



Does any specific infection cause Kawasaki disease?

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Kawasaki disease (KD) is an acute self-limited vasculitis of unknown etiology that occurs predominantly in infants and children. The etiology of this disease remains a major pediatric mystery. Nonetheless, the self-limited clinical findings and generally nonrecurring nature of this febrile illness are highly suggestive of an infection rather than an autoimmune process.¹⁾

Numerous reports confirming viral and bacterial infections associated with KD outbreaks have been reported.²⁾ However, multiple investigations over several decades have demonstrated that no known unique infectious agent is closely related with KD etiology.^{1,3,4)}

Taken together, many epidemiologic and clinical findings best support the hypothesis that KD is caused by a very common but unidentified infectious agent resulting in KD children with an underlying genetic predisposition.

Early studies of isolation of superantigen-producing bacteria or selective expansion of V β family T-cell receptor suggested group A *Streptococcus* or *Staphylococcus aureus* as a powerful cause of KD.^{5,6)} However, several subsequent papers reported no significant difference in superantigens between KD patients and controls.⁷⁾ Thus, the current understanding of the immune response favors the classic antigen that is protective against repeated exposure in most patients.^{1,3)}

The recently published article entitled “High antistreptolysin O (ASO) titer is associated with coronary artery lesions in patients with Kawasaki disease” was interesting.⁸⁾ The authors found that high ASO titers showed higher rates of a severe clinical course or coronary artery lesions (CALs). This is a very interesting results, because it has not been clearly demonstrated that a specific infection causes CALs in KD. However, there appears to be insufficient evidence to determine the acute infection of group A *Streptococcus*. Additionally, specific examinations such as throat culture, rapid antigen test, or other streptococcal antibody tests may be needed to determine the timing of infection. Analyses of whether patients had already known high risk factors or high ASO levels acted as risk factors are also needed since no reports to date have examined whether a high ASO increases the risk in KD patients. But detailed evaluation of group A streptococcal infection is required in future KD patients.

Another interesting topic is that if infectious diseases are identified, intravenous gamma globulin (IVIG) resistance or CALs may increase in KD patients.

According to one report, the simultaneous infection of group A *Streptococcus* in KD patients showed no difference in treatment response or CAL rate.⁵⁾ A single-center retrospective study was performed to determine the effect of coincident infection (including streptococcal infection) at the time of KD diagnosis on treatment response and coronary artery outcomes. As a result, a broad spectrum of infectious agents was found, but infections at the time of KD diagnosis were not statistically significantly associated with IVIG treatment response or coronary artery outcomes compared to those of patients without infections, even after the adjustment for other factors that may influence CALs.²⁾ Based on these results, it is believed that there are no unique infections in KD patients that respond particularly poorly to IVIG treatment or cause CALs.

Recent reports suggested the importance of viral infection in KD-related infectious diseases.

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Failure to respond to antibiotic therapy, a common susceptible age, specific seasonality, and the similar spread pattern of viral illness in patients with KD makes a viral etiology more likely than a bacterial one.^{1,3)}

Moreover, the prevalence of CD8T cells and the upregulation of cytotoxic T cells and interferon pathway genes in the coronary arteries of children who have died of KD are highly suggestive of a viral etiology.³⁾ The molecular analysis of the oligoclonal immunoglobulin A response in acute KD led to the production of synthetic KD antibodies that identify RNA-containing cytoplasmic inclusion bodies in acute KD ciliated bronchial epithelial tissues. Light and electron microscopic observations showed that the inclusion bodies are consistent with aggregates of viral proteins and nucleic acids.⁹⁾ These biochemical and pathological features increase the likelihood of a viral infection as the cause of KD.

In conclusion, although the cause of KD remains to be elucidated, it is believed that infectious diseases are the most likely. Although no solitary causative infectious agents have been discovered to date, studies should continue to determine the etiology of KD. These efforts will bring novel strategies for the treatment and prognosis of KD patients in the near future.

Conflicts of interest

No potential conflicts of interest relevant to this article was reported.

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