The association between Kawasaki disease and allergic diseases, from infancy to school age

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ABSTRACT

Kawasaki disease (KD) is the most common acquired heart disease among preschool children in most industrialized countries. An atopic trend after KD illness has been observed in epidemiological studies. This is consistent with the findings of elevated IgE levels and increased IL-4 in KD patients. However, studies on the early allergic association among children with KD are still limited. This study aimed to evaluate the association between KD and allergic diseases, from infancy to school age. Allergic diseases included atopic dermatitis, allergic rhinitis (AR), asthma, and urticaria. This matched case-control study used the National Health Insurance Research Database of Taiwan as its data source. Patients born between 1997 and 2004 and with a main diagnosis of KD were retrieved for analysis. A 1:4 matched control group was selected by zip code, gender, and age. The prevalence rates and progression sequence of allergic manifestations were analyzed. During the first 5 years of life, children with KD had higher rates of allergic manifestations. Both groups have similar atopic march. In 2010, at the age of 6–13 years, there were 7072 children with KD and 27,265 children without KD. Children with KD had more AR (odds ratio [OR], 1.30; 95% confidence interval [CI], 1.22–1.38) and asthma (OR, 1.16; 95% CI, 1.05–1.27) than controls. Children with KD have a higher allergic susceptibility recognized from their 1st year of life. The atopic tendency persists until school age. Additional studies are needed to elucidate the underlying determinants of this distinct immune phenotype.

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Kawasaki disease (KD) is a systemic vasculitis and the most common acquired heart disease among preschool children in most industrialized countries. Although it is often self-limiting, KD could cause serious long-term coronary arteries sequelae.[1,2]

A variety of theories on the pathogenesis of KD have been postulated, and immune dysregulation plays a central role.[3] The diverse systemic inflammation is attributed to the activated innate and adaptive immune responses. Cytokines and enzymes released from myofibroblasts and inflammatory cells destroy the arterial wall, resulting in aneurysm formation.[4] Characteristics of allergic immune response such as increased Th2 cytokines, elevated IgE levels, and eosinophilia[5] were noted in the peripheral blood of KD patients.[6–8] Furthermore, few surveys conducted by clinicians and researchers reveal an atopic trend among children with KD.[9–11] Most of the investigations indicate the atopic trend after KD illness. However, studies on the early allergic association among children with KD are still limited.[11]

The National Health Insurance (NHI) program has been providing comprehensive and unified health care for ~98% of the population in Taiwan since its implementation in 1995.[12] The resulting NHI Research Database (NHIRD) contains information on inpatient and outpatient care nationwide. Taiwan has the third highest incidence of KD in the world (69/100,000 children <5 years old), just after Japan (218/100,000) and Korea (113/100000).[13,14] In Taiwan, allergic diseases are not uncommon,[15] and the medical care is easily accessible. From the all-inclusive database, we are confident to assume that the information on the association between these two disorders can reflect the actual relationship.

The aim of the present study was to evaluate the association between KD, allergic diseases, and later outcomes.

MATERIALS AND METHODS

This nationwide matched case-control study used data from the NHIRD. Information about the beneficiaries that could be obtained from the database included scrambled patient identification number, birth-

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days, gender, insured area, diagnostic codes, and date of visit to medical institutes. The diagnosis obtained from the NHIRD was physician coded, based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) coding standards.

KD cases were defined as patients born between 1997 and 2004, continuously enrolled in the NHI program until 2010, and were ever admitted with a main diagnosis of KD (ICD-9-CM code: 446.1). If the patients were not continuously enrolled in the NHI program in 2010, they were excluded. On the other hand, the control group was chosen from 1,000,000 randomly sampled beneficiaries enrolled in the NHI program in 2010 (Longitudinal Health Insurance Database 2010). Those ever admitted due to KD were excluded. This control group was matched by zip code, gender, and age at a ratio of approximately four controls to each KD case (Fig. 1).

Allergic diseases were defined as having at least one diagnosis of atopic dermatitis (AD), allergic rhinitis (AR), asthma, or urticaria (ICD-9-CM codes: 691, 477, 493, and 708, respectively). The rates of the three common allergic diseases (AD, AR, and asthma) in the first 5 years of life were compared between the KD cases and control group. The progression of these three allergic diseases was also analyzed. In 2010, when the age of the study cohorts was 6–13 years old, the period prevalence of allergic diseases was compared between these two study groups.

