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Kawasaki disease may be a hyperimmune reaction of genetically susceptible children to variants of normal environmental flora

Kyung-Yil Lee *, Ji-Whan Han, Joon-Sung Lee

Department of Pediatrics, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

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Summary Kawasaki disease (KD) is an acute febrile systemic vasculitis of unknown etiology that occurs predominantly in children <5 years of age. For the etiopathogenesis of KD, there is no agreement even as to whether KD is an infectious disease or an immune-mediated disease. The epidemiologic characteristics of KD, including the strict predilection of age in all ethnic groups and the gradually increased incidence after the KD emergence, suggest that KD is affected by the immune maturation in early childhood that may be determined by genetic factors, and KD is also affected by the changed environmental circumstances such as improved public hygiene.

We postulated that the pathogenesis of KD is a hyperimmune reaction in genetically susceptible children to the variants of normal flora, which are induced by the environmental factors. Using this hypothesis, we might partly explain the clinical and epidemiological characteristics of KD. We expect that this hypothesis may help to determine the causative agents for KD in the near future.

Introduction

Kawasaki disease (KD) is an acute febrile systemic vasculitis of an unknown etiology that predominantly occurs in children <5 years of age [1]. It is characterized by prolonged fever (of at least five days duration) and a collection of clinical features (bilateral conjunctival injection, oropharyngeal changes, polymorphorus rash, changes of the extremities, and cervical lymphadenopathy) that together comprise the standard diagnostic criteria [1–4]. Coronary artery lesion (CAL) is a major complication of KD, and KD has been the most common cause of acquired heart diseases in the developed countries, including in Korea [2,3]. Although >40 years have passed since Dr. Kawasaki's initial report of 50 cases in 1967 [1], the etiology of KD remains still unknown. Clinical and epidemiologic studies have suggested that KD represents an abnormal host response in genetically susceptible children to one of more widely distributed infectious agents [2–4]. For the etiopathogenesis of KD, there is no agreement even as to whether KD is an infectious disease or an immune-mediated

* Corresponding author. Address: Department of Pediatrics, The Catholic University of Korea, Daejeon St. Mary's Hospital, 520-2 Daeheung-dong, Jung-gu, Daejeon 301-723, Republic of Korea. Tel.: +82 42 220 9541; fax: +82 42 221 2925.
E-mail address: leekyungyil@catholic.ac.kr (K.-Y. Lee).

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disease. It has also been debated whether the related etiologic agents of KD are bacterial or viral in origin, and if this is related to superantigens or conventional antigens [2—4]. Despite of unknown etiology, intravenous immunoglobulin (IVIG) is established as a standard treatment modality for KD. Although mode of action of IVIG on KD is also unknown, IVIG is very effective at rapidly improving clinical symptoms and preventing CAL [5].

In this article, we postulated the etiologic agents for KD based on the epidemiological and clinical characteristics of KD together with the role of environmental factors and genetic factors, and this postulation was also based on our clinical and epidemiological observations for a variety of pediatric infectious diseases.

Epidemiological characteristics of Kawasaki disease

KD is first seen in the early 1960s in Japan. Epidemiological studies in Japan revealed that KD showed a gradual increase up till 1978; after the nationwide epidemic in 1979, KD occurred elsewhere with relatively constant incidence rates, but it has continued to increase steadily with >6000 cases annually (Fig. 1) [6—8]. It is worthy of notice that nearly 3 decades of time after the emergence of KD were need to reach the incidence rates of ~100 cases per 100,000 children age < 5 years in early 1990s in Japan. In Korea, KD was first reported in the early 1970s [9], and the subsequent epidemiological patterns are similar to those of Japan. Although nationwide epidemiological survey in Korea started in the mid-1980s with some limited and missing dada during the study period, ~3000 cases have currently reported since late 1990s, and the incidence rates of ~100 cases per 100,000 children age < 5 years reached in early 2000s; further, nearly 3 decades of time were needed to achieve this incidence rate after the first emergence of KD in Korea (Fig. 2) [10—13].

