



ORIGINAL ARTICLE

# Analysis of serum total IgE, specific IgE and eosinophils in children with acute and chronic urticaria

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## KEYWORDS

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**Background/Purpose:** Increased IgE and eosinophil levels are frequently observed in cutaneous inflammation and are thought to provoke the occurrence of urticaria. However, the relationship of these factors with the disease duration of urticaria remains unclear. The aim of this study was to compare serum total IgE levels, specific IgE sensitization rates and eosinophil percentages between acute and chronic urticaria in children.

**Methods:** A total of 165 patients (104 with acute and 61 with chronic urticaria) from a tertiary referral hospital were enrolled in this study. Serum levels of total IgE, prevalence of sensitization to food and aeroallergens and blood eosinophil percentages were compared by the disease duration of urticaria.

**Results:** There were no statistical differences in total IgE production, positive sensitization to specific allergens and eosinophil percentages between the patients with acute and chronic urticaria. There is a higher prevalence of sensitization to aeroallergens than food allergens in children with urticaria. In terms of gender, males had significantly higher serum IgE levels than females.

**Conclusion:** Boys potentially have a higher serum IgE expression than girls children with urticaria. IgE levels and eosinophil percentages are not good indicators for a prolonged course of urticaria. The prevalence of sensitization to aeroallergens was significantly higher than that

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of food allergens in children with urticaria. Routine laboratory analysis for common allergens is not appropriate, and it could be a feasible approach to detect a predilection for atopy when respiratory infections are causative factors of urticaria occurrence.

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## Introduction

Urticaria is an allergic skin disease that affects 15% to 25% of the population at some point in their life.<sup>1,2</sup> It is characterized by the appearance of transient wheals, which may be accompanied by angioedema. Wheals are edematous skin lesions of variable size with well-demarcated surrounding reflex erythema. Individual rashes usually last for minutes or a few hours and rarely persist for up to 24 hours. Itch is the dominant symptom. Angioedema appears as pronounced swelling of subcutaneous tissue, with a predilection for the periorbital and perioral areas and may involve mucous membranes. Pain is sometimes complained of rather than itching, with a slower resolution time of up to 72 hours compared to wheals.<sup>3</sup>

Urticaria can either occur acutely or evolve in a chronic mode. Acute urticaria is defined as wheals presenting for less than 6 weeks, whereas chronic urticaria means a duration lasting beyond 6 weeks.<sup>3</sup> A variety of studies have indicated that urticaria results from a complex pathophysiology involving multiple inflammatory pathways, which explains the wide heterogeneity of clinical symptoms and the variable therapeutic responsiveness.<sup>4,5</sup> However, the exact mechanisms contributing to the different clinical manifestations remain obscure.

The natural history of acute and chronic urticaria is particularly important because different treatment modalities vary with the disease course. IgE-mediated mast cell activation is regarded as the major immunologic pathway in acute urticaria. In chronic urticaria, the auto-immune dimension became apparent when Greaves et al<sup>6</sup> identified specific IgG antibodies for the  $\alpha$ -chain of the high-affinity IgE receptor (Fc $\epsilon$ RI $\alpha$ ) in patients. This auto-immune origin represents at least 30% to 50% of patients with chronic urticaria,<sup>6,7</sup> suggesting that IgG auto-antibodies rather than IgE contribute to the occurrence of chronic forms. However, reports on the possible association between the clinical course and IgE are very limited.

Eosinophils are also proposed to play a key role and contribute to tissue damage in urticaria. The crucial potential of eosinophils in the inflammatory process of urticaria is supported by the association of urticarial skin lesions in individuals with eosinophilic disorders, such as hyper-eosinophilic syndrome. Although there is strong evidence in the literature supporting the role of eosinophils in urticaria, few reports exist concerning children, and little is known about the influence on sustained disease course. To investigate the relationship of IgE and eosinophils with the disease course of urticaria in children, we carried out a comparison of these factors between children with acute and chronic urticaria.

## Methods

### Patients and study design

Children who visited the pediatric allergy or dermatologic clinic of National Taiwan University Hospital between May 2002 and August 2006 with a diagnosis of urticaria were included in this study. Those with comorbidities of other major systemic diseases were excluded. A total of 165 children were enrolled in this study, with a mean age of  $7.61 \pm 4.64$  years (range 1–17 years). The patients were classified as either acute or chronic urticaria. Acute urticaria was defined by the recurrence of the lesions over a time period of less than 6 weeks, while chronic urticaria was defined as wheals that had been continuously or intermittently occurring for at least 6 weeks.<sup>3</sup> Serum total IgE levels, positive sensitization rates of specific IgE antibodies, and eosinophil percentages were compared between the two groups.