The software SAS 9.1 (SAS Institute, Inc., Cary, NC) was used for data retrieval and analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using the proportional hazard model (PROC PHREG) by both univariate and multivariate models. Statistical significance was set at $p < 0.05$. The control group was randomly sampled three times to test the stability for points of estimate.

In accordance with the Personal Electronic Data Protection Law of Taiwan and the regulation of NHIRD, data that could be used to identify patients or care providers, including medical institutions and physicians, were scrambled before being released to researchers.[16] This study protocol has been approved by the Institutional Review Board of Taichung Veterans General Hospital. M.-C. Lin and Y.-C. Fu contributed equally to this work.

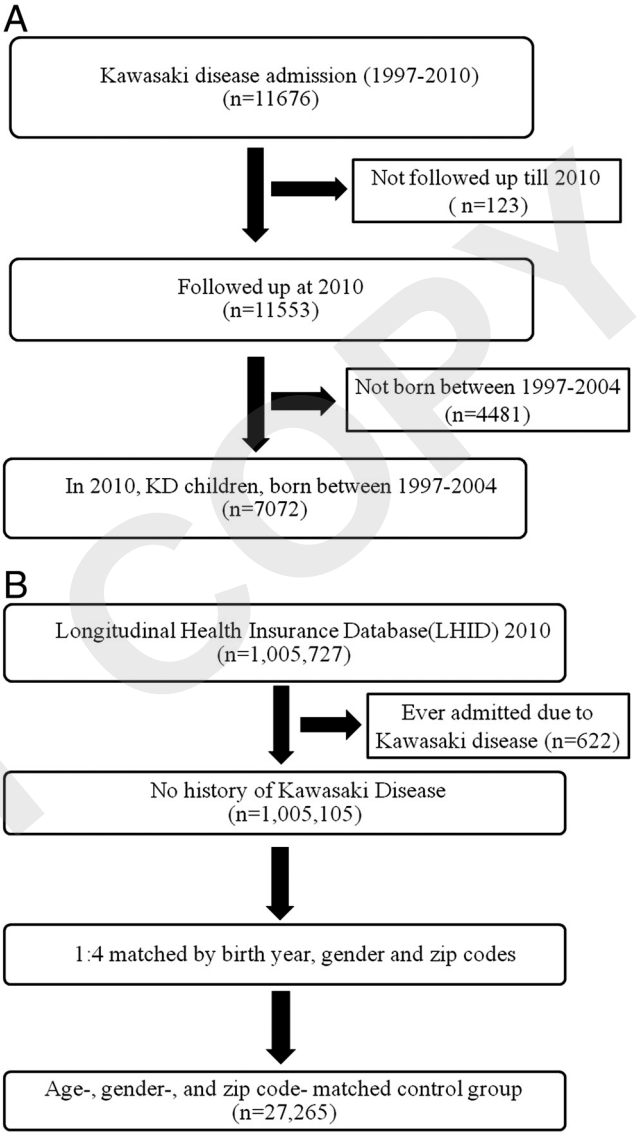

Figure 1. *(A) The study cohort of children with Kawasaki disease (KD). From January 1997 to December 2010, patients ever admitted with a main diagnosis of KD were selected (n = 11,676). After excluding those who were not continuously followed up in the National Health Insurance (NHI) program in 2010 (n = 123), there were 11,553 KD patients. Those who were not born between 1997 and 2004 were eliminated (n = 4481). In 2010, KD patients born between 1997 and 2004 were retrieved for analysis (n = 7072). (B) The control group; matched by age, gender and zip codes. From 1,000,000 randomly sampled beneficiaries enrolled in the NHI program in 2010 (Longitudinal Health Insurance Database 2010; n = 1,005,727), patients without KD history were chosen (n = 1,005,105). A 1:4 matched control group was randomly selected by age, gender, and zip code (n = 27,265).*

RESULTS

In 2010, among children born between 1997 and 2004, there were 7072 KD children and 27,265 non-KD children matched for age, gender, and zip codes. The male-to-female ratio was 1.63 (Table 1).