An important epidemiological characteristic of KD is that the disease is rare in children less than 6 months old (or 3 months in Japan) or greater than 5 years old, with a peak incidence in children between 6 and 24 months old. This trait has not changed since the emergence of KD and this appears in all ethnic groups. This fact suggests that protection against KD may depend on passively acquired maternal antibodies, and the older children and adults have acquired immunity after infection of unknown pathogens(s), but it also suggest that the maturing immune system in early childhood may be involved in the pathogenesis of KD. In addition, the low rate of transmission in family members and the lack of outbreaks in day-care settings or hospitals indicate that although personal transmission of causative agent(s) of KD is highly prevalent in younger children like common viral infections, other factors may play a role in disease development. Another important epidemiological characteristic of KD is that over a decade of time was needed from the time of the initial case reports to the establishment of nationwide disease both in Korea and Japan. It may indicate that the long time period needed for the spread of KD and such environmental factors as improved public hygiene play roles in the emergence and establishment of KD. Other epidemiological findings of KD such as the different incidence among ethnic groups and between the countries, the relatively higher incidence among family members and the male predominance, they all indicate that genetic factors play a role in the pathogenesis of KD. In addition, patients with KD do not transmit the disease to others, they do not respond to antibiotics and they experience the recurrences in ~3% of cases [2,3]. If the etiopathogenetic agent(s) of KD must satisfy all these conditions, then what is the agent? This has been a main brain-buster for

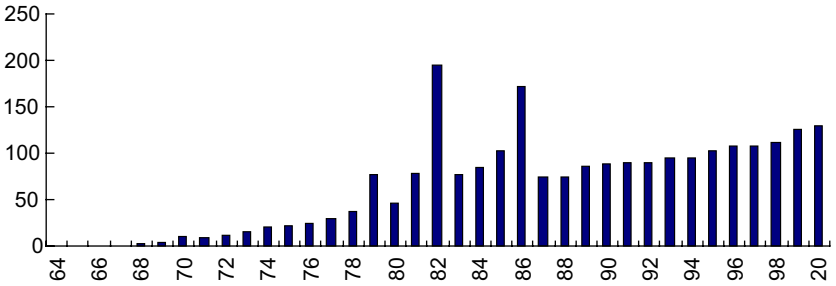

Figure 1 Annual incidence of KD cases per 100,000 children age < 5 years in Japan, 1961—2000.

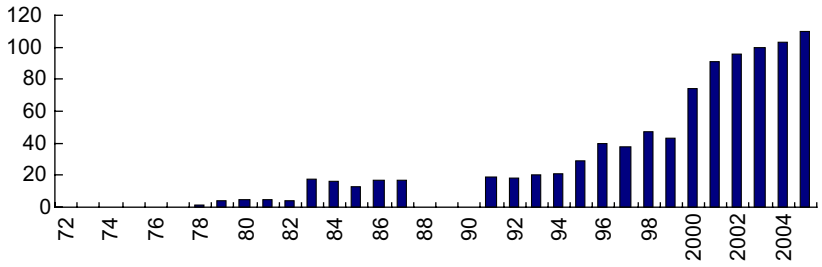

Figure 2 Annual incidence of KD cases per 100,000 children age < 5 years in Korea, 1972—2005.

all the physicians and scientists who have studied KD.

Is Kawasaki disease related to viruses?

KD is clinically similar to acute viral illnesses such as adenoviral infection, measles and infectious mononucleosis. In Korea, age predilection of KD is similar to other common viral infections such as Epstein-barr virus, rota virus and respiratory syncytial virus infection. It is presumed that the majority of children may be infected with these viruses till 5 years old, similar to KD. After nationwide establishment of KD in Japan, 3 epidemics occurred at ~3 year intervals (1979, 1982 and 1986) in a manner similar to measles during the pre-vaccine era (Fig. 1). During such epidemics, KD spread from one region of the country to another regions [6]. These findings have strongly suggested the hypothesis that KD is closely related to a viral infection. Although there is a debate as to whether KD is a newly emerged disease or a re-emerged disease from a previously existing disease (infantile polyarteritis nodosa), the epidemiological characteristics of KD, including the constant age predilection since KD emergence, are in conflict with the possibility of newly emerged viruses from other species such as retroviruses and avian influenza viruses. Thus, one postulates that common viral agents that mainly affect children less than 5 years old lead to a systemic vasculitis in genetically susceptible children. The seroprevalence of common viral agents such as herpes virus family, including Epstein-Barr virus (EBV), may be different among the populations of developed countries [14,15]. Several studies have been conducted on this concept, including the difference of the seropositivity of EBV antibodies in KD patients [16], but there is no convincing data for proving this postulation [14,15,17]. Common viral infections that occur before the age of 5, for instance, such as EBV and cytomegalovirus and both are transmitted through saliva and urine, were more likely to occur in the past period of poor hygiene in Korea [14,18]. Thus, the other postulates that together with a viral infection, the exposure to drugs, chemicals or co-infection with other microbial species that come about from industrialization may play adjuvant but essential roles, similar to the association between acetylsalicylic acid and Reye syndrome in the past [19]. However, this postulation may not explain the gradual increase in incidence rates, the lack of spatial disparity with temporal clustering in disease prevalence in Korea and Japan [13,20] and the difference of attack rates among the developed countries. Also, re-infection of systemic viral infections such as measles and chicken pox has not been reported.

