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Original article

Increased risk of Kawasaki disease in children with common allergic diseases

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ABSTRACT

Purpose: Growing evidence reveals a link between Kawasaki disease (KD) and allergic diseases. This population-based case-control study is to investigate the onset of allergic diseases in children and the associated risks of KD.
Methods: From 1996 to 2008, 2748 children with KD and 10,656 randomly selected controls were enrolled. Odds ratios of KD were calculated for the association with pre-existing allergic diseases.
Results: The children with a single allergic disease had an increased risk of KD, with adjusted odds ratios of having KD of 1.82 for urticaria (95% confidence interval [CI], 1.54–2.14), 1.44 for allergic rhinitis (95% CI, 1.23–1.70), and 1.22 for atopic dermatitis (95% CI, 1.06–1.39). The adjusted odds ratios increased with the number of concurrent allergic diseases, from 1.61 (95% CI, 1.43–1.82) for those with only one allergic disease to 1.71 (95% CI, 1.48–1.98) for those with at least two allergic diseases. The children who made two or more medical visits for associated allergic diseases per year had an increased risk of KD.
Conclusions: Children with onset of allergic diseases were at increased risk for KD, and the increased risk was associated with the cumulative effect of concurrent allergic diseases and frequency of seeking medical care.

Introduction

Kawasaki disease (KD) is a systemic vasculitis which mainly affects infants and young children [1]. Although KD is an acute illness in most patients, coronary artery aneurysms develop in about 25% of patients without prompt diagnosis and treatment, and this is a leading cause of acquired heart disease in children [2]. The incidence of KD has increased globally in recent years [3]. Asian populations have a much higher incidence of KD, and Taiwan has the third highest incidence of KD worldwide [4]. In Japan, the incidence of KD has doubled during the past 2 decades [5]. Although KD has been identified for more than 40 years, the etiology remains unclear.

There is a growing interest in a potential link between atopic disorders and autoimmune diseases, and there is increasing epidemiologic evidence for an association of KD and allergic disease [6–12]. However, the relationship between pre-existing allergic diseases and KD risk remains unclear. In this nationwide, population-based case-control study, we investigated temporal relationships between subsequent KD risk and the onset of allergic diseases in children to better understand the pathogenesis of these diseases.

Methods

Data source

The National Health Insurance (NHI) program in Taiwan was implemented in 1995 and is a single-payer, social insurance plan

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[13]. The Bureau of NHI has contracts with 99% of hospitals and the NHI program covers up to 99% of the population of Taiwan. The NHI program also provides data sets from the National Health Research Insurance Database (NHIRD) for corresponding research on issues related to cost, quality of health services, medical practice patterns, accessibility to health care programs, and treatment outcomes at national and local levels (http://www.nhi.gov.tw/english/index.aspx) [13,14]. The data set used in this study consisted of a randomly selected sample of half of all insured children in Taiwan, which included more study subjects than previous studies using the claims data of the Longitudinal Health Insurance Database, which includes 1 million randomly selected individuals [10–12]. This study was exempt from institutional review board approval because the NHIRD database contains de-identified encrypted information which is publicly available through the proper application process.

Study design

The claim data retrospectively collected since 1996 and prospectively recorded up to 2008, contained demographic information on insured children (including sex, birth date, and residential area) and medical care received for ambulatory and inpatient visits. The diagnosis of KD was confirmed by the *International Classification of Diseases, Ninth Revision of the Clinical Modification* (*ICD-9-CM*) code, and the Registry for Catastrophic Illness Patient Database, which includes selected major injuries or illnesses and is published by the Department of Health, Executive Yuan, Taiwan. The diagnosis of KD is made by a board-certified specialist, and the application is further reviewed and approved by the Bureau of NHI, which ensures the accuracy and reliability of the diagnosis.

We identified a total of 2748 patients aged 1–18 years with newly diagnosed KD (*ICD-9-CM* code 446.1) from 1998 to 2008 as the KD group. For each KD patient, four controls with no history of KD were matched by age (every 1-year span), sex, and urbanization level. Urbanization level was defined according to an NHRI report. City districts and townships where subjects were registered for insurance purposes were grouped in to four levels of urbanization based on population density (people/km^2). Level 1 indicates the most urbanized area and level 4 indicates the least urbanized area. The diagnoses of allergic conjunctivitis (*ICD-9* codes: 372.05, 372.10, and 372.14), allergic rhinitis (AR) (*ICD-9* code: 477), asthma (*ICD-9* codes: 493 and 494), atopic dermatitis (AD) (*ICD-9* code: 691), and urticaria (*ICD-9* codes: 708.0 and 708.9) before the diagnosis of KD were identified. All diagnoses of the allergic disorders were given at least twice by physicians for diagnostic validity. The cumulative effect of disease severity was evaluated by the number of allergic comorbidities and frequency of seeking medical care.

