Atopic Diathesis in Patients with Kawasaki Disease

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Objective To determine the association between Kawasaki disease (KD) and atopic diathesis (atopic dermatitis [AD], allergic rhinitis, and asthma) in children younger than 5 years of age.

Study design In this nationwide study, we aimed to analyze the association and temporal relationship between KD and atopic diathesis. Data were obtained from the National Health Insurance Research Database of Taiwan from 1997 to 2010. In total, 200 patients with KD younger than 5 years of age and 800 age- and sex-matched control subjects were enrolled.

Results In the whole study population, an increased risk of any concomitant atopic diseases was observed in patients with KD (OR 1.61, 95% CI 1.15-2.26). The risk of AD was increased in male patients between 1 and 5 years of age (OR 3.02, 95% CI 1.22-7.50). More than 60% of the patients developed atopic diseases after the diagnosis of KD.

Conclusion There appears to be an association between KD and risk of AD. Most of the atopic diseases occurred after the episode of KD. *(J Pediatr 2013;163:811-5)*.

Kawasaki disease (KD) is a generalized vasculitis that mostly occurs in children younger than 5 years of age. According to several epidemiologic studies, the incidence of KD is greater in Asian populations.[1] It typically presents as fever, mucosal lesions, skin rash, and cervical lymphadenopathy.[2] Although treatment may reduce long-term cardiovascular complication, KD is still the leading cause of acquired cardiac disease in childhood.[1,3-6] The cause of KD remains unclear, but it has been suggested that infectious agents and immune function dysregulation might both contribute to the etiology.[2,3,5,7]

Atopic diathesis is another disorder commonly occurring in childhood that also involves immune dysfunction.[8,9] Atopic diathesis includes 3 closely related diseases, namely atopic dermatitis (AD), allergic rhinitis (AR), and asthma, and is considered a hyperactivated state of the immune system.[10] Because KD and atopic diathesis share similar susceptible populations and are both associated with immune system dysregulation, we sought to investigate the relationship between them.

A limited number of extant studies have demonstrated that patients with KD have a greater prevalence of AD, asthma, and allergies.[3,5,7,11,12] However, there has been no analysis of the interaction and temporal relationship between these diseases. In this nationwide case-control study, we used multiple logistic regression models to investigate the correlation between KD and atopic diathesis, hoping to deepen the understanding of the pathogenesis of these diseases.

Methods

The Taiwan National Health Insurance Research Database is a claims database maintained by the Department of Health and the National Health Research Institutes of Taiwan.[13] The National Health Insurance program was launched in Taiwan on March 1, 1995, and by the end of 2010, it covered more than 99% of Taiwan's population.[14] The database provides information about the beneficiaries, including scrambled patient identification number, sex, date of birth, diagnostic codes, and date of visit to medical institutes. The diagnostic codes were recorded according to *International Classification of Diseases, Ninth Revision* (ICD-9) coding standards. This study was approved by the institutional review board of Taipei Veterans General Hospital.

In this study, we used data from the Longitudinal Health Insurance Database 2000 (LHID2000), which is a subset of National Health Insurance Research

AD	Atopic dermatitis
AR	Allergic rhinitis
CAA	Coronary artery aneurysm
ICD-9	*International Classification of Diseases, Ninth Revision*
KD	Kawasaki disease
LHID2000	Longitudinal Health Insurance Database 2000

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Database, as the study sample. LHID2000 contains medical claims data of 1 million randomly sampled beneficiaries from 1996 to 2010 from among the enrollees of National Health Insurance. There were no statistically significant differences in sex ratio, age distribution, or health care costs between the LHID2000 and all enrollees, as reported by the National Health Research Institute in Taiwan.

We identified the patients hospitalized with KD (ICD-9: 446.1) as their primary diagnosis from the inpatient database between January 1, 1997, and December 31, 2010. Because we focused on the most susceptible population of KD, that is, only children younger than the age of 5 years, those older than 5 were excluded. Subjects with questionable basic data, such as conflicting sex data or uncertain date of birth, were also excluded.

Those who did not have KD were used as the control group. From LHID2000 we randomly selected 4 age- and sex-matched individuals without KD for each KD patient as the control group.