Since the epidemiological characteristics in KD are very unique, the cause of KD may not be explained by the conventional viral agents or their variants alone, and additional environmental and genetic factors are probably needed.

Is Kawasaki disease related to bacteria?

The clinical symptoms, signs and natural course of KD are similar to those of scarlet fever and toxic shock syndrome, and both of these are caused by bacterial exotoxins from streptococci and staphylococci. Such bacterial diseases are characterized by the existence of localized infection sites (pharynx, skin lesion, vagina or burn infection); specific exotoxins are produced from these sites and spread to the systemic circulation. In addition, proper antibiotic therapy rapidly resolves the systemic symptoms and signs. The exotoxins from staphylococci and streptococci are known as superantigens. It is believed that superantigens promote the activation of a large numbers of T cells (5—20% of T cell clones) leading to an extensive immunological reaction [21]. Although localized colonization of superantigen-producing gram-positive bacteria in the skin and gut and an increase of some subset of T cell clones has been reported in KD patients, their clinical relevance needs further studies [22,23]. With improved

public hygiene, the incidence of bacteria-associated diseases such as rheumatic fever has been decreasing steadily in the developed countries and in Korea [24]. Although some of the KD laboratory findings, including leukocytosis, neutrophilia and elevation of CRP, are more pathognomic for bacterial infection rather than viral infection, there may be few systemic bacteria-associated infections that show the strict age predilection with a relatively higher incidence like KD [25].

Thus, some characteristics in KD such as the lack of response to antibiotics, a gradual increase of incidence and the consistency of age predilection may not be explained by the previously established conventional bacterial pathogens or their variants.

Clinical characteristics of Kawasaki disease: Is KD an immune-mediated disease?

For making the diagnosis, KD manifests an acute onset of fever together with the unique clinical signs. In addition, the striking activation of the entire immune system is a characteristic for laboratory finding of KD. A large number of studies have revealed that all immune cells are activated, and proinflammatory cytoknes including TNF-α, chemokines and other inflammation-associated proteins are nearly all up-regulated in KD [2,3]. This immune perturbation may be responsible for the systemic arteritis and CAL seen in KD patients. The direct substances inducing CAL in KD may depend upon two factors: one from a pathogen(s)-origin such as virus particles, bacterial walls or exotoxins (superantigens), and the other from inflammatory mediators that resulted from a hyperimmune reaction to unknown pathogens. For other explanations, it has been debated that KD is an infectious disease for which the etiology is not yet proven or it is an immune-mediated disease after an infection that is caused by unknown multiple pathogens.

KD presents with an acute onset of fever, which is similar to other infectious diseases. However, even in severely affected children with KD, there is little evidence of a septic condition such as peripheral artery involvement, hypotension, multi-organ failure or evidence of laboratory findings for sepsis. A septic condition has been shown in severe cases of any infectious diseases, including toxic shock syndrome and even viral infections. Most of the fatal KD cases are the result of carditis or CAL [2—4]. Thus, it is unlikely that the components of the pathogen themselves are not the causes of inflammation in KD.

