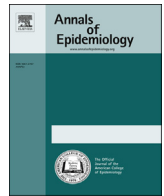




Contents lists available at ScienceDirect

Annals of Epidemiology

journal homepage: www.annalsofepidemiology.org

Original article

Increased risk of Kawasaki disease in children with common allergic diseases

Chang-Ching Wei MD^{a,b}, Cheng-Li Lin MS^{c,d}, Chia-Hung Kao MD^e, Yen-Hsiu Liao MD^f,
Te-Chun Shen MD^{b,g}, Jeng-Dau Tsai MD^h, Yen-Jung Chang PhD^{i,*}, Tsai-Chung Li PhD^d^a Department of Pediatrics, China Medical University Hospital, Taichung, Taiwan^b Department of Pediatrics, College of Medicine, China Medical University, Taichung, Taiwan^c Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan^d Department of Public Health, China Medical University, Taichung, Taiwan^e Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan^f Department of Radiology, China Medical University Hospital, Taichung, Taiwan^g Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan^h Department of Pediatrics, Chung Shan Medical University Hospital, Taichung, Taiwanⁱ Department of Health Promotion and Health Education, National Taiwan Normal University, Taipei, Taiwan

ARTICLE INFO

Article history:

Received 6 October 2013

Accepted 7 February 2014

Keywords:

Allergic conjunctivitis

Allergic rhinitis

Asthma

Atopic dermatitis

Kawasaki disease

Urticaria

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.

© 2014 Elsevier Inc. All rights reserved.

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

Financial Disclosure: The authors have indicated that they have no financial relationships relevant to this article to disclosure.

Conflict of Interest: none.

* Corresponding author. Department of Health Promotion and Health Education, National Taiwan Normal University, 162 He-Ping E. Rd., Sec. 1, Da-An District, Taipei, 106, Taiwan, Republic of China. Tel.: +886-4-2205-2121 ext. 7520; fax: +886-4-2203-2798.

E-mail addresses: yjchang2012@gmail.com, weilonger@gmail.com (Y.-J. Chang).

1047-2797/\$ – see front matter © 2014 Elsevier Inc. All rights reserved.

<http://dx.doi.org/10.1016/j.annepidem.2014.02.003>

[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/km²). 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) n (%)	Control (n = 10,656) n (%)	KD (n = 2748) n (%)	<i>P</i>
Age (y), mean $\pm$ SD*	2.83 $\pm$ 2.8	2.82 $\pm$ 2.8	2.83 $\pm$ 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				.0005
AC				
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.

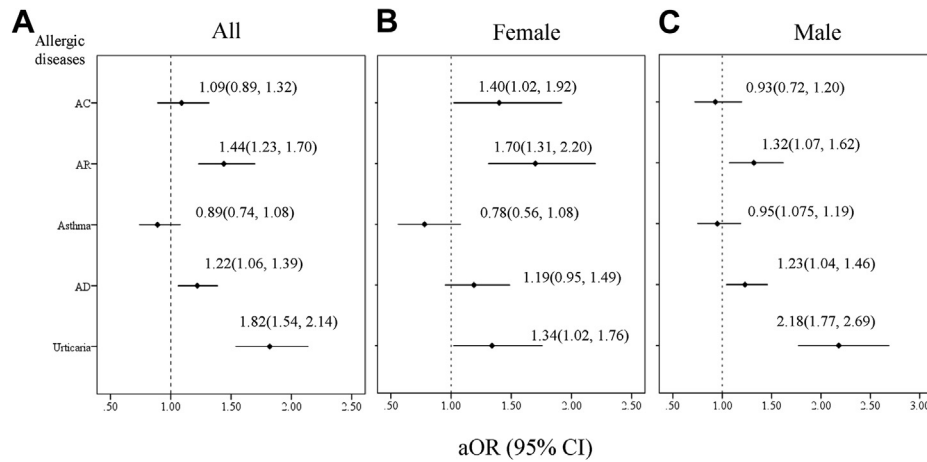


Fig. 1. Odds ratio and 95% CI between specific allergic disease and subsequent risk of KD. Estimates from multiple conditional logistic regression models adjusted for sex, age, urbanization, and mutual five allergic diseases.

diseases (Table 2). We further examined the association between the annual frequency of medical visits due to allergic diseases and the risk of KD and found that the aORs increased in AR, AD, and urticaria with two or more medical visits per year 1.53 (95% CI, 1.27–1.83); 1.57 (95% CI, 1.30–1.89); and 3.05 (95% CI, 2.43–3.83), respectively) (Table 3).

Discussion

There are a number of strengths to this study. First, it robustly demonstrates the relationship between atopic diathesis and risk of KD using a large number of study subjects. Second, we analyzed the effect not only of a specific type of allergic disease but a large number of common allergic diseases, the cumulative effect of comorbid allergic diseases, and the frequency of seeking medical care. Third, the present study is a population-based study with physician-diagnosed atopic diseases which minimizes selection and recall bias. Fourth, the diagnosis of KD was determined by both ICD-9-CM and Registry for Catastrophic Illness Patient Database, thereby ensuring internal validity. Fifth, we adjusted for possible confounding factors including age, gender, and urbanization level. Ethnic influence was not considered in this study because of homogenous ethnicity in Taiwan.

