Update on association between Kawasaki disease and infection

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Abstract: The relationship between infection and Kawasaki disease (KD) remains unclear. Infection has long been considered a key predisposing factor for KD. Bacterial and viral agents may be related to the onset of KD because of superantigen and cytokine production. Various bacterial and viral infections have been reported to be associated with KD, but the actual mechanism remains unknown. The higher association between KD and enterovirus has been well documented by using Taiwan National Health Insurance Research Database. However, no evidence has been obtained that various bacterial and viral infections induce KD. Comprehensive research, including infectious agents, should be conducted to elucidate the pathogenesis of KD.

Keywords: Enterovirus; Infection; Kawasaki disease

1. INTRODUCTION

Kawasaki disease (KD), first defined in 1967 in Japan, occurs mainly in children aged under 5 years.[1] It is characterized by prolonged fever, nonpurulent conjunctival injection, oral mucosal changes with red lips and strawberry tongue, polymorphous skin rash, cervical lymphadenopathy, and swollen and red hands and feet followed by desquamation in the subacute stage.[1] Coronary artery lesions (CALs) are the most prominent complication of KD and develop in 15% to 25% of untreated cases.[2,3] Treatment with a single high dose of intravenous immunoglobulin (IVIG) is effective in reducing the incidence of CALs to approximately 5%.[2,3] The annual incidence of KD in Taiwan is estimated to be 45.8 to 82.8/100,000 children younger than 5 years old, the third highest in the world after Japan and Korea.[4] The cause of KD is unclear, but may be related to the combined effects of infection, immune response, and genetic susceptibility.[1]

2. ASSOCIATION BETWEEN KD AND BACTERIAL INFECTION

Infection has long been postulated to be the main cause of KD. The evidence of infection in KD includes similar symptoms, marked seasonality, epidemic occurrence, and a peak incidence among children aged 6 months to 2 years with relative immunodeficiency.[5] The superantigens related to infection is considered the most crucial factor involved in the pathogenesis of KD.[6]

Studies have reported that bacterial agents may be related to the onset of KD because of superantigens.[6–9] Bacteria isolated from patients with KD include *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Mycoplasma pneumonia*, which had a possible association with the pathogenesis of KD.[6–10] The similar clinical and immunological presentations of KD, toxic shock syndrome, and streptococcal toxic shock syndrome further support the notion that a common superantigen-mediated immune response is involved in the development of the three diseases.[6] Bacterial superantigens are a group of proteins that can adversely affect immunity by bypassing the mechanisms of conventional major histocompatibility complex-restricted antigen processing.[11] Superantigens can bind the variable region of the β chain (the Vβ region) in T-cell receptors and induce global changes in lymphocyte composition through massive systemic release of cytokines.[11] The excessive release of proinflammatory cytokines may account for the numerous similar clinical and immunological features of KD, toxic shock syndrome, and streptococcal toxic shock syndrome.[11,12]

Evidence supporting the role of superantigens in the development of KD may include a skewed T-cell Vβ repertoire, isolation of superantigen-producing bacteria in patients with KD, and serological evidence obtained in previous case–control studies.[6] The skewed T-cell Vβ repertoire in KD is the strongest evidence of the superantigen theory and has been supported by numerous studies.[13–19] Leung et al.[7] first reported the significantly higher incidence of superantigen-producing bacteria (*S. aureus* and Streptococci) in patients with KD (n = 16) than in controls (n = 15). Their results suggest that the expansion of Vβ+ T cells in patients with KD might be induced by superantigen-producing bacteria.[7] Leung et al.[20] also demonstrated the association of superantigen-producing bacteria with CALs in three patients with KD and suggested that superantigens perform a key role in the pathogenesis of KD. However, subsequent large-scale studies reported no significant differences between patients with KD and controls in terms of the isolation rates of superantigen-producing bacteria.[21–23] Although the incidence of superantigen-producing bacteria in KD is unknown, the potential inflammatory effect of superantigens cannot be overlooked, and a low dose may induce KD, especially in susceptible patients, as in toxic shock

syndrome.[7,24] Serological studies in KD provide a third line of evidence on the association of KD with superantigens. Yoshioka et al.[19] discovered significantly more antistreptococcal immunoglobulin (Ig) G antibodies in patients with acute KD (n = 16) than in controls (n = 206). Nomura et al.[25] reported significantly more antistaphylococcal antibodies in patients with KD aged less than 6 months (n = 15) than in controls (n = 22), which suggested that staphylococcal-related superantigens are involved in the development of KD in infants aged less than 6 months. They subsequently observed a significantly higher antistreptococcal IgG antibody titer in patients with KD older than 6 months (n = 81) than in controls (n = 88), which suggested that streptococcal-related superantigens might be involved in KD development among those older than 6 months.[26] Matsubara et al.[9] demonstrated that patients with KD (n = 65) had a significantly higher IgM titer to the superantigens than did controls (n = 120), and their results suggest that multiple superantigens are involved in the pathogenesis of KD. However, some studies have provided no evidence of the involvement of superantigens in KD,[27,28] and considerable debate persists about the role of superantigens in the pathogenesis of KD.