Although KD shows an acute inflammatory nature, the pathogenesis of KD may be the result of inflammatory mediators, including TNF-α, after the activation of the immune system to unknown pathogens, like what occurs with other immune-mediated disorders such as rheumatic fever. Rheumatic fever and acute poststreptococcal glomerulonephritis (APSGN) are the representative immune-mediated disorders after primary bacterial infection from a variety of Group A β-streptococci. Both disorders have a 1—4 weeks incubation period after initial infection, and usually show a self-limited clinical course despite the serious complication seen in severe cases. The pathogenesis of the disorders is still unknown, and it is explained by abnormal host immune response to invading pathogens. The patients with rheumatic fever complain of fever, carditis, arthritis, and skin rash (erythema marginatum), with no components of etiologic agents being found in the pathologic tissues as is the case for APSGN and KD as well. Some patients with KD, especially young infants, do not satisfy the diagnostic criteria during their clinical course as having the 'incomplete', 'atypical' or 'suspected' KD. These children are at a higher risk of developing CAL because of delay in both the diagnosis and IVIG treatment [2—4]. Variations of clinical manifestation are often observed in immune-mediated disorders such as rheumatic fever and rheumatoid arthritis, and these disorders also have diagnostic criteria for the clinical and laboratory findings. In addition, it is uncertain whether there are some differences for the clinical manifestations of KD between different ethic groups.

Among extracardiac manifestations of KD, arthritis is commonly observed in 7.5—18% of KD patients during the acute and subacute stage [1,26,27]. Some KD patients develop arthritis regardless of receiving high-dose acetylsalicylic acid therapy in the pre-IVIG era [1,26], and also after receiving high-dose IVIG therapy [28]. This suggests that the pathogenesis of arthritis in KD may be a reactive arthritis from an immune reaction to unknown pathogens [28]. Together with acute conjunctival injection of KD, anterior uveitis (acute iridocyclitis) is another common ocular manifestation of KD. Although detection of the disorder with a slit lamp examination is difficult for the majority of young patients of KD, >80% of the KD patients who are examined within the first week of illness are noted to have the anterior uveitis [29]. The anterior uveitis of KD is self-limited and dose not leave complications, and may help to diagnosis for KD, especially for the incomplete cases [30]. Although anterior uveitis is observed in some infectious diseases such as toxoplasmosis, this disorder is more frequently observed in im-

mune-mediated diseases such as Behcet disease and juvenile rheumatoid arthritis [31]. Pathologically, the vasculitis of KD is classified as a necrotizing vasculitis. The pathologic findings of vasculitis of KD are not distinct from those of the other necrotizing vasculitides that may have an immune-mediated pathogenesis, including adult poly arteritis nodosa (PAN), although there are some minor differences [32].

IVIG is very effective for treating KD as well as for immune-mediated disorders such as idiothrombocytopenic purpura (ITP) and Guillain-Barre syndrome [33]. However, approximately 10—20% of patients with KD fail to respond to initial to IVIG treatment [2,3,34], and the more severely affected patients do not response to additional doses of IVIG. For this small group of patients, the treatments with immunosuppresants, including pulsed corticosteroids, cyclophosphamide and methotrexate have been reported to be effective as an additional treatment [35—37]. This treatment modality has been commonly used for the immune-mediated disorders including PAN, but it has been regarded as a contraindication for acute infectious diseases. The mode of action of IVIG for KD remains unknown, but high-dose IVIG administration (2 g/kg) down-regulated the levels of all proteins including inflammation-associated proteins, white blood cells (WBC) and neutrophils in KD patients [38,39]. With this effect of IVIG, we proposed a unified explanation for the variety of immunomodulating effects exerted by IVIG [40]. The effects of IVIG on KD may be the removal of pathogenic or over-expressed proteins (inflammatory mediators) via IgG that is derived from healthy donors who have the competent 'protein homeostasis system'. This effect of IVIG is dependent on the dose being administered in vivo and in vitro [40,41]. Thus, the effect of IVIG on KD may also depend on the severity of KD inflammation.

The intensity of inflammatory reaction in KD may vary from individual to individual, but the mean duration of fever lasts for 10-11 days without intravenous immunoglobulin therapy (IVIG) [1,26]. Clinical course of KD parallels the characteristic of common inflammatory diseases in that the inflammatory processes progress to a peak stage and then regress to a convalescent stage, and the mid point of the expected fever duration may be a peak stage in KD [42]. Together with a dose-dependent effect of IVIG, this observation may justify the importance of early treatment with a proper dose of IVIG for KD patients. Since high-dose IVIG (2 g/kg) induce the rapid down-regulation of inflammatory indices including WBC, neutrophil and CRP level within 24 h in the majority of KD patients [38,39], a rapid follow-up examination for obtaining the laboratory values after IVIG infusion may help make the decision for the earlier treatment modality for those IVIG-resistant patients [42].