### Total IgE and specific IgE antibodies

Venous blood samples were obtained from the study patients on their clinic visit. Sera were separated by centrifugation and analyzed for concentration of total IgE or specific IgE antibodies. Thirty-nine types of specific IgE antibodies, including 23 to inhalant and 16 to food allergens, were assayed. Serum levels of total IgE (kU/L) were determined by the commercial ImmunoCAP250 system (Pharmacia, Uppsala, Sweden), while those of specific IgE antibodies (kU/L) by the ImmunoCAP250 system or MAST Immunosystems (Hitachi, Kernersville, NC, USA) according to the manufacturer's instructions. The sensitivity of the assay for total IgE detection was between 2 kU/L and 5000 kU/L. Sensitization rates to specific allergens were regarded as positive if at least one of the results of specific IgE against the selected allergen was  $\geq 2+$ , with values  $>0.7$  kU/L in the CAP test or  $>2.5$  kU/L in the MAST test.

### Statistical analysis

Total IgE levels were converted to  $\log_{10}$  and expressed as geometric means for comparison by the Student's *t* test between different groups. IgE levels too small to be detected ( $<2$  kU/L) were ascribed a value of 1 kU/L for log transformation; there was only one such instance in the chronic group. The Chi-square test was used to analyze differences of sensitization rates to specific allergens, and proportions of elevated eosinophil percentages between the acute and chronic groups. Statistical significance of

eosinophil percentage between the two groups was measured using the Mann-Whitney test. Results were considered significant if the  $p$  value was  $<0.05$ . All of the statistical analyses were performed with SPSS version 13.0 for Windows (SPSS Inc., Chicago, IL, USA).

## Results

Among the 165 study patients, 104 had acute and 61 chronic urticaria. The mean age at time of blood sampling was  $6.39 \pm 4.04$  years in the acute group and  $9.70 \pm 4.88$  years in the chronic group. The age distribution in the two groups is shown in Table 1. The enrolled children had an approximately 1:1 female to male ratio, which continued through the two groups (Table 1). The frequency of the patients with a personal history of other allergic diseases (allergic rhinitis, asthma, and atopic dermatitis) was similar between the acute and chronic groups (Table 1), and the most common disease was allergic rhinitis in both groups.

Total serum IgE levels of our samples ranged from undetectable (read as  $<2$  kU/L) to 2000 kU/L. Sixty-two percent of the acute group and 41.67% of the chronic group had levels of  $\leq 150$  kU/L, and 11.54% of the acute group and 21.3% of the chronic group had levels  $>500$  kU/L. Less than 10% of the levels exceeded 1000 kU/L in either group. The overall distribution of total IgE values in the acute and chronic groups showed a marked skew to the right (Fig. 1). Following logarithmic conversion the distribution of values became Gaussian, with a significantly higher geometric mean of 159.58 kU/L in the chronic group compared to 94.25 kU/L in the acute group ( $p < 0.05$ ) (Table 2). The patients were then classified into two distinct subgroups according to whether there were other allergic diseases exit, and a significantly higher IgE levels in the chronic group than that in the acute group was found in the subgroup of patients without other allergic diseases ( $p < 0.05$ ) (Table 2).

We further divided the patients into subgroups by age to assess differences of total IgE levels between the acute and chronic groups. As might be anticipated, total IgE levels had a trend of increasing with age. This age-related rise was

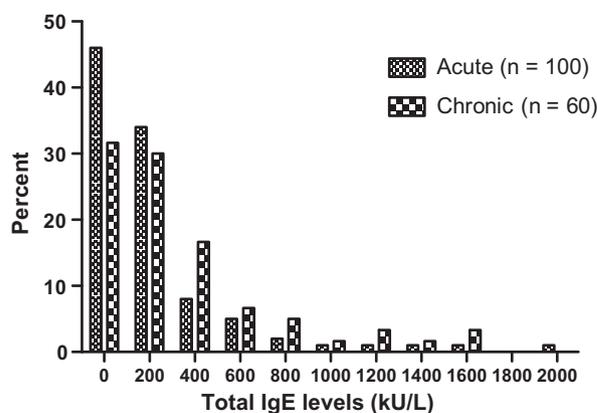


Figure 1. Arithmetic distribution of serum total IgE in the acute and chronic groups.

steeper and reached higher levels in the chronic group (Fig. 2). Although a higher mean IgE level in the chronic group compared to the acute group was apparent in the 13 years to 18 years group, it did not show statistical significance (Table 2).

