

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; ■: ■-■).

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

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

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 $\pm$ 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

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.

between January 1, 1997 and December 31, 2010. The mean $\pm$ 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.

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

Table II. Multivariate analysis for atopic diseases in patients with KD compared with control subjects

	All (n = 200)			Male (n = 118)			Female (n = 82)		
	n (%)	cOR (95% CI)	aOR (95% CI)*	n (%)	cOR (95% CI)	aOR (95% CI)	n (%)	cOR (95% CI)	aOR (95% CI)*
AD	15 (7.5%)	1.54 (0.83-2.85)	1.25 (0.66-2.37)	13 (11.02%)	2.31 (1.14-4.69)	2.02 (0.97-4.23)	2 (2.44%)	0.49 (0.11-2.16)	0.34 (0.07-1.61)
AR	62 (31%)	1.63 (1.16-2.30)	1.31 (0.88-1.94)	41 (34.75%)	1.75 (1.13-2.71)	1.56 (0.93-2.62)	21 (25.61%)	1.45 (0.82-2.55)	1.02 (0.54-1.94)
Asthma	56 (28%)	1.53 (1.08-2.18)	1.19 (0.80-1.78)	36 (30.51%)	1.48 (0.95-2.31)	1.11 (0.66-1.87)	20 (24.39%)	1.64 (0.91-2.93)	1.27 (0.66-2.43)
AD and AR	8 (4%)	1.63 (0.71-3.75)	1.20 (0.51-2.84)	8 (6.78%)	2.79 (1.11-6.99)	2.36 (0.91-6.15)	0 (0%)	-	-
AD and asthma	7 (3.5%)	1.49 (0.62-3.60)	1.10 (0.44-2.73)	7 (5.93%)	2.64 (1.00-6.97)	2.00 (0.73-5.50)	0 (0%)	-	-
AR and asthma	33 (16.5%)	1.50 (0.98-2.31)	1.01 (0.57-1.78)	25 (21.19%)	1.75 (1.04-2.92)	1.54 (0.90-2.66)	8 (9.76%)	1.07 (0.47-2.44)	0.80 (0.33-1.91)
AD, AR, and asthma	7 (3.5%)	2.20 (0.86-5.58)	1.88 (0.73-4.87)	7 (5.93%)	3.66 (0.13-10.30)	3.52 (1.23-10.02)	0 (0%)	-	-
Any atopic diathesis†	92 (46%)	1.81 (1.32-2.48)	1.61 (1.15-2.26)	57 (48.31%)	1.76 (1.17-2.64)	1.74 (1.12-2.69)	35 (42.68%)	1.91 (1.16-3.15)	1.42 (0.83-2.43)

cOR, crude OR.

Statistically significant data are presented in bolded text.

*Models adjusted for age, sex, number of health care visits, presence of CAA, and atopic diseases are listed.

†Patients with at least one atopic disorder listed in this Table.

greater (in all subjects with KD, OR 1.77, 95% CI 1.27-2.46). Nevertheless, male patients with KD who were older than 1 year still had a greater risk of AD (OR 2.74, 95% CI 1.33-5.65). As to other atopic diseases, the OR of asthma in male patients with KD older than 1 year (OR 1.75, 95% CI 1.00-3.05) increased significantly.

Discussion

The strength of this study is its internal validity; as a large-scale nationwide study, it minimizes selection bias. With the help of this nationwide database, we were able to adjust for possible confounding factors, including age, sex, and number of health care visits. Second, we analyzed the effect of KD on not only each atopic disease but also on multiple concomitant atopic diseases. Understanding the interrelationships is important, for patients with different concurrent atopic diseases could have different comorbidity profiles.¹⁰ Many of the ORs in the present study lost significance after adjustment for comorbid atopic diseases, further supporting the notion that these atopic diseases affect each other (Tables II and IV).