The coexisting atopic comorbidities were identified from the ambulatory dataset between January 1, 1997, and December 31, 2010, by having the corresponding ICD-9 codes in the diagnosis field. The atopic diseases included AD (ICD-9: 691.0), AR (ICD-9: 477.0, 477.1, 477.2, 477.8, 477.9), and asthma (ICD-9: 493.0, 493.1, 493.2, 493.8, 493.9). To improve diagnostic accuracy and avoid overestimation of prevalence, only those having at least 2 consecutive corresponding diagnoses could be designated as having certain comorbidity. The time intervals between KD and comorbid atopic diseases also were collected to study their temporal relationship.

Statistical Analyses

We first analyzed the demographic data of the study subjects. Continuous data were presented as mean ± SD. The prevalence of each of the atopic diseases (AD, AR, asthma) in the study group and control group was calculated. We used multiple logistic regression models to calculate the OR and 95% CI after adjusting for sex, age, number of health care visits, presence of coronary artery aneurysm (CAA), and atopic comorbidities to estimate the magnitudes of the associations between atopic diseases and KD. For intergroup comparisons, the Pearson χ^2 test or the Fisher exact test was used for nominal data where appropriate. A 2-tailed $P < .05$ was considered statistically significant. Sensitivity analyses were conducted to evaluate the persistence of associations when the definition of having certain comorbidity required the presence of corresponding diagnosis code only once.

Microsoft SQL Server 2008 (Microsoft Corporation, Redmond, Washington) and SPSS Statistics 17.0 for Windows (SPSS Corporation, Chicago, Illinois) were used to analyze the data in this study.

Results

Two hundred subjects with KD, 118 male (59%) and 82 female (41%), were identified from the LHID2000 database between January 1, 1997 and December 31, 2010. The mean ± SD age of diagnosis was 3.02 ± 1.31 years. Among the subjects with KD, AR was the most prevalent atopic disease (31%), followed by asthma (28%) and AD (7.5%) (Table I). Nearly one-half of the patients (46%) were diagnosed with at least one atopic disease. The prevalence of atopic diseases was greater in the KD group. However, except for AR ($P < .01$) and asthma ($P = .02$), none of them reached statistical significance.

Table I. Comparisons of characteristics of patients with KD and control subjects

	KD	Control group	*P*-value*
Case number, N	200	800	
Age, y, mean, SD	3.02, 1.31	3.02, 1.31	
Age, y, n (%)			
≤1	34 (17)	136 (17)	
>1	166 (83)	664 (83)	
Sex, n (%)			
Male	118 (59)	472 (59)	
Female	82 (41)	328 (41)	
Atopic diathesis, n (%)			
AD	15 (7.5)	40 (5)	.17
AR	62 (31)	173 (21.63)	<.01
Asthma	56 (28)	162 (20.25)	.02
AD and AR	8 (4)	20 (2.5)	.25
AD and asthma	7 (3.5)	19 (2.38)	.25
AR and asthma	33 (16.5)	93 (11.63)	.06
AD, AR, and asthma	7 (3.5)	13 (1.63)	.09
Any atopic diathesis†	92 (46)	256 (32)	.09

*P values were calculated by Pearson χ^2 test or Fisher exact test where appropriate. All P values were 2-tailed.
†Patients with at least one atopic disorder are listed.

In the whole study population, an increased risk of any concomitant atopic disease was observed in patients with KD (OR 1.61, 95% CI 1.15-2.26). When sex- and sex-stratification analyses were performed, we found increased risk only in male subjects with KD who were between 1 and 5 years of age (OR 1.95, 95% CI 1.20-3.17) (Tables II-IV).

With regard to individual atopic diseases, increased risk of AD was found in male subjects with KD between 1 and 5 years of age (OR 3.02, 95% CI 1.22-7.50). We also found that male subjects, especially those older than 1 year of age, had a greater risk of all 3 concomitant atopic diseases (OR 6.05, 95% CI 1.64-22.28; Table IV). When we stratified the patients by the presence of CAA, we found an increased OR for atopic diseases in male subjects with KD who did not have CAA (OR 1.74, 95% CI 1.11-2.73).

We further evaluated the time intervals between the diagnoses. More than 60% of the patients with KD developed atopic diseases after the diagnosis of KD (AD: 10 cases [66.67%]; AR: 39 cases [62.90%]; asthma: 35 cases [37.50%]). In these subjects, the median time interval between onset of KD and these atopic diseases were as follows: AD: 313.5 days, AR: 457 days, and asthma: 486 days.

When the definition of having a certain comorbidity required the presence of corresponding diagnosis code only once, the association of "any atopic diathesis" in all subgroups remained unchanged, only the ORs were slightly