REVIEW ARTICLE

Role of Infectious Agents in the Etiology of Kawasaki Disease

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Abstract

Kawasaki disease (KD) is a multisystemic childhood vasculitis that predominantly affects the coronary arteries. The constellation of clinical features in KD, such as, acute onset of fever, redness of lips and oral mucosa, rash, swelling over palms and feet, cervical adenopathy, and perineal peeling followed by periungual peeling suggests an infection or toxin-mediated etiology. Occurrence of cases in clusters and epidemics also support an infectious etiology for KD. Many infectious agents—bacteria, fungi, and viruses—are reported to be associated with KD. This review article gives a comprehensive overview of available literature that supports an infective etiology for KD.

Keywords: Infections, Kawasaki disease, RNA virus, Superantigen, Wind hypothesis.

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Introduction

Kawasaki disease (KD) is a childhood systemic vasculitic illness that has predilection to involve coronary arteries. Unlike other vasculitis syndromes, KD is seen predominantly in the first few years of life. Globally, incidence of KD is on an increasing trend, and in many parts of the world, it has already overtaken IgA vasculitis to become the commonest pediatric vasculitis. Despite being a vasculitis, the standard treatment is intravenous immunoglobulin (IVIg). KD often presents with distinct set of clinical features, such as, fever, conjunctival injection, lip cracking, strawberry tongue, unilateral cervical lymphadenopathy, polymorphous skin rash, and edema of hands and feet followed by periungual skin peeling. The exact etiology of KD still remains an enigma. In simplest terms, KD can be said to be triggered by environmental stimuli, especially infections, in genetically predisposed individuals.[1] In this short review, we aim to summarize the infections implicated in the pathogenesis of KD.

Infectious Trigger in KD?

The profile of KD strongly suggests an infectious trigger. KD is seen predominantly in children <5 years of age, which typically is the age profile of viral infections in childhood. It is relatively uncommon in infants <6 months of age suggesting protection afforded by maternally transferred antibodies. Seasonal clustering especially in winter and spring resembles the clustering of cases seen in respiratory tract infections. Epidemics of KD have occurred in the past just like epidemics of infectious illnesses. Presence of fever and rash resembles viral exanthems. However, the lack of multiple cases in a household or day care setting suggests a strong genetic predisposition to develop the illness. Siblings have a 10-fold higher risk of developing KD, especially in close temporal proximity to each other, which together reflects the possibility of an infectious trigger and genetic susceptibility. Although, KD has been reported in many monozygotic twin pairs, not all monozygotic twins develop KD. The recurrence rate of KD in <1% of affected individuals is also odd for an infectious trigger.

Viruses and KD

A Specific Novel RNA Virus Causing KD?

Studies to discover a specific virus as a cause of KD have been pioneered by Anne H. Rowley and Stanford T. Shulman. In a series of studies,[1–9] they identified oligoclonal IgA secreting plasma cells in coronary arteries of patients with KD in addition to CD8 T cell response. Subsequently, they went on to identify inclusion bodies, virus like particles, and RNA in respiratory epithelium of children with KD. They also showed an upregulated type I interferon signature in coronary arteries of patients with KD. It was hypothesized that a ubiquitous RNA virus infects the respiratory epithelium causing asymptomatic infection or KD. The virus then affects the coronary arteries by hematogenous spread. Initial infection confers life-long immunity, explaining the low recurrence rate in KD.[10] These studies were conducted primarily in a limited number of postmortem patients. Therefore, a thorough validation is definitely required before it can be convincingly said that KD is caused by the virus suggested by Rowley and Shulman.

Other Viruses and KD

A number of other viruses have been implicated in the pathogenesis of KD. Kawasaki disease - like syndrome (KLS) has been reported in many adults with HIV infection that responds to IVIg. Just like KD shock syndrome, KLS shock syndrome has also been reported with clinical features of hypotension and cardiac dysfunction.[11,12] However, not all KLS patients have had evidence of HIV infection. In adults with KLS and HIV, one-fourths have experienced a recurrence as compared to 4% HIV negative adults with KLS.[13] This suggests HIV is a trigger in genetically predisposed adults rather than a causal agent for KLS.

Reports of viral infections in relation to KD can best be described as triggers if not coincidental and certainly far from being causal.