AD is a chronic, relapsing, pruritic dermatitis caused by a defect of the epidermal barrier function.¹⁵⁻¹⁷ It has been found to be associated with KD in the literature.^{7,11,12} The clinical presentation, epidemiology, and pathophysiology of AD all change with age. For example, during infancy, the skin lesions involve mostly the cheeks and/or extensor areas,

and in childhood the lesions evolve to affect flexor areas.^{15,16} We also found that the association between KD and AD changed with age in the present study. In male patients with KD, only those between 1 and 5 years of age had a significantly increased risk of AD after we adjusted for sex, age, number of health care visits, presence of CAA, and comorbidities (OR 3.02, 95% CI 1.22-7.50) but not those younger than 1 year of age. An important theory in the pathogenesis of AD involves percutaneous sensitization as the result of barrier dysfunction.^{15,16,18-20} In the present study, among the 3 atopic diseases, only the risk of AD was found to be increased.

AR and asthma are manifestations of atopic diathesis in the airways.^{17,18,21,22} The epithelia of the skin and airways are regarded as a continuum. Although hypersensitivity of the skin causes AD, that of the respiratory system leads to AR and asthma.²² Patients with AD are prone to have AR and asthma in later life.¹⁹ A filaggrin mutation, which is an important predisposing factor for AD, is also found to play a role in the presentation of AR and asthma.^{18,19} However, the relationship between these atopic diseases is complex, and the filaggrin mutation alone cannot explain it completely. Several questions remain unanswered. For example, the filaggrin mutation is not found in asthma patients who do not have AD, and most of the genes associated with asthma are not found to be associated with AD.^{18,19}

CAA is a potentially lethal complication of KD, and the severity of KD is sometimes measured by its occurrence.^{1,3,5,7}

Table III. Multivariate analysis for atopic diseases in patients with KD (younger than or equal to 1 year of age) compared with control subjects

	All (n = 34)			Male (n = 23)			Female (n = 11)		
	n (%)	cOR (95% CI)	aOR (95% CI)*	n (%)	cOR (95% CI)	aOR (95% CI)*	n (%)	cOR (95% CI)	aOR (95% CI)*
AD	5 (14.71%)	1.50 (0.50-4.51)	1.46 (0.48-4.44)	3 (13.04%)	1.00 (0.26-3.88)	0.95 (0.24-3.78)	2 (18.18%)	4.67 (0.58-37.65)	5.01 (0.56-44.50)
AR	11 (32.35%)	1.55 (0.68-3.53)	1.48 (0.59-3.75)	9 (39.13%)	1.55 (0.60-4.00)	1.54 (0.52-4.56)	2 (18.18%)	1.73 (0.29-10.41)	1.88 (0.29-12.44)
Asthma	8 (23.53%)	1.00 (0.41-2.43)	0.83 (0.32-2.13)	6 (26.09%)	1.00 (0.35-2.83)	0.85 (0.28-2.59)	2 (18.18%)	1.00 (0.18-5.55)	0.98 (0.15-6.50)
AD and AR	2 (5.88%)	1.64 (0.30-8.83)	1.79 (0.30-10.79)	2 (8.70%)	1.66 (0.30-9.14)	1.78 (0.29-11.01)	0 (0%)	-	-
AD and asthma	1 (2.94%)	0.79 (0.09-7.03)	0.65 (0.07-6.28)	1 (4.35%)	0.79 (0.09-7.12)	0.63 (0.06-6.26)	0 (0%)	-	-
AR and asthma	5 (14.71%)	1.50 (0.50-4.51)	1.34 (0.42-4.25)	4 (17.39%)	1.28 (0.38-4.37)	1.21 (0.34-4.37)	1 (9.09%)	4.30 (0.25-74.78)	4.72 (0.26-84.67)
AD, AR, and asthma	1 (2.94%)	1.00 (0.11-9.25)	1.02 (0.11-9.62)	1 (4.35%)	1.00 (0.11-9.40)	1.01 (0.11-9.57)	0 (0%)	-	-
Any atopic diathesis†	17 (50%)	1.35 (0.63-2.86)	1.22 (0.53-2.81)	12 (52.17%)	1.19 (0.48-2.97)	1.08 (0.40-2.93)	5 (45.45%)	1.79 (0.47-6.86)	1.55 (0.33-7.30)

*Models adjusted for age, sex, number of health care visits, presence of CAA, and atopic diseases are listed.

†Patients with at least one atopic disorder listed in this Table.