A few studies have reported a high prevalence of allergic diseases in patients with KD; however, these findings have been inconsistent due to the limited number of patients and because most of the studies only investigated one or two diseases such as AD, AR, and asthma [6–9]. More recently, several population-based studies in Taiwan enhanced the understanding of the interaction between KD and allergy. One cohort study revealed that KD was a risk factor for the subsequent development of asthma and AR [10].

Another two studies revealed an association between KD and the risk of AD [11,12]. However, there are several limitations to these studies. First, they used claims data of a sample of 1 million subjects from the NHIRD, which limited the number of study subjects resulting in a loss of statistical significance for some atopic diseases. Second, no previous study has included large scale of allergic diseases as the present study. Third, the relationship between allergy and KD risk has not been discussed. Only one recent study using a large population investigated the association between KD and large scale of allergic disease [15]. However, the KD risk after the onset of allergic diseases has not been elucidated. This study is the first to report that the children with pre-existing allergic diseases had an increased future risk of KD and that this risk increased with the number of concurrent allergic diseases and associated medical care visits.

Our findings may suggest that atopic diseases have a positive influence on the development of KD or that they may share common early-life determinants. Studies have shown that KD is associated with immune dysregulation involving not only Th1/Th2 but also Th17 cells/regulatory T-cell imbalance [16–18]. This immune dysregulation may, therefore, explain the temporal interaction between KD and allergic diseases. In addition, autoimmune and allergic diseases may share genetic predisposition or genes that interact with shared environmental risk factors [19–23]. Therefore, immunogenetic factors and early-life environmental factors may both contribute to the development of allergies and KD.

There are several limitations to this study. This is a cross-sectional study and the causality between allergic diseases and KD could not be established. However, this study clearly shows an association between allergy and the risk of KD by using a large number of subjects. Another limitation is the lack of data on genetic

Table 2
Association between the number of allergic diseases and KD*

Age (y)	All	≤2	2–5	5–12	>12
	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Number of concurrent allergic disease					
0	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1	1.61 (1.43–1.82)***	1.71 (1.48–1.97)**	1.37 (1.06–1.77)*	1.57 (1.01–3.36)*	1.15 (0.41–3.23)
2+	1.71 (1.48–1.98)***	1.79 (1.45–2.20)**	1.36 (1.06–1.75)*	2.30 (1.57–3.26)***	2.19 (0.80–6.02)
P for trend	<.0001	<.0001	.0085	<.0001	.057

* Estimates from multiple conditional logistic regression models adjusted for sex, age, urbanization, and mutual five allergic diseases; *P < .05, **P < .001, *** P < .001.

Table 3Association between frequency of annual medical visit due to allergic disease and KD^a

Frequency	None	≤2	>2	P
	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	for trend
Allergic diseases				
AC	1.00 (Reference)	1.09 (0.86–1.38)	1.08 (0.79–1.47)	.46
AR	1.00 (Reference)	1.27 (0.97–1.65)	1.53 (1.27–1.83)***	.22
Asthma	1.00 (Reference)	0.82 (0.62–1.10)	0.94 (0.75–1.17)	.46
AD	1.00 (Reference)	0.99 (0.83–1.18)	1.57 (1.30–1.89)***	.0002
Urticaria	1.00 (Reference)	1.14 (0.90–1.44)	3.05 (2.43–3.83)***	<.0001

AC = allergic conjunctivitis.

^a Estimates from multiple conditional logistic regression models adjusted for sex, age, urbanization, and mutual five allergic diseases; ****P* < .001.

and environmental factors, which might have affected the risks for KD and atopic diathesis.

Conclusions

Present study indicates that the onset of allergic diseases was associated with the increased risk of the subsequent development of Kawasaki disease. In addition, the risk of KD was consistently associated with the number and severity of comorbid allergic diseases. Future investigations on environmental and genetic factors related to the childhood onset of allergies and subsequent risk of KD are warranted.

Acknowledgments

The study was supported in part by China Medical University Hospital (DMR-101-061 and DMR-100-076), Taiwan Department of Health Clinical Trial and Research Center and for Excellence (DOH102-TD-B-111-004), Taiwan Department of Health Cancer Research Center for Excellence (DOH102-TD-C-111-005), Bureau of Health Promotion, Department of Health, R.O.C. (Taiwan) (DOH99-HP-1205), and International Research-Intensive Centers of Excellence in Taiwan (I-RiCE) (NSC101-2911-I-002-303).

Author contribution: C.-C.W. and T.-C. S conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted. C.-L.L., C.-H.K., Y.-H.L., J.-D.T., and T.-C.L. carried out the initial analysis, reviewed and revised the manuscript, and approved the final manuscript as submitted. Y.-J.C. coordinated and supervised data collection, critically reviewed the manuscript, and approved the final manuscript as submitted.