We also compared total IgE concentrations by gender, and found that males had a greater geometric mean value than females (164.24 kU/L,  $n = 82$  in males vs. 78.82 kU/L,  $n = 78$  in females,  $p < 0.05$ ) (Fig. 3).

Thirty-nine specific IgE antibodies to inhaled or food allergens were documented by MAST or CAP test. The MAST/CAP tests ratio was 20/79 (0.25) in the acute group and 6/50 (0.12) in the chronic group. Fifty out of 99 (50.5%) subjects in the acute group and 31 out of 56 (55.4%) subjects in the chronic group had positive sensitization rates. There were no significant differences between the two groups ( $p = 0.561$ ; Table 3). We further compared the prevalence of sensitization to specific allergens between the acute and chronic groups within the subgroups of patients with and without other allergic diseases separately, and they were also not statistically different (Table 3). With regards to the rates of positive sensitization to inhaled and food allergens separately, there were no statistical differences between the acute and chronic groups (Table 3). The prevalence of sensitization to aeroallergens was significantly higher than that of food allergens in both the acute and chronic groups ( $p < 0.05$ ) (Table 3), with the highest prevalence and mean values of specific IgE to mite allergens in both groups (sensitization to Der p and Der f = 37.4% and 39.4%, respectively, in the acute group, and 47.3% and 49.1%, respectively, in the chronic group). Among the food allergens tested, milk was the most common allergen in the acute group (9 patients).

To compare the significance of eosinophil percentage between the acute and chronic groups, 84 and 54 patients were included, respectively, and the results showed no statistical difference (median of 2.1% in the acute group vs. 2.0% in the chronic group,  $p = 0.836$ ; Fig. 4). The proportion of patients with elevated eosinophil percentages was also analyzed and compared between the two groups. The upper normal limit was set at 5%. A great majority of values lay within the normal range, with only 12 (14.3%) subjects in the acute group and 7 (13%) subjects in the chronic group with values exceeding the reference range. There was no

Table 1 Demographic characteristics of the study populations in the acute and chronic groups

Characteristics	Acute ( $n = 104$ ) No. (% of total)	Chronic ( $n = 61$ ) No. (% of total)
<b>Sex</b>		
Male	50 (48)	33 (54)
Female	54 (52)	28 (46)
<b>Age (years)</b>		
1–3	24 (23)	8 (13)
3–7	40 (38)	9 (15)
7–13	30 (29)	25 (41)
13–18	10 (10)	19 (31)
<b>Other allergic diseases</b>		
(–)	64 (61.5)	40 (65.6)
(+)	40 (38.5)	21 (34.4)

**Table 2** Age-specific geometric mean IgE levels in the acute and chronic groups

	Acute		Chronic	
	No.	Geometric mean IgE $\pm$ SD (kU/L)	No.	Geometric mean IgE $\pm$ SD (kU/L)
<b>Total</b>	100	94.25 $\pm$ 4.38	60	159.58 $\pm$ 4.43*
<b>Other allergic diseases (-)</b>	60	77.02 $\pm$ 4.13	39	139.43 $\pm$ 3.94*
<b>Other allergic diseases (+)</b>	40	127.58 $\pm$ 4.61	21	205.03 $\pm$ 5.45
<b>Age (years)</b>				
1-3	23	50.73 $\pm$ 3.41	8	58.67 $\pm$ 6.81
3-7	38	52.90 $\pm$ 3.74	9	75.78 $\pm$ 6.40
7-13	29	203.23 $\pm$ 3.60	24	151.37 $\pm$ 3.20
13-18	10	200.89 $\pm$ 6.57	19	369.92 $\pm$ 2.86

\* $p < 0.05$  compared with the acute group.

statistical difference between the two groups ( $p = 0.826$ ; Table 3).