Table IV. Multivariate analysis for atopic diseases in patients with KD (aged between 1 and 5 years of age) compared with control subjects

	All (n = 166)			Male (n = 95)			Female (n = 71)		
	n (%)	cOR (95% CI)	aOR (95% CI)*	n (%)	cOR (95% CI)	aOR (95% CI)*	n (%)	cOR (95% CI)	aOR (95% CI)*
AD	10 (6.02%)	1.57 (0.74-3.33)	1.14 (0.52-2.50)	10 (10.53%)	3.61 (1.51-8.63)	3.02 (1.22-7.50)	0 (0%)	-	-
AR	51 (30.72%)	1.65 (1.13-2.40)	1.28 (0.82-2.00)	32 (33.68%)	1.82 (1.11-2.97)	1.53 (0.84-2.79)	19 (26.76%)	1.42 (0.78-2.59)	1.00 (0.50-2.03)
Asthma	48 (28.92%)	1.67 (1.14-2.46)	1.30 (0.83-2.04)	30 (31.58%)	1.63 (0.99-2.67)	1.20 (0.66-2.18)	18 (25.35%)	1.76 (0.94-3.27)	1.55 (0.76-3.17)
AD and AR	6 (3.61%)	1.62 (0.62-4.25)	1.09 (0.40-2.95)	6 (6.32%)	3.59 (1.18-10.95)	2.88 (0.90-9.20)	0 (0%)	-	-
AD and asthma	6 (3.61%)	1.74 (0.66-4.60)	1.23 (0.45-3.35)	6 (6.32%)	4.20 (1.32-13.34)	3.14 (0.94-10.46)	0 (0%)	-	-
AR and asthma	28 (16.87%)	1.50 (0.94-2.40)	1.26 (0.77-2.07)	21 (22.11%)	1.87 (1.06-3.31)	1.64 (0.89-3.02)	7 (9.86%)	0.96 (0.40-2.30)	0.78 (0.30-2.00)
AD, AR, and asthma	6 (3.61%)	2.73 (0.96-7.78)	2.23 (0.77-6.47)	6 (6.32%)	6.34 (1.75-22.93)	6.05 (1.64-22.28)	0 (0%)	-	-
Any atopic diathesis†	75 (45.18%)	1.94 (1.37-2.75)	1.72 (1.19-2.50)	45 (47.37%)	1.95 (1.24-3.08)	1.95 (1.20-3.17)	30 (42.25%)	1.93 (1.13-3.31)†	1.44 (0.81-2.57)

Statistically significant data are presented in bolded text.

*Models adjusted for age, sex, number of health care visits, presence of CAA, and atopic diseases are listed.

†Patients with at least one atopic disorder listed in this Table.

Liew et al³ revealed reduced risk of atopic diathesis in patients with KD and CAA. However, Matsubara et al⁷ stated that the presence of CAA does not alter the incidence of atopic diathesis among these 2 groups. In a subgroup analysis, we also found no significant difference in the risk of individual atopic diseases between patients with and without CAA. However, the OR of “any atopic diathesis” was increased in male patients with KD who did not have complications of CAA (OR 1.74, 95% CI 1.11-2.73).

The temporal relationship between KD and atopic diseases has rarely been discussed. Our study revealed that approximately two-thirds of the atopic diseases developed after the occurrence of KD. During the acute phase of KD, the serum levels of IgE are found to be increased,⁷ and during the subacute phase, there is a T-helper type 2 predominant immune response.⁵ Elevated IgE and T-helper type 2 phenotype are both observed in patients with atopic diseases.^{9,23-26} The authors of previous studies have shown that allergen sensitization begins as early as the fetal period. Moreover, allergy sensitization with IgE production in early childhood has been identified as a predictor of atopic diseases.⁹ This could be a reason why these 2 diseases are related.

There were some limitations to our study. First, the laboratory test results (such as the level of IgE and the result of skin prick test), family history of atopic diathesis/allergy, environmental exposure, and lifestyle were not documented in the database. Thus, we could not analyze how these atopic diathesis-related factors affect the risk of atopic diathesis in patients with KD. Second, because this study focused on patients younger than 5 years of age, follow-up was relatively short. Although atopic diathesis is mainly a disease of young children, a considerable proportion of the patients develop the disease after age 5.²⁷⁻²⁹ This could result in an underestimation of the risk. These results help to provide a better understanding of the relationships, especially the temporal relationships between KD and atopic diathesis. Additional studies should be carried out to further clarify these relationships. ■

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