References

- [1] Yim D, Curtis N, Cheung M, Burgner D. Update on Kawasaki disease: epidemiology, aetiology and pathogenesis. *J Paediatr Child Health* 2013;49:704–8.
- [2] Uehara R, Belay ED. Epidemiology of Kawasaki disease in Asia, Europe, and the United States. *J Epidemiol* 2012;22:79–85.
- [3] Hahn Y, Kim Y, Jo S, Han H. Reduced frequencies of peripheral interferon-gamma-producing CD4+ and CD4- cells during acute Kawasaki disease. *Int Arch Allergy Immunol* 2000;122:293–8.
- [4] Huang WC, Huang LM, Chang IS, Chang LY, Chiang BL, Chen PJ, et al. Epidemiologic features of Kawasaki disease in Taiwan, 2003–2006. *Pediatrics* 2009;123:e401–5.
- [5] Hirao J, Hibi S, Andoh T, Ichimura T. High levels of circulating interleukin-4 and interleukin-10 in Kawasaki disease. *Int Arch Allergy Immunol* 1997;112:152–6.
- [6] Brosius CL, Newburger JW, Burns JC, Hojnowski-Diaz P, Zierler S, Leung DY. Increased prevalence of atopic dermatitis in Kawasaki disease. *Pediatr Infect Dis J* 1988;7:863–6.
- [7] Matsuoka S, Tataru K, Nakagawa R, Mori K, Kuroda Y. Tendency toward atopy in Kawasaki disease. *Eur J Pediatr* 1997;156:30–2.
- [8] Liew WK, Lim CW, Tan TH, Wong KY, Tai BC, Quek SC, et al. The effect of Kawasaki disease on childhood allergies—a sibling control study. *Pediatr Allergy Immunol* 2011;22:488–93.
- [9] Webster RJ, Carter KW, Warrington NM, Loh AM, Zaloumis S, Kuijpers TW, et al. Hospitalisation with infection, asthma and allergy in Kawasaki disease patients and their families: genealogical analysis using linked population data. *Plos One* 2011;6:e28004.
- [10] Kuo HC, Chang WC, Yang KD, Yu HR, Wang CL, Ho SC, et al. Kawasaki disease and subsequent risk of allergic diseases: a population-based matched cohort study. *BMC pediatr* 2013;13:38.
- [11] Peng YW, Wei CC, Liang CC, Hsu CH, Klahan S, Huang YH, et al. Increased risk of atopic dermatitis in preschool children with Kawasaki disease: a population-based study in Taiwan. *Evid Based Complement Alternat Med* 2013;10:1–7.
- [12] Hwang CY, Hwang YY, Chen YJ, Chen CC, Lin MW, Chen TJ, et al. Atopic diathesis in patients with kawasaki disease. *J Pediatr* 2013;163:811–5.
- [13] Davis K, Huang AT. Learning from Taiwan: experience with universal health insurance. *Ann Intern Med* 2008;148:313–4.
- [14] Wei CC, Yu IW, Lin HW, Tsai AC. Occurrence of infection among children with nephrotic syndrome during hospitalizations. *Nephrology* 2012;178:681–8.
- [15] Tsai YJ, Lin CH, Fu LS, Fu YC, Lin MC, Jan SL. The association between Kawasaki disease and allergic diseases, from infancy to school age. *Allergy Asthma Proc* 2013;5:467–72.
- [16] Jason J, Gregg L, Han A, Hu A, Inge KL, Eick A, et al. Immunoregulatory changes in Kawasaki disease. *Clin Immunol Immunopathol* 1997;84:296–306.
- [17] Afzali B, Mitchell P, Lechler RI, John S, Lombardi G. Translational mini-review series on Th17 cells: induction of interleukin-17 production by regulatory T cells. *Clin Exp Immunol* 2010;159:120–30.
- [18] Furuno K, Yuge T, Kusuhara K, Takada H, Nishio H, Khajoo V, et al. CD25(+) CD4(+) regulatory T cells in patients with Kawasaki disease. *J Pediatr* 2004;145:385–90.
- [19] Simpson CR, Anderson WJ, Helms PJ, Taylor MW, Watson L, Prescott GJ, et al. Coincidence of immune-mediated diseases driven by Th1 and Th2 subsets suggests a common aetiology. A population-based study using computerized general practice data. *Clin Exp Allergy* 2002;32:37–42.
- [20] Kim JJ, Hong YM, Sohn S, Jang GY, Ha KS, Yun SW, et al. A genome-wide association analysis reveals 1p31 and 2p13.3 as susceptibility loci for Kawasaki disease. *Hum Genet* 2011;129:487–95.
- [21] Burgner D, Davila S, Breunis WB, Ng SB, Li Y, Bonnard C, et al. A genome-wide association study identifies novel and functionally related susceptibility loci for Kawasaki disease. *PLoS Genet* 2009;5:e1000319.
- [22] Tsai FJ, Lee YC, Chang JS, Huang LM, Huang FY, Chiu NC, et al. Identification of novel susceptibility loci for Kawasaki disease in a Han Chinese population by a genome-wide association study. *PLoS ONE* 2011;6:e16853.
- [23] Liao WL, Tsai FJ. Personalized medicine: a paradigm shift in healthcare. *BioMedicine* 2013;3:66–72.