Based on the rates of allergic diseases (AD, AR, and asthma) in the KD and control groups at each separate age during the first 5 years of life, the KD group had higher rates of allergic manifestations (Fig. 2, *A*–*C*). Both groups had the highest rates of AD in the 1st year of life (KD, 18.3%; controls, 16.08%; $p < 0.001$), which declined with age. By the age of 5 years old, the AD

Table 1 **Demographic data of patients with KD and matched controls**

	KD Cases		Controls	
	n	%	*n*	%
Birth year				
1997	1032	14.59	4003	14.68
1998	861	12.17	3351	12.29
1999	918	12.98	3570	13.09
2000	1062	15.02	4121	15.11
2001	827	11.69	3179	11.66
2002	821	11.61	3107	11.4
2003	786	11.11	3014	11.05
2004	765	10.82	2920	10.71
Sex				
Male	4391	62.09	16,881	61.91
Female	2681	37.91	10,384	38.09
Total	7072		27,265	

KD = Kawasaki Disease.

rate had declined to 4% (KD, 4.68%; controls, 4.05%; $p < 0.05$; Fig. 2 *A*). Regarding AR, the trend rose from 6 to 8% (KD, 8.57% versus controls, 6.27%; $p < 0.001$) to the peak rate of 24–29% at 5 years old (KD, 29.38% versus controls, 24.32%; $p < 0.001$; Fig. 2 *B*). As for asthma, the rate was 4–5% (KD, 5.63% versus controls, 4.42%; $p < 0.001$) in the 1st year of life and peaked at 14–17% at the age of 4 years old (KD, 17.96% versus controls, 14.85%; $p < 0.001$; Fig. 2 *C*). The age, when reaching peak rate, was the youngest for AD, followed by asthma and AR (Fig. 2 *D*).

In 2010, when the study cohort was at the age of 6–13 years old, the period prevalence of allergic diseases was determined (Table 2). The period prevalences of AD, AR, asthma, and urticaria were 3.48, 26.5, 9.13, and 6.73%, respectively, in the KD group, and 3.43, 21.94, 8.04, and 6.28%, respectively, in the control group. In univariate model, children with KD had more AR (OR, 1.30; 95% CI, 1.22–1.38) and asthma (OR, 1.16; 95% CI, 1.05–1.27) than controls. In multivariable model, the points of estimate did not change significantly. However, asthma became borderline significant.

DISCUSSION

This study reveals higher rates of allergic manifestations (AD, AR, and asthma) in children with KD than in non-KD children throughout early childhood. For KD children, this allergic association is manifested from the 1st year of life and persists until school age. School-aged children have more AR (OR, 1.3) and asthma (OR, 1.16). In addition to higher rates, the progression sequence of three common allergic diseases in KD children is similar to that of controls as well as the atopic march established in a previous population-based birth cohort study.[16]

In the nationwide study in Taiwan during the period 2000–2007, the overall prevalences of AD, AR, and asthma in people <20 years old are 9.6, 37.8, and 15.7%, respectively.[17] Recent surveys based on the questionnaire designed by the International Study of Asthma and Allergies in Childhood shows the prevalence rates of allergic disorders for children.[18,19] In northern Taiwan, the prevalences of AD, AR, and asthma are 10.2, 29.8, and 12.2%, respectively, for children aged 6–8 years old, and 4.7, 18.3, and 9.6%, respectively, for children 10–12 years old.[18] In central Taiwan, the prevalence rates of AD, AR, and asthma are 3.35, 27.59, and 6.99, respectively, for children aged 6–15 years old.[19] There is no significant difference in the prevalence rate between the present study and previous questionnaires conducted with nationwide studies. Thus, our control sampling can represent the general population of Taiwan. We also repeated the sampling of controls three times with very similar results.

Previous studies have revealed an atopic trend in children with KD.[9–11] A small study from Taiwan reports higher risk of subsequent allergic diseases in children with KD, but the sample size is limited.[9] A sibling study conducted in Singapore suggests that KD is a possible risk factor for subsequent allergic diseases.[10] The two studies emphasize the increased risk of allergic diseases after KD. However, an Australian study showed that KD-affected children have more admissions due to allergy and that the majority of these admissions occurred before KD.[11] The main question is whether KD itself or an underlying shared susceptibility contributes to allergic diseases. In the present study, children with KD begin to express allergic manifestations at infancy and the association with allergic diseases has persisted until school age.

A series of experimental studies support the clinical findings of an association between allergy and KD. In the painstakingly detailed description presented by Dr. Tomisaku Kawasaki in the 1967, eosinophilia was noted in KD children.[20] Thereafter, numerous investigations on immune cascades of KD have been conducted in succession. The findings include the following: (1) increased $CD23^+$ B lymphocytes with elevated serum IgE levels,[6] (2) increased generation of cysteinyl leukotrienes,[21] (3) eosinophilic infiltration of coronary microvessels,[7] and (4) higher IL-4 and IL-5 levels.[8] Such inflammatory cells, mediators, and cytokines are the driving force behind allergic expression.

