proposition.

An unexpected observation from an immunohistochemical study of coronary arteries taken from infants and young children who had died in the acute phase of KD initiated this line of investigation. [109, 110]. IgA-secreting plasma cells were found infiltrating the vascular wall, pancreatic ducts

and kidneys of 100% of KD patients compared to none of the age-matched control patients. This observation was intriguing in view of the relative immaturity of the systemic IgA response in infancy as compared to a fully developed and more robust secretory IgA response at this age. A polyclonal response to an SA might engender infant B cells to respond with a predominantly IgM reaction. A viral or other microbe presented to a mucosal site in a similar patient might stimulate vigorous IgA response [111]. Also observed was a heavy infiltration of IgA-secreting plasma cells in the upper respiratory tract of KD patients as compared to controls [112].

Subsequently, the same investigators demonstrated that the vascular IgA response was oligoclonal in nature and, therefore, probably resulted from stimulation by a conventional antigen, not a superantigen [112]. As a next step, the group developed synthetic antibody from prevalent IgA gene sequences found in acute-phase KD arterial tissue. They then exposed the tissues to the antibody and detected antigen in the respiratory epithelium of proximal bronchi from lungs and in subsets of invading macrophages from the myocardium of other inflamed tissues. The strength of the antigen signal paralleled the concentration of IgA plasma cell infiltration. These findings were not present in tissue from non-KD control patients [113]. Spheroid bodies were seen in the region between the nucleus and apical surface of ciliated epithelium of the proximal bronchi. Similar bodies were seen in the splenic and lymph node tissues. Evaluation of these tissues was undertaken using light microscopy (LM) and transmitting electron microscopy (TEM) focusing on areas containing the spheroid bodies [114]. LM revealed round-to-oval intracytoplasmic perinuclear inclusion bodies in medium-sized bronchi. They stained with both eosin and hematoxylin, suggesting they contained both protein and nucleic acid. TEM showed regular electron-dense inclusion bodies in the perinuclear region of ciliated bronchial epithelial cells resembling aggregates of viral proteins and nucleic acids that are found in respiratory tissues during infection with RNA viruses [114].

A recent report of association between newly described human coronavirus [115, 116] and KD raised hope that the etiology of KD had finally been identified [117]. Unfortunately, a series of reports from Japan and Taiwan and the United States found no consistent association between the new RNA respiratory virus and KD [118–121].

Thus, the search for the etiology of KD continues. Hopefully, with the application of histochemical and molecular techniques described above, the cause will soon be identified, possibly among the many new viral agents being identified at an increasing rate [122, 123].

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