On the other hand, Kikuchi-Fujimoto disease (KFD) is a benign, self-limited disease of an unknown etiology, and is characterized by cervical lymphadenitis [43,44]. However, some patients with lymphadenopathy complain of prolonged fever, malaise, fatigue, night sweats, weight loss, gastroenteric symptoms, and death has also been reported [45]. The pathogenesis of this disease is unknown, but the histologic and immunologic findings with the typical clinical presentation also suggest a hyperimmune reaction of immune cells to unidentified agents [46]. We found that removal of the affected lymph node(s) of patients with prolonged fever induced immediate defervescence [47]. This suggests that the clinical manifestations of KFD, including prolonged fever, are induced by the inflammatory mediators from the lymph nodes in which the hyperimmune response is elicited by unidentified pathogens. Like that for KFD, it is a reasonable assumption that KD may also have the primary sites for the hyperimmune reaction and for the production of inflammatory mediators that induce systemic vasculitis.

If KD is a presentation from immune-mediated phenomena, it is not unnatural that the KD's etiologic agents have not been detected through the intensive studies. The pathogenesis for most of the immune-mediated disorders, including reactive arthritis, Henoch-Schönlein purpura, Stevens-Johnson syndrome, that are related to various infectious agents also remains unknown, whereas most of the infectious diseases eventually have their etiologic agents proven.

Is Kawasaki disease related to environmental factors?

Environmental factors, including socio-economic status and cultural habits in a society, affect on the occurrence of infectious and autoimmune diseases. The epidemiolocal pattern of infections diseases depends largely on the use of vaccines, improved public hygiene and the genetic changes of pathogens. Several viral infections such as measles and poliomyelitis have nearly been eradicated in the developed countries with the use of vaccines.

Aseptic meningitis caused by enteroviruses, as well as hepatitis A, may be a representative disease that reflects the effect of the public hygiene

on the emergence or disappearance of a viral disease. Before the 1970s in Korea, hepatitis A might have affected most of the children until <15 years of age [48]. However, the seroprevalence of hepatitis A in the entire children population <15 year of age, as evaluated in the mid-1990s, was nearly zero, and recent infections have mainly occurred in the young adult group [48,49]. In contrast, aseptic meningitis caused by entoroviruses was very rare in the 1960—1970s in Korea, but after the transitional period of the 1980s, the disease spread to nationwide epidemics in the early 1990s with an interval of ~3 years [50]. In Japan, nationwide epidemics of enteroviral meningitis have reported since early 1980s, and these occurred ten years ahead of Korea [51]. It is very interesting that the times of first emergence and the nationwide establishment of KD and those of aseptic meningitis were nearly identical in Korea, and perhaps in Japan too. It strongly suggests that environmental factors such as improved public hygiene may play important roles for emergence of KD in both countries. The age distribution pattern of viral illnesses that have no available vaccines represents the herd immunity of the population, and it informs us of the epidemiological characteristic of pathogens. The age distributions in the Japanese epidemics of aseptic meningitis in 1980s and in the Korean epidemics in 1990s also were nearly identical for the peak frequency in infants and children aged 4—7 with a relatively even distribution in the children 0—15 years of age and only rare cases in the adult population [50,51]. In the United States, aseptic meningitis from enteroviruses was rare before the 1950s, but the recent cases in 1990s occurred most often in infants and in adults between 20 and 40 years old [52]. This indicates that improvement of public hygiene in the US was achieved several decades ahead of Korea and Japan.

Korea and Japan are closely related for the historical, geographical, ethnical and socio-cultural circumstances. Both countries have a dense population with only limited land for inhabitants, and the lifestyle and methods of child rearing may be dissimilar to those in the western countries. In Japan, the improved public hygiene probably began in the early 1960s after the World War II. In Korea, the plans for economic development began in the early 1960s after the Korean War, and the improved public hygiene might be noticeable in the early to mid-1970s, as assessed by the hepatitis A seroepidemiology [48]. Along with improved public hygiene, other environmental factors that are related to the western lifestyle and industrialization such as westernized foods, sanitation, antibiotics, vaccines and living in apartments with a hot water supply may be related to the pathogenesis of KD. It is also interesting that the incidence of inflammatory bowel disease (IBD) in Korea and Japan has increased in recent decades and one reason could be assumed to be due to environmental factors, and the increased intake of a westernized diet [53,54].