Furthermore, in a large, family-based genotyping study of KD, Burns *et al.* propose that genetic variations in the IL-4 gene and linked regions, including the IL-4C (−589) T allele, are implicated in KD pathogenesis and disease susceptibility.[22] Intriguingly, this ge-

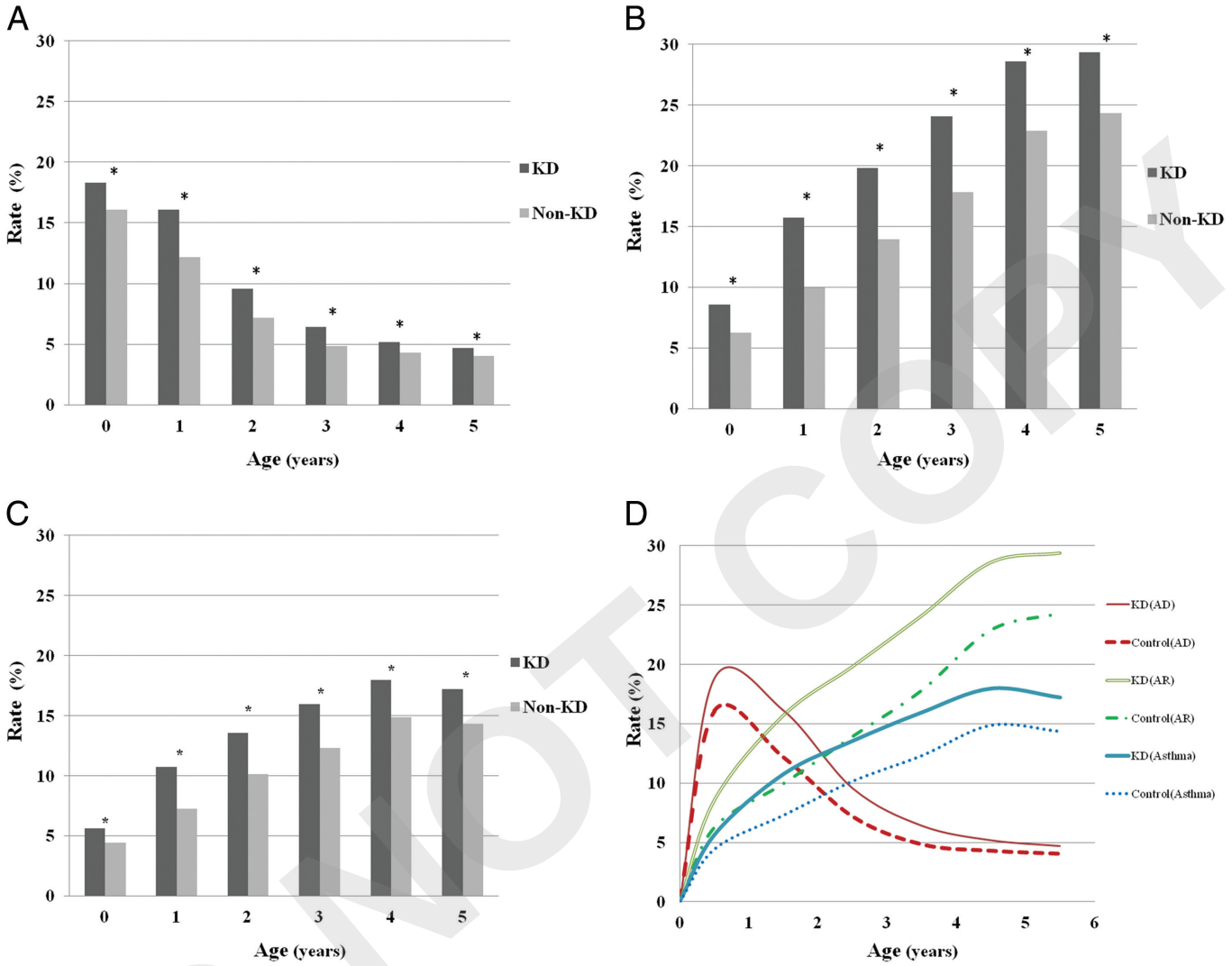

Figure 2. *(A) Rates of atopic dermatitis (AD). The rates of AD were the highest in the 1st year of life and then declined with age in both groups. Kawasaki disease (KD) children had higher rates of AD (*p < 0.05). (B) Rates of allergic rhinitis (AR). The rates of AR reached the peak at 5 years old. KD children had higher rates of AR (*p < 0.05). (C) Rates of asthma (Asthma). The rates of asthma reached the peak at 4 years old. KD children had higher rates of asthma (*p < 0.05). (D) Atopic trend in the KD and non-KD (control) groups. The age when reaching peak rate was the youngest for AD, followed by asthma and AR.*

