Atopic Predilection among Kawasaki Disease Patients: A Cross-Sectional Study of 1,187,757 Teenagers

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Key Words

Kawasaki disease · Allergic rhinitis · Asthma · Angioedema · Urticaria

Abstract

Background: Kawasaki disease (KD) is an acute, systemic vasculitis in children, with an etiology that is not completely understood. It is assumed that the development of KD is mediated by an immunologic response. Several reports from East Asia have found a higher prevalence of atopic diseases among patients with KD, but a large-scale study of a non-Asian population regarding this correlation is still lacking. The purpose of this article was to achieve this goal. **Methods:** We conducted a cross-sectional, large-scale study to estimate the correlation of KD with allergic diseases. The medical history of 1,187,757 Israeli teenagers (aged 16–20 years during the years 1998–2013) was retrieved. The study population was divided into 3 groups according to a past history of noncomplicated and complicated KD and a control group. The prevalence of allergic diseases among these groups was further investigated. **Results:** The prevalence of atopic diseases in the 3 study groups was presented (asthma in 11.4,

8.1 and 3.5%, respectively; angioedema/urticaria in 7.1, 0 and 0.46%, respectively; allergic rhinitis in 20, 12.1 and 6.7%, respectively). In noncomplicated KD, a statistically significant link to asthma [odds ratio (OR) 2.4; $p = 0.048$] and a borderline significant link to allergic rhinitis (OR 1.9; $p = 0.06$) were found. In KD complicated with cardiac disease, statistically significant links were found for all the allergic conditions, asthma (OR 3.5; $p = 0.003$), allergic rhinitis (OR 3.5; $p < 0.001$) and angioedema/urticaria (OR 16.48; $p < 0.001$). **Conclusion:** KD is associated with allergic diseases. This association increases with the severity of the disease.

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Introduction

First described in 1967, Kawasaki disease (KD) is an acute, systemic vasculitis that occurs predominantly among children aged ≤ 5 years [1]. It affects the blood vessels, skin, mucous membranes and lymph nodes. The

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skin and mucous membranes become red and inflamed, the hands and feet swell, lymph nodes in the neck are often enlarged, and there is recurrent fever. Coronary artery aneurysms or ectasia develop in 15–25% of children with untreated disease and may lead to myocardial infarction, sudden cardiac death or ischemic heart disease, comprising the most deleterious complications [1–3]. In fact, KD is now the leading cause of acquired heart disease among pediatric populations in the developed world [2, 3].

The precise etiology of KD remains unknown, although clinical and epidemiological features, such as the wave-like, geographic spread with community outbreaks, strongly suggest a transmittable childhood infectious cause. However, efforts to identify an infectious agent with conventional bacterial and viral cultures or serological methods, as well as with animal inoculation, have failed [4, 5]. It may be that KD results from an immunologic response that is triggered by any of several different and yet unidentified microbial agents [6–9].

An alternative leading hypothesis involves a ubiquitous infectious agent that produces clinically apparent disease only in certain genetically predisposed individuals. In Israel, the estimated incidence of KD is 11.9/100,000 [10] in children <5 years of age, with a male-to-female ratio of 1.7:1, and a peak incidence in winter and spring. Among Asian populations, the incidence reported is much higher, ranging from 69 to 239/100,000 [6]. A hypothesis involving genetic predisposition is supported by the increased incidence of the disease among these populations, also when compared to European and American populations, where the estimated incidence rates are 5.8/100,000 [11].

Reports from East Asia have found a higher prevalence of atopic dermatitis, allergic rhinitis and asthma among children diagnosed with KD compared to the normal population [12–16]. However, to the best of our knowledge, large-scale studies regarding the incidence of allergic diseases occurring in KD patients are still lacking, especially regarding non-Asian populations.

The goal of this study was to evaluate the prevalence of allergic diseases among a heterogenic population of Israeli adolescents diagnosed with KD.

Methods

We conducted a cross-sectional study to estimate the epidemiologic relationship between KD and allergic diseases.

Source of Data

As part of the military preconscription assessment, most Israeli civilians undergo a routine medical evaluation and fitness-for-service classification at a prespecified age (usually 17 years). The medical evaluation includes questionnaires filled in by the candidate and his/her family practitioner as well as further tests and consultations as required. The result of this process is ≥ 1 fitness-for service (FFS) classification numerical codes indicative of a medical diagnosis.

From the conscripts' medical records, we retrieved demographic details and FFS codes. The presence of KD was determined by a corresponding numerical code and graded as complicated/noncomplicated. The meaning of complicated KD is that there was any kind of cardiac manifestation. The presence of asthma, allergic rhinitis and angioedema or chronic urticaria was also determined. Patients with chronic urticaria were assigned the same code as angioedema. We must emphasize that the group of patients with either angioedema or urticaria is problematic. These individuals were grouped together for technical reasons, and, unfortunately, we could not separate them into 2 groups. There were no data regarding atopic dermatitis.