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Recently, a novel torque teno virus 7 was identified in 2 out of 11 KD patients but in none of the 22 controls.[14] Human bocavirus DNA was detected in serum and nasopharyngeal specimens of less than one-third of 32 French children with KD.[15] The list of viral infections associated with KD is huge and notably includes human parvovirus B19,[16] dengue,[17] chickenpox,[18,19] coxsackie A4,[20] Epstein-Barr virus,[21–24] and others. Even infections that may mimic KD have been reported in conjunction with KD which includes influenza H1N1 pdm09 virus[25] and measles.[26] More than 40% patients with KD have been reported to have a positive respiratory viral PCR that includes adenovirus, a close mimic of KD.[27] To summarize, a positive viral test should not be used to exclude KD and it seems attractive to conclude that any virus might tip off predisposed children to develop KD. However, these associations need to be analyzed in thorough detail to make suitable conclusions about causality, which is difficult in the absence of a gold standard diagnostic test for KD.

KD: A Superantigen-mediated Disease?

Streptococcal and Staphylococcal Superantigens and KD

Investigating the role of staphylococcal and streptococcal superantigens in pathogenesis of KD is based on its clinical resemblance with these superantigen-mediated disorders. These analyses have been carried out primarily at three different levels: superantigen gene detection, antibodies directed against superantigens, and studies of Vβ repertoire of T cells. In a study on Japanese children with KD, streptococcal pyrogenic exotoxin (SPE) G (SPE-G) gene was found in stool in more than 40% as compared to less than 20% in healthy and febrile controls and was the only 1 of 5 superantigens found at statistically higher levels in KD patients as compared to each control group.[28] In other study on Japanese children, KD patients had higher levels of antibodies against multiple superantigens at each week of illness as compared to healthy controls.[29] In another Japanese study, polyclonal expansion of Vβ2 and Vβ6.5 T cells was noted in children with acute KD as compared to controls and SPE-C was implicated in the pathogenesis of KD.[30] Studies conducted in Japan and elsewhere have demonstrated similar results.[31–34] In addition, studies aimed at culturing superantigen producing streptococci and staphylococci at various anatomical sites in KD patients as compared to controls have demonstrated increased colonization of toxic shock syndrome toxin-1 or SPE-B/SPE-C producing strains.[35,36] Based on these studies, implicating a specific superantigen as a cause for KD is not possible; however, the complex interplay between various superantigens may have a role to play. On the contrary, profound immune activation due to any cause may trigger poly or oligoclonal T cell expansion and antibody production, and hence, the above-mentioned findings may just represent a para-phenomenon.

Other Superantigens and KD

Superantigens of *Yersinia pseudotuberculosis* (YPT) have also been implicated in the etiopathogenesis of Kawasaki disease. Association between the two entities was noted as early as 1983.[37,38] Kawasaki disease and YPT have been noted to have similar epidemiological findings,[39] and outbreaks of KD in Japan[39] and Finland[40,41] have corresponded with YPT outbreaks. Patients with KD and positive YPT/YPT - derived mitogen (YPM) antibody or positive stool culture have demonstrated higher risk of cardiac sequelae including coronary artery lesions as compared to YPT negative KD patients.[42,43] In fact, YPT strains in Japan and Korea have been shown to express a novel superantigen YPM and result in a KD-like illness whereas the European strains express high pathogenicity island (HPI) virulence factor predominantly rather than YPM resulting in fever and gastrointestinal involvement.[44] This might help to explain the high prevalence of KD in Japan and Korea. Not only YPT but also *Y. enterocolitica* has been reported to result in KD-like illness.[45,46] However, the SAg of YPT results oligoclonal expansion of Vβ3, Vβ9, Vβ13.1, or Vβ13.2 human T cells and Vβ7 or Vβ8 murine T cells[47–50] in contrast to Vβ2, Vβ6.5, or Vβ8 T cell expansion in human KD patients.[30–34]

Other Bacteria and KD

Other bacteria like mycoplasma and mycobacteria have also been associated with KD. In addition to case reports,[51,52] at least three studies noted a significant percentage of KD patients to have concomitant mycoplasma infection. These children with mycoplasma infection and KD were older than other KD patients. In a South Korean study, 15% KD patients had pneumonia out of which anti-Mycoplasma pneumonia antibody titers were elevated in about one-fourth.[53] In a Chinese cohort, antibody and PCR positive infection was seen in about 15% of KD cases.[54] In another South Korean study, 10% KD patients had serological evidence of mycoplasma infection, and in about one-fifth of these patients, fever persisted despite initial IVIg therapy and improved only after macrolide antibiotics.[55] In fact, a randomized control trial conducted in Japan demonstrated more than twofold lower relapse rate of fever in children treated with clarithromycin plus IVIg as compared to IVIg alone.[56] Surprisingly, when multiplex nasopharyngeal swab PCR was performed, none of the children in this study were positive for *Mycoplasma pneumoniae*, *Chlamydia pneumonia*, *Legionella pneumophila*, or *Bordetella pertussis*, pathogens that typically respond to macrolides. However, *Streptococcus pneumonia* and *Hemophilus influenzae* were positive in more than three-fourths and more than half, respectively. The mechanism of association of *M. pneumoniae* with KD is largely unknown, but it may also be mediated *via* superantigens as one of the mycoplasma species, namely, *M. arthritidis* is well-known to produce a superantigen.[57]