The human immune system and microbials are trying to adapt to a changing environment. Although it is not unclear whether the total frequencies of the exposure to environmental microbials including pathogens and normal flora, have been reduced in recent years compared to the past, it is apparent that there has been a significant change in incidence of infectious and immune-mediated diseases such as parasite infections and atopic diseases in the developed countries. Bacteria can easily transform their genomic materials according to environmental risks. In addition, it has been reported that gut microflora of infants were different to according to ethnic groups [55], and the changing environment factors from industrialization may affect on the distribution of gut microflora in infants [56]. Thus, it is very possible that normal flora also adjust to a changing environment.

Is Kawasaki disease related to the immune maturation of early childhood?

The immune systems of the vertebrates, including human, have two categories of immune system: an innate immune system and an adaptive immune system. Innate immune system is an ancient part of the host defense mechanisms, and adoptive immune system is a relatively newcomer on the evolutionary landscape [57].

Although the human adoptive immune system at birth is nearly matured, some immune function may mature during childhood [58]. The size of thymus and level of immunoglobulins such as IgG and IgE are different according to age. The severity of an infectious disease such as hepatitis A, coronavirus-associated severe acute respiratory syndrome (SARS), and *Mycoplasma pneumoniae* pneumonia tended to be milder in younger children than in the older population [59—61], and this suggests that maturing immune system is involved in the presentation of the disease phenotype. The atopic children tend to show the 'allergic march' according to age, and atopic dermatitis is improved till 5 years of age in majority of patients [62]. With the improved neonatal intensive-care modalities in recent years, the systemic circulation (mainly

bacteremia or rarely sepsis) of normal flora such as coagulase-negative staphylococci (CoNS) and Candida species has frequently been observed in premature neonates [63,64] but this is very rare in infants. It also suggests that the immune function for the colonization of normal flora may be affect by immune maturation. In addition, Kuijper et al. reported that T cells from KD patients showed the 'split T cell anergy' and KD patients had transiently reduced responsiveness to measles-mumps-rubella vaccination. From these observations, the authors postulated that KD is associated with a subtle maturational defect in immune system [65].

The distinct characteristics of KD such as the consistency of the strict age predilection of KD in all the ethnic groups and the even regional incidence of KD in Korea and Japan strongly suggest that maturing immune system in early childhood is involved in the pathogenesis of KD, and the extent of immune maturation probably is determined by genetic factors.

Predicted etiopathogenesis of Kawasaki disease

The human and normal flora in a variety of regions in human, including gut and airway, are closely linked, and the gut normal microflora are now recognized as an important part of the human immune system. In the mucosal immune system, the gut microflora have a crucial role in the establishment of immune cells within the epithelium and lamia propria, which is a major effector system against invading enteropathogens [66,67], and gut T cells from the host do not respond to antigens of their own gut flora [68]. Thus, it is postulated evolutionally that normal flora have finished their evolutionary adaptation for the symbiosis with the host, while the pathogens are still evolving for adaptation to the host.

The newborns experience colonization in the gut, airway and skin by a variety of microbial species, mainly of bacterial origin as soon as after birth. The mechanism of host's immune tolerance to normal flora, i.e., the immune system discriminating between pathogens and normal flora, is not fully understood. There may exist an innate immune system for adaptation of colonization for the normal flora to be seen as self, although few studies have performed on this issue [57,68]. It has been well recognized that some microbials that colonize as normal flora in healthy persons act as pathogens for inducing illness in other persons, and the disturbance of the normal flora in the gut caused by antibiotics can induce overgrowth of pathogenic bacteria [66,67]. However, there have been few studies determining what types of disorders are elicited when the immune system of the host loses tolerance to normal flora, i.e., the immunological confusion is encountered with variants of normal flora as self commensals or non-self pathogens, and if this were to happen what kind of the inflammatory and immune reactions would be provoked. For example, one presumed pathogenesis of inflammatory bowel disease is a loss of immune tolerance to the gut normal microflora [68,69].

Here, we postulated the pathogenesis of KD is immunological confusion that comes from an imbalance between the innate immune system and the adoptive immune system. It is postulated that a part of immune system for tolerance to normal flora is maturing through early childhood, and the extent and period of maturation is genetically determined. The environmental factors from the improved public hygiene or a western lifestyle in industrialization may transform a group of normal microflora to their variants in the gut, oral cavity or skin of the parents/caregivers of infants and young children. After colonization of the variants of normal flora in some young children who have a genetic defect of proper immune maturation, the variants of normal flora do not induce immune tolerance as self commensals, but rather, they induce a state of confusion on the immune system as the variants being seen non-self or pathogens, leading to a hyperimmune reaction and the manifesting KD. It is also postulated that occurrence of the variants of normal flora needs a long time and this is individualized by genetic and environmental influences.