The data were based on family practitioners' declarations of KD in the past. The data were gathered when the subjects were 17 years old, without knowledge, however, of their exact age when they had the illness. In addition, these same declarations were used in order to gather data regarding cardiac manifestations. We only had data according to the questionnaires regarding nonspecific cardiac manifestations without any further details. We must emphasize that the distinction between KD with or without cardiac manifestations was done retrospectively and without enough data as to the nature of the complications, medical therapy or timing. We still included the distinction in the study because we thought it was important to examine the data for each group separately, the assumption being that most cardiac manifestations were coronary aneurysms (without noting the medical treatment).

The study was approved by the Israeli Defense Forces' (IDF) institutional review board, and the subjects' anonymity was strictly kept. Socioeconomic status (SES) was one of the demographic features and was graded on a scale of 1–10 (lowest to highest).

Study Population

The study population included all Israeli teenagers who underwent medical evaluation by the IDF as part of the preconscription assessment during the years 1998–2013. We excluded all subjects who were younger than 16 years or older than 20 years at their medical evaluation.

Statistical Analysis

All data were summarized and displayed as mean ($\pm$ SD when applicable) for continuous variables and as number (or %) of patients in each group for categorical variables. Continuous variables were compared using the independent-samples *t* test or ANOVA (the Scheffé test was used for post hoc multiple comparisons) while categorical variables were compared using the χ^2 test and binary logistic regression models. Based on the presence of the corresponding FFS code, we divided the study population into 2 groups, i.e. cases (of the respective allergic condition tested) and controls (general population). We then divided both cases and controls into 2 groups of KD cases and controls in a similar manner, yielding a 2×2 table. We calculated the odds ratio (OR) for the presence of

Table 1. Characteristics and prevalence of diseases in the study cohort

Variable	Complicated KD	Noncomplicated KD	General population	p value ¹
Subjects, n	70	74	1,187,757	
Mean (SD) age at evaluation, years	17.43 (0.733)	17.51 (0.561)	17.32 (0.586)	0.001
Males, %	78.5	71.6	58.5	0.031
Mean (SD) SES	6.77 (1.553)	6.31 (1.743)	5.8 (1.675)	0.036
Mean (SD) BMI	22.2 (3.376)	22.62 (3.989)	22.11 (3.92)	0.267
Born in Israel, %	90	89.2	81.1	0.047
Asthma prevalence, %	11.4	8.1	3.55	0.048
Angioedema/chronic urticaria prevalence, %	7.1	0	0.46	1
Allergic rhinitis prevalence, %	20	12.1	6.7	0.06

¹ Calculated with a t test for the noncomplicated KD group versus the general population group.

Table 2. OR of cases of KD and allergic conditions compared to the general population group

	OR	CI	p value
<i>Noncomplicated KD</i>			
Asthma	2.391	1.038–5.51	0.048
Angioedema/chronic urticaria	0.995	0.995–0.995	1
Allergic rhinitis	1.918	0.955–3.852	0.06
<i>Complicated KD</i>			
Asthma	3.497	1.675–7.304	0.003
Angioedema/chronic urticaria	16.48	6.634–40.941	<0.001
Allergic rhinitis	3.464	1.928–6.222	<0.001
<i>All KD patients</i>			
Asthma	2.919	1.682–5.067	0.001
Angioedema/chronic urticaria	7.706	3.156–18.813	0.001
Allergic rhinitis	2.634	1.686–4.114	<0.001

the tested allergic condition between KD cases and controls. Confidence interval (CI) and statistical significance were calculated for the OR after adjusting for age and gender. A 2-tailed $p < 0.05$ was considered statistically significant. All analyses were performed with SPSS v21.0 software (SPSS Inc., Chicago, Ill., USA).

Results

Study Population

We examined the computerized military medical data of 1,187,757 Israeli adolescents for the years 1998–2013. Of these, 144 (0.01%) had KD, 74 of whom were classified as noncomplicated and 70 as complicated (table 1).

Significant differences were found in the demographic details of the KD group in comparison to the general population (controls). There was a larger percentage of males,

78.5 and 71.6% in the complicated and noncomplicated KD groups, respectively, compared to 58.5% in the general population. The SES was significantly higher in the KD groups, and a larger proportion of the KD groups was born in Israel. No statistically significant differences were found with regard to BMI in comparison to the general population.

Prevalence of Atopic Disease in the Study Cohort

The prevalence of asthma was higher in the KD group, 11.4 and 8.1% in the complicated and noncomplicated groups, respectively, in comparison to 3.55% in the general population. The prevalence of angioedema or urticaria was higher in the complicated KD group at 7.1%, in comparison to 0.46% in the general population. The prevalence of allergic rhinitis was 20% in the complicated KD group, 12.1% in the noncomplicated KD group and 6.7% in the general population.