Statistical analysis

We used the χ^2 and *t*-tests to analyze the demographic data between the KD and non-KD control groups, and multivariate conditional logistic regression models to calculate the odds ratios and 95% confidence intervals (CI) after adjusting for sex, gender, and urbanization of residential area for the association between allergic diseases and KD. All data analyses were performed using SAS 9.1 (SAS Institute Inc., Cary, NC), and a value of *P* less than .05 was considered to be statistically significant.

Results

In total, 2748 subjects with KD were identified, including 1744 males (64%) and 1004 females (37%). The mean age at the diagnosis of KD was 2.83 (standard deviation, 2.80) years. More than half of the subjects with KD resided in urban areas (approximately 57%) and were younger than 2 years (67%). The prevalence of all atopic diseases was significantly higher in the KD group compared with the non-KD group, with AC (7% vs. 5%), AR (12% vs. 8%), asthma (8% vs. 6. %), AD (15% vs. 11%), and urticaria (10% vs. 5%), respectively (Table 1).

In the whole study population, an increased subsequent risk of KD was observed in the children with each allergic disease except for asthma (Fig. 1). The mean duration between diagnosis of allergic diseases and KD is 21.7 months (standard deviation = 21.9; median = 15.1; interquartile range = 5.07–31.0). The adjusted odds ratio (aOR) were 1.82 for urticaria (95% CI, 1.54–2.14), 1.44 for AR (95% CI, 1.23–1.70), and 1.22 for AD (95% CI, 1.06–1.39). When the association was evaluated by gender, the adjusted risk for both genders was significantly related to AR and urticaria (Fig. 1). Comparing the allergic patients with those without any allergic diseases, the adjusted OR of having KD increased with the number of allergic comorbidities. The aOR increased with the number of allergic diseases, from 1.61 (95% CI, 1.43–1.82) for those with only one allergic disease to 1.71 (95% CI, 1.48–1.98) for those with at least two allergic diseases (*P* for trend <.0001) (Table 2) in multivariate conditional logistic regression. The adjusted ORs of KD increased to 1.79 (95% CI, 1.45–2.20), 1.36 (95% CI, 1.06–1.75), 2.30 (95% CI, 1.57–3.26), and 2.19 (95% CI, 0.80–6.02) in each age group (≤2, 2–5, 5–12, and >12 years) for those with two or more allergic

Table 1
Comparisons in sociodemographic factors and comorbidities between cases with KD and non-KD controls

Subject	Total (n = 13,404)	Control (n = 10,656)	KD (n = 2748)	*P*
	n (%)	*n* (%)	*n* (%)	
Age (y), mean ± SD*	2.83 ± 2.8	2.82 ± 2.8	2.83 ± 2.8	.87*
Age (y)				.99
≤2	9038 (67)	7188 (68)	1850 (67)	
2–5	2960 (22)	2352 (22)	608 (22)	
5–12	1174 (9)	932 (9)	242 (9)	
>12	232 (1)	184 (2)	48 (2)	
Gender				.93
Female	4888 (37)	3884 (37)	1044 (37)	
Male	8516 (64)	6772 (64)	1744 (64)	
Urban status†				.99
Level 1	3940 (30)	3132 (30)	808 (30)	
Level 2	3718 (28)	2952 (28)	766 (28)	
Level 3	2669 (20)	2124 (20)	545 (20)	
Level 4	2927 (22)	2328 (22)	599 (22)	
Comorbidity				
AC				.0005
No	12,695 (95)	10,129 (95)	2566 (93)	
Yes	709 (5)	527 (5)	182 (7)	
AR				<.0001
No	12,227 (91)	9808 (92)	2419 (88)	
Yes	1177 (9)	848 (8)	329 (12)	
Asthma				.03
No	12,508 (91)	9969 (94)	2539 (92)	
Yes	896 (7)	687 (6)	209 (8)	
AD				<.0001
No	11,805 (88)	9462 (84)	2343 (85)	
Yes	1599 (12)	1194 (11)	405 (15)	
Urticaria				<.0001
No	12,583 (88)	10,103 (85)	2480 (90)	
Yes	821 (6)	553 (5)	268 (10)	

SD = standard deviation.
χ^2-test.
* *t*-test.
† The urbanization level was categorized by the population density of the residential area into four levels, with level 1 as the most urbanized and level 4 as the least urbanized.