Two unique characteristics of KD, i.e., the strict age predilection and gradually increasing incidence in KD may be easily explainable by the above postulation. In addition, if the transplacental substances, including maternal antibodies, play a role in the prevention of the disease, then the maternal generation in the improved hygiene era may experience less random-chance to KD pathogens, which results in decreased level of antibodies. Thus, the prevalence of young infants of <6 months in KD tends to be increased as time elapses. In recent years, the epidemiological patterns of KD also seem to be changing, with significantly increasing cases of <6 month of age group compared to a decade ago in Daejeon, Korea, although there may be a trend for our increasing confidence to diagnose incomplete KD (unpublished data).

The lack of person to person transmission, no response to anti-microbials and the failures to identifying of pathogens may be explainable that the pathogens (variants) of KD derived from normal flora do not cause a disease in other individuals as the self commensals, but only induce a hyperimmune reaction in genetically susceptible young children. The majority of normal flora in extravascular compartments in human is not affected significantly by the conventional antibiotic therapy [70], and/or KD may be an immune-mediated disease.

The difference prevalence of KD among the ethnic groups, including the developed countries and developing countries, is also explained by this hypothesis. The normal microflora in various ethnic groups may be different and environment factors and possibly genetic factors may affect on the distribution of microflora [55,56]. Earlier industrialized countries, like the United States, Western Europe and Australia, and the developing countries with poor public hygiene, in that people have had relatively stable environment factors for lifestyle, have all shown a low prevalence for KD [2]. In addition, the incidence of KD in these countries has not significantly changed with the passage of time [71,72]. Moreover, there are several recent reports on the increasing incidence of KD in the countries that may be on a course of industrialization [73,74]. It is very intriguing that with the similar ethnic back ground of the Far East countries, the time of appearance and the incidence rates of KD may be correlated with the time of the beginning of industrialization and the adoption of a western lifestyle, i.e., in the order of Japan, Korea, Taiwan and China [4,75,76]. In addition, the incidence of KD in these countries continues to increase steadily.

The previously postulated bacterial pathogens for KD such as *Proprionibacterium acne* [77] and staphylococcus species [22] may be regarded as normal flora, although their clinical relevance is not proven. There is less than 3% recurrent cases of KD, including the ones who experience relapse several times, and these cases may be result of different agents among the normal flora.

Whether our postulation is true or not, one important issue for KD may be the location of the primary site(s) for the strong systemic inflammatory reaction. Like scarlet fever, KD patients display an injected oropharynx and cervical lymphadenopathy. Certain species among the normal flora that colonize the oropharynx and possibly induce the inflammatory mediators might be regarded as non-pathologic agents on throat culture testing. One study group has presented the evidences for oligoclonal IgA immune responses, suggesting that the conventional pathogens are involved in KD [78]. The investigators found a significant IgA plasma cells infiltration in the trachea in patients who died of acute KD and that was similar to findings of children with fatal respiratory viral infection. From these observations, the authors postulated that entry of the unknown pathogens of KD is via the upper respiratory tract. However, it has been reported that the pathogenesis of the aggravation of some respiratory infections that induce adult respiratory distress syndrome (ARDS) and even death by viruses such as coronavirus (SARS) or *Mycoplasma pneumoniae*, may be a hyperimmune reaction of the host after the primary infection [79,80]. When considering the most frequent cases of infant at the stage of weaning, the steadily increased intake of western style diet (such as red meat) in Korea, and the coincidental occurrence in KD and aseptic meningitis caused by enteroviruses, it is also possible that gut pathogens are responsible for the pathogenesis of the disease. In addition, animal models of KD could be induced by the gut microflora such as *Lactobacilli* or *Candida* species including those obtained from KD patients [81,82].

In conclusion, we postulated that the pathogenesis of KD is a hyperimmune reaction in the genetically susceptible children to the variants of normal flora, and these variants are induced by the environmental factors. Using this hypothesis, we might partly explain the clinical and epidemiological characteristics of KD. We expect that this hypothesis may help to determine the causative agents for KD in the near future.

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