Table 2 **OR of allergic diseases in patients with KD and control group in 2010**

	KD		Control		OR (95% CI)	OR (95% CI)
	Numbers	%	Numbers	%	Univariate	Multivariate
AD	246/7072	3.48	934/27,265	3.43	1.02 (0.89–1.18)	0.95 (0.82–1.10)
AR	1874/7072	26.5	5983/27,265	21.94	1.30 (1.22–1.38)	1.28 (1.20–1.37)
Asthma	646/7072	9.13	2191/27,265	8.04	1.16 (1.05–1.27)	1.03 (0.93–1.13)
Urticaria	476/7072	6.73	1711/27,265	6.28	1.07 (0.96–1.19)	1.04 (0.93–1.15)

OR = odds ratio; CI = confidence interval; KD = Kawasaki disease; AD = Atopic dermatitis; AR = Allergic rhinitis.

netic variation has been linked to elevated serum IgE levels and allergic diseases.[23,24] Thus, susceptibility to KD and atopy may be ascribed to a shared genetic determination. Taken together, a specific immune phenotype may be contributing to KD and the allergic predisposition.

The possible infectious etiology of KD seems to play a role in allergy-related immune cascades. Superanti-

gens have been previously considered as the most potential villains of KD owing to a selective expansion of certain T-cell receptor families in some KD patients.[25] They are also involved in skewing cytokine response toward the Th2 phenotype and in the induction of chronic rhinosinusitis, AD, and asthma.[26–28] In the course of KD, there is a prolonged state of neutrophil activation with increased human neutrophil elastase and matrix metalloproteinases (MMP).[29] The imbalance between MMP and tissue inhibitors of MMPs contributes to arterial aneurysm formation[29,30] as well as being implicated in the allergic diseases.[31,32] Mannose-binding lectin (MBL), an important role in the innate immunity, facilitates immune defense against microbes. Polymorphisms of the MBL gene might be associated with the trigger of pathogenesis of KD.[33] The role of MBL polymorphisms is also linked with the susceptibility of allergic diseases.[34,35] During acute KD, IgA plasma cells infiltrate coronary arteries, upper airway epithelium, kidneys, and pancreas.[36] When using synthetic versions of IgA antibodies mimicking those of KD patients, antigens reside in cytoplasmic inclusion bodies in KD ciliated bronchial epithelium are detected. Accordingly, Rowley *et al.* propose a pathogenic model of KD which characterized by an antigen-driven IgA response.[37] The etiologic agent of KD might be an intracellular pathogen and enters through the respiratory tract. While invading ciliated bronchial epithelium, KD agents evoke inflammatory responses and damage the epithelial barrier. Some of the KD agents reside in the cytoplasmic inclusion bodies of bronchial epithelium, and the others are taken by the macrophages to circulate and traffic through susceptible organs and tissues.[4,37] Intriguingly, the epithelial barrier defect of the respiratory tract is crucial for the development and persistence of asthma.[38] The impaired barrier function resulting from disruption of epithelial tight junctions provides an entry for inhaled substance to interact with immune and inflammatory cells underlying the wall of airway and, finally, asthma attacks.[38,39]

The present study has certain limitations. First, the prevalence rates provided by the NHIRD are treatment prevalence rates. The prevalence of allergic diseases may be lower than those derived from questionnaire-conducted studies. Second, individual allergic sensitization, eosinophil count, cytokines, and histopathology are not analyzed because the patients' identification numbers are scrambled, making it impossible to confirm the data. Thus, we cited the related information from previous important studies to validate the results of this study. Nonetheless, because the NHI program covers almost the entire population in Taiwan, these data reflect the actual relationship between KD and allergic diseases.

In conclusion, this study shows the association between KD and allergic diseases. For children with KD, the allergic association has been manifested from infancy until school age. Additional investigations are warranted to elucidate the underlying determinants of this distinct immune phenotype.

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