Recently, Kusuda et al[29] reported that KD-specific serum molecules possessed molecular structures similar to microbe-associated molecular patterns (MAMPs) from *Bacillus cereus*, *Bacillus subtilis*, *Yersinia pseudotuberculosis*, and *S. aureus*. They speculated that KD-specific MAMPs may induce vascular inflammation, leading to the occurrence of KD.[29] From an epidemiologic perspective, Pellegrino et al.[30] demonstrated the strongest association between KD and pertussis-related admissions, and epidemiologic observations suggested that *Bordetella pertussis* had a role in the pathogenesis of KD. The Bacille de Calmette et Guerin (BCG) vaccination was reported to be associated with the development of KD,[31] but this relationship remains uncertain. *Lactobacillus casei* cell wall extract induced coronary arteritis in a mouse model of KD and resulted in acceleration of atherosclerosis.[32] The relationship between KD and bacterial infection remains controversial and requires further study, including investigation of other pathogenesis.

3. ASSOCIATION BETWEEN KD AND VIRAL INFECTION

Studies have reported the role of viral infection in KD, including enterovirus (EV),[5,33,34] retrovirus,[35] herpesviruses,[36] adenoviruses,[37] influenza,[37] parainfluenza,[37] and coronaviruses.[38] The coexistence of KD and viral infection can delay the diagnosis of KD.[33] Because delayed KD diagnosis and treatment can result in a high probability of CALS,[39] the role of viral infection in KD is a crucial topic. The mechanism that explains the relationship between KD and viral infection remains unclear. Large amounts of cytokines can be produced by viral-infected cells;[40] these cytokines, such as interleukin 1 (IL-1)[2] and IL-18,[41] may damage the vascular endothelium and result in CALs in patients with KD. However, no evidence exists that a specific virus induces KD.[42] Some studies have reported that KD might be associated with the vaccinations of hepatitis A, hepatitis B, influenza, and rotavirus.[43–46] By contrast, the review performed by Hua et al.[47] did not suggest a higher KD risk for those receiving live rotavirus vaccines or other vaccines according to the vaccine adverse event reporting system 1990-2007. Abrams et al.[48] also demonstrated that pediatric vaccination did not increase the risk of KD but may be associated with a transient reduction in KD incidence. Continuous monitoring of various vaccines for KD risk is suggested.

The peak incidence of KD in the summer coincides with the outbreak season of EV in Taiwan.[5,49] Chang et al[5] conducted a case–control study (n = 226) to ascertain the possible relationship between EV and KD in Taiwan. They proposed that heterogeneous infectious agents—such as EV, adenoviruses, rhinoviruses, and coronaviruses—trigger KD in children.[5] Recently, Weng et al.[50] used Taiwan National Health Insurance Research Database

to elucidate the relationship between KD and EV infection (n = 285,636). Their results showed that the cumulative incidence of KD was significantly higher in the EV-infected cohort than in the non–EV-infected cohort (log-rank test, $p < 0.001$).[50] The overall incidence of KD was 56% higher in the EV-infected cohort than in the non–EV-infected cohort, with an adjusted hazard ratio of 1.56 (95% CI = 1.44-1.69).[50] A higher association exists between KD and previous EV infection in Taiwanese children according to the results.[50] However, the relationship between KD and EV remains unclear. Rowley et al.[51] reported intracytoplasmic inclusion bodies containing RNA in lung tissues from late-stage KD fatalities and suggested that a previously unidentified RNA virus causing persistent infection in macrophages is the cause of KD. Their investigation suggests the association of KD with a novel RNA virus infection in the upper respiratory tract.[51] Rowley et al.[52] then further examined lung specimens from acute KD fatalities and identified virus-like particles that may constitute a new virus family. This finding is compatible with their previous hypothesis that a new respiratory RNA virus may be associated with the development of KD in genetically predisposed children.[52] The association between KD and an RNA virus in the studies of Rowley et al.[51,52] may partially elucidate the increase in KD risk among those with previous EV infection.[50] Efforts to study the molecular details of intracytoplasmic inclusion bodies and virus-like particles have been restricted by the rarity of autopsy tissues available for evaluation. Investigating relevant tissues such as coronary arteries in surviving patients with KD is infeasible except in the case of cardiac transplantation. Further study, including using animal models, remains necessary to investigate the specific infectious agents related to KD.

In conclusion, various bacterial and viral infections have been reported to be associated with KD, but the actual mechanism remains unknown. The higher association between KD and EV is further well documented by using Taiwan National Health Insurance Research Database. However, no strong evidence has been obtained that various bacterial and viral infections induce KD. Comprehensive research, including infectious agents, should be conducted to elucidate the pathogenesis of KD.

ACKNOWLEDGMENTS

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