Association of Various Allergic Conditions with KD

We examined the link between asthma, angioedema or allergic rhinitis and noncomplicated and complicated KD and compared it to the general population (table 2). In cases of noncomplicated KD, a significant link to asthma was discovered (OR 2.391; $p = 0.048$), and a nearly significant link to allergic rhinitis (OR 1.9; $p = 0.06$). No significant link was discovered between noncomplicated KD and angioedema/chronic urticaria. In the cases classified as complicated KD with cardiac complications, a statistically significant link was discovered to all the allergic conditions that were examined, i.e. asthma (OR 3.5; $p = 0.003$), allergic rhinitis (OR 3.5; $p < 0.001$) and angioedema/chronic urticaria (OR 16.48; $p < 0.001$).

Discussion

In this study, we evaluated the association between KD and allergic conditions in a large non-Asian population. The main findings of our analysis are: (1) the prevalence of KD in our cohort was 12.1/100,000, (2) SES was higher among KD patients in comparison to the general population, (3) there was a higher prevalence of atopic diseases among individuals with a history of KD, and (4) the link between KD and atopic diseases was more significant among the complicated KD cases.

The major strength of this study is the large and mostly unbiased study population forming the basis for the data we retrieved. Its weakness is the fact that mostly questionnaire data were used to characterize the clinical course of the patients. This can lead to a possible bias. We had no information on the type of KD cardiac complication, medical treatment or timing.

The association between KD and atopic diseases has been proven before, but for Asian populations only. Our study is the first to reveal that KD is linked to allergic diseases in a non-Asian population as well. In previous studies from Taiwan, Tsai et al. [12] found that KD patients aged 0–13 years had a higher prevalence of asthma, urticaria and allergic rhinitis. Kuo et al. [13] reported an increased risk for atopic diseases among KD patients, with the highest hazard ratio being 1.5 among asthma patients; however, the OR reported by Liew et al. [14] is more similar to our findings at 3.75 for any allergy among KD patients. Our higher OR could be attributed to the lack of chronological insight as well as to the large sample size.

We further proved that this link is associated with the severity of KD, as complicated KD patients were more prone to allergic diseases compared to noncomplicated KD

patients. To the best of our knowledge, this is the first study to examine the link to allergic diseases among subjects with the noncomplicated and the complicated forms of KD.

Since our study was designed as a cross-sectional study, we cannot determine whether the KD preceded the atopic disease or vice versa. Webster et al. [15] showed that atopic tendency existed prior to the onset of KD and was also persistent among family members of KD patients. Wei et al. [16] reported the OR for developing KD among atopic patients. In their study, patients with urticaria had the highest risk, followed by patients with allergic rhinitis and atopic dermatitis (OR 1.8, 1.44 and 1.22, respectively).

The underlying etiology or mechanism for this association between KD and atopic disease is not completely understood. Despite intensive studies, the analysis of T-cell functions in KD has shown variable and often conflicting results [16–18]. Th1 cells activate macrophages and cytotoxic T cells while Th2 cells initiate humoral immunity and allergic inflammation. Th1 and Th2 have a reciprocal effect on each other. There is still not enough information regarding a possible mechanism related to T-cell activation that links the inflammatory process in KD to allergies. Studies exploring the immune system of KD patients have reported mutations in the mannose-binding lectin gene, a part of the innate immune system, as holding a potential role for developing KD [19, 20]. Of note are the increased levels of IgE and eosinophilia that were found in the peripheral blood of KD patients [17, 21].

Matsuoka et al. [18] investigated environmental risk factors for developing allergic diseases, and found higher rates of smoking among KD patients which can predispose patients to allergic diseases. However, the paradox reported in the same study was the higher rates of household pets among KD patients, which is thought to be a protective factor against asthma according to the 'hygiene hypothesis'.

Other studies reported increased levels of matrix metalloproteinase in both asthma and KD patients [22, 23]. There is also a possible bias regarding health-seeking patterns among KD patients compared to the general healthy population, which may render overdiagnosis of allergic diseases when making comparisons.

Our study has several limitations. Most were mentioned earlier in this paper. The main limitation is that data were based on personal questionnaires and reviewing of past medical records, so inaccurate data may have led to a possible misclassification of the relevant diseases. However, since we used a large database, it is reasonable to assume that this limitation would have only a minor effect on the results.

As discussed above, based on our cross-sectional study, we could not ascertain whether allergy is a long-term complication of KD or a prior phenomenon with an established link. Furthermore, we have no data regarding the treatments that were given for the KD patients, and the potential effects these might have for developing allergic diseases. We could also not differentiate the link to angioedema and chronic urticaria into 2 separate groups.

Last, we must mention that there is a contradiction between our data regarding the prevalence of atopic diseases in the general population and previous studies that were conducted in Israel [24–26]. A possible explanation can be that our data were based only on the population

eligible for military service. There are no data on patients who emigrated from Israel at an early age, died of the illness or were conscientious objectors.

While more facts are being elucidated, the exact pathophysiology of KD remains an enigma. The unidentified infectious agents, the strong genetic predilection even though low familial incidence rates are reported as well as the clear relationship with atopic diseases in KD cases and in their family members, all point towards a multifactorial mechanism. Further research is required for better understanding of this disease. The caring physician should be alert to the link between KD and allergic diseases, and conduct proper follow-up and tests as needed.

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