Interest in the role of mycobacteria in KD derives from the fact that BCG site reaction is a characteristic manifestation of KD; however, it has also been reported in association with measles and human herpes virus 6 infections.[58,59] The proposed mechanism is both a humoral and cellular immune response against mycobacterial heat shock protein 65 in having molecular mimicry with human antigens.[60,61] The association appears to be more of an epiphenomenon rather than causal but needs a more robust reevaluation.

Gastrointestinal Tract Microbiome and Immune Response in KD

In a study by Yamashiro et al., jejunal swab specimens in 15 children with KD demonstrated presence of *Streptococcus* spp.: *mitis*, *salivarius*, *oralis*, *sanguis*; *Gemella haemolysans*; *Staphylococcus* spp.: *capitis*, *hyicus*; Veillonella and *Bacteroides* spp. that were not detected in 11 controls (food sensitive enteropathy children in remission). In contrast, *Leuconostoc cremoris*, *Bifidobacterium* spp., and *Lactobacillus* spp. were seen in controls and in none of the KD patients.[62] Subsequently, the same group[63] demonstrated similar microbiological profile in a separate cohort of 19 KD

patients and demonstrated significant proliferation of autologous peripheral blood mononuclear cells (PBMCs) when co-cultured with supernatants of bacterial cultures (reflective of positive screening test for heat shock proteins) in all KD patients and in none of the controls. In addition, they also detected seropositivity for bacterial hsp60 in 11 patients and sequence homology between bacterial and human self-hsp 60. Therefore, molecular mimicry could be another etiopathogenic mechanism underlying KD. These culture supernatants also resulted in expansion of Vβ2 repertoire of cultured T cells in almost all KD patients (reflective of positive screening test for superantigens) as compared to none of the controls. The same group had previously demonstrated significant increase in Vβ2+ T cells in jejunal mucosa[34] and increased HLA-DR+CD4+ cells in lamina propria with decreased CD8+ in lamina propria and epithelium[64] in acute stage of KD. In another study, proportion of KD patients positive for Lactobacillus in stool specimens was 7–8folds lower than healthy and diseased controls.[65] The role lactobacilli play in KD needs to be studied; however, many studies have demonstrated anti-inflammatory and anti-infective effects of Lactobacilli spp. *in vitro*, *in vivo*, and *ex vivo*; few of them have been quoted.[66–72] Evaluation of gut microbiota based on genomic methods, rather than traditional culture methods, also has revealed high abundance of *Streptococcus* spp.: *mitis*, *sanguinis*, *gordonii*, *oralis*, *pneumoniae*, and *pseudopneumoniae* in acute KD.[73]

Tropospheric Winds and KD

Intensive search for etiology of KD has not spared the atmospheric air currents! An intriguing association between wind pattern and incidence of KD was first described by Rodó et al. in the year 2011. It was noted that the large KD epidemics in Japan in late 1970s and 1980s coincided with north-westerly winds blowing from Asia toward Japan. Also the seasonal variation in the incidence of KD could be explained by the wind pattern with increase in incidence corresponding to strong north-westerly winds blowing across Japan. Similar association with the wind pattern was observed for KD incidence in San Diego and Hawaii.[74] Metagenomic analysis of the tropospheric microbiota revealed that *Candida* spp. was the dominant fungus amongst the tropospheric aerosols. Also, an incubation period of 6–48 hours was estimated for KD, favoring antigenic or toxic exposure as the trigger.[75] On further analysis, association of annual dust cycles and KD outbreaks have suggested that dust particles may help transport *Candida* spp. and shield it from the deleterious effect of ultraviolet radiation in the atmosphere.[76] Similar association between tropospheric winds and KD incidence has been reported in Central Chile.[77] KD would be the first human disease to occur by natural transport of a pathogen across large distances, as large as across the Pacific Ocean, if these associations turn out to be causal.[78] However, it needs to be noted that transport of *Aspergillus sydowii* by dust particles across the Atlantic Ocean has been implicated in sea fan disease of corals and demise of the Caribbean coral reefs.[79]

Conclusion

From a clinical standpoint, it is important to realize that concomitant infection(s) do not rule out the presence of KD, as infections have been reported amply to trigger KD. In such cases, it is prudent to treat both the infectious trigger and KD.[80] Kawasaki disease may be viewed as a dysregulated immune response triggered by environmental stimuli, including infections, in genetically predisposed individuals.[81]

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