Editorial

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Understanding Kawasaki Disease on the Ground of Pediatric Growth and Lymphoid Tissue Maturation

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In Kawasaki disease (KD), this systemic vasculitis may be complicated by severe cardiac morbidity in young children or sudden cardiac death of which the initial pathological change starts within just a few febrile days. With regard to the etiology of KD, it is an enigma that many researchers have attempted to solve, but unfortunately, the cause of KD is unknown. There are no confirmative diagnostic laboratory tools for diagnosis of KD. Therefore, diagnosis of KD still depends on clinical criteria and cardiovascular imaging findings. Prolonged fever, among other clinical symptoms and signs, is one of the most important risk factors causing coronary complications in KD. In clinical practice, in patients with the incomplete form of KD, there is controversy between pediatric subspecialists, such as infection specialists, immunologists, and pediatric cardiologists. This controversy occurs during the narrow period of the therapeutic window regarding which immune modulation therapy could work and might reduce coronary complications. There has been an increasing incidence of KD in Korea and Japan,[1)2)] and increasing trends of atypical or incomplete forms of KD complicated by severe coronary complications. Deciding on therapeutic options in patients with prolonged fever and partial features of KD is not easy. Therefore, performing randomized, controlled trials of therapeutic options in young patients with KD is difficult. Current consensus on the etiology of KD remains vague. Genetically susceptible individuals are thought to be triggered by a certain infectious agent, which develops clinical features of KD. KD then becomes complicated by coronary dilatation or aneurysms in severe cases. When diagnosing KD only with clinical criteria, several infectious diseases that commonly share clinical manifestations with KD are possible as a differential diagnosis. There is also a subgroup of patients with KD whose clinical course starts with marked enlargement of a cervical lymph node or neck mass. Typically, this group of patients is initially treated with several types of antibiotics. Finally, clinical features of full blown KD suddenly appear a few days later. Remission can be obtained by immune therapy along with suspending antibiotic therapy. Severe cases with prolonged fever and cervical lymphadenopathy may be complicated by coronary aneurysms. These findings have been reported by several studies.[3-5)]

Jun et al.[6)] presented the clinical characteristics of a subgroup of KD patients, in order to give information on the prevention of a delay in early diagnosis of KD and a coronary arterial lesion (CAL). The authors showed that this KD subgroup initially presented with only cervical lymphadenopathy (lymphadenopathy-KD [LKD] group). The LKD group showed typical diagnostic criteria of KD later during the febrile period. The age of the LKD group was older than patients of non-KD group, with a higher incidence of CALs during the acute phase of KD. The authors also used major Japanese scoring systems in this subgroup of patients for predicting an intravenous immune globulin-resistant group of KD, and they revealed that these scoring system not universally eligible in this subgroup.

Most patients who are diagnosed with KD are younger than 5 years old. This time point during childhood is important for development of the immune system. Peripheral lymphoid tissue rapidly increases in mass during infancy and childhood. This tissue reaches adult size by approximately 6 years of age.[7)] Therefore, until lymphoid organs become mature, overt clinical features related to

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lymphoreticular systems may not be frequently observed in young children in patients who are 5-6 years old although clinical features depend on the individual.

With regard to Jun et al.'s study,[6] there are several factors that could have been limitations. First, in the analysis of incidence of CALs, they used conventional diagnostic criteria of the Japanese Ministry of Health and Welfare. These criteria involved the definition of coronary arterial dilatation as a coronary diameter >3 mm in patients younger than 5 years, and >4 mm in those older than 5 years. This dichotomic criterion may cause confusion when classifying whether patients have CAL, especially in patients who are approximately 5 years old. The major portion of enrolled LKD patients of this study belonged to ages around 5 years. Second, the authors compared coronary diameters in patients with KD between the LKD and non-LKD groups, and found a significant difference during the acute phase of KD. However, patients in the LKD group were older than those in the non-LKD group. Because body surface area and the diameter of coronary arteries increase as children grow, a simple comparison of diameters between the two groups can lead to bias in the conclusion. If the z-scores of each patient's coronary arteries had been compared, these scores in the LKD group in the acute febrile phase might not have been significantly different compared with the non-LKD group. Third, enrolled patients in this study were treated aggressively with immune modulation therapy without a delay in diagnosis of KD. They were also treated with additional intravenous immunoglobulin, high doses of steroids, and even infliximab within 9 days from the onset of fever, achieving complete defervescence. This might explain why there were no patients with severe coronary complications. These findings suggest that the authors closely monitored LKD patients who initially presented with cervical lymphadenopathy. Shortly after clinical features changed to those typical of KD, they switched to therapeutic strategies of immune therapy, suspending antibiotic therapy. This swift conversion of therapeutic strategy might have been critical in reducing coronary complications in this LKD subgroup because we infrequently experience patients with CAL late after the strategy of treatment with only antibiotics. Fourth, there are no confirmatory laboratory findings in the diagnosis of KD. There also appear to be no confirmatory tools in ruling out a certain microbial infection. However, in Jun et al.'s study,[6] all of the intended diagnostic tests showed negative results. The authors attempted to exclude all of the non-KD patients with an infection by a certain microbe who commonly shared clinical features of KD. Infrequently, there are false negative findings in initial serological tests. If the patients in Jun et al.'s study[6] underwent a follow-up serological study for microbes several days later, positive conversion might have been observed.

Considering that the monthly incidence of KD varies,[8] certain infectious agents may trigger KD in susceptible hosts. In clinical practice, discrimination of patients who initially solely present with cervical lymphadenopathy from those with lymph node infection by a microbe, which is resistant to all the current antibiotics, remains difficult. Choosing therapeutic options is even more difficult when considering that the therapeutic window during febrile days is relatively narrow when trying to prevent coronary complications by reducing the total number of febrile days. Therefore, unraveling the enigma of KD is expected to require further research.

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