## Discussion

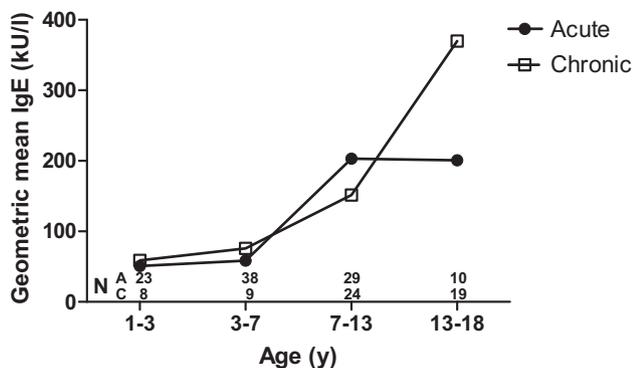
Urticaria occurred equally in both sexes in our study, which is different from previous studies based on the general population or adults, where urticaria occurred more commonly in females than in males.<sup>8,9</sup> It has been established that sex hormones can play a part in the pathogenesis of many diseases and account for differences in the prevalence of diseases between genders. A lack of sex hormone stimulation before puberty may provide a partial explanation for the discordant results in our study. More patients and a younger mean age in the acute urticaria group correspond to previous studies, where acute urticaria was found to be a more frequent type than chronic urticaria in childhood.<sup>10,11</sup> Because our hospital is a tertiary referral center, more patients with severe and prolonged skin lesions may have come to our clinic. We postulate that the frequency of chronic urticaria is higher in our study and it does not reflect the prevalence in the general population.

Our estimates of serum total IgE levels demonstrated a wide distribution, with higher geometric mean levels than those previously reported based on nonallergic children.<sup>12-14</sup> This implies a pathogenic role of IgE in urticaria. The results also showed significantly higher IgE mean levels in the chronic group compared to the acute group, which

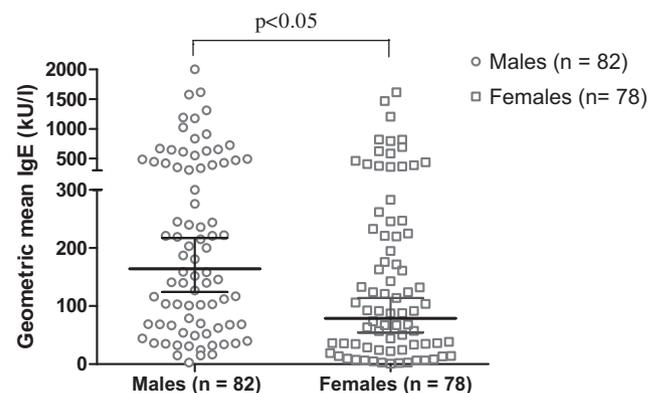
continued through the subgroup of patients without other allergic diseases. Although chronic urticaria is usually regarded as non-IgE mediated, previous studies reported that total IgE was elevated among chronic urticaria patients compared to normal controls.<sup>15,16</sup> Kessel et al<sup>16</sup> also found that total IgE was associated with disease severity and duration, and suggested that IgE should be considered as a marker to evaluate chronic urticaria patients. Additional studies should be conducted to clarify the pathogenic role of IgE in chronic urticaria and thus provide a basis for directing therapeutic strategies.

The mean levels of total IgE in patients with acute urticaria in our study are similar to a previous report based on general population samples where values rose steadily from birth to age approximately 10 years.<sup>17</sup> A steeper rise of IgE levels after puberty was noted in our chronic group. An older mean age in the chronic group may have contributed to the higher IgE expression compared the acute group, while there were no significant differences in IgE levels in the age subgroups between the two groups.

Our finding of a significant tendency for total IgE levels to be higher in males than in females was in keeping with other reports.<sup>14,18-22</sup> Because females predominate in autoimmune diseases,<sup>23</sup> a greater pathogenic role of the autoimmune component rather than IgE in the disease process for females may explain this sex difference. The different immune competence encountered between



**Figure 2.** Age-specific geometric mean IgE levels in the acute (●) and chronic (□) urticaria patients.



**Figure 3.** Geometric IgE levels in the male (○) and female (□) groups. The thick bars represent the geometric means, and the thin bars represent the 95% CI.

**Table 3** Positive sensitization rates to inhaled and food allergens and frequency of elevated eosinophil percentage in the acute and chronic groups

	Acute	Chronic	<i>p</i> value
<b>Sensitization rate</b>			
Total	50/99 (50.5%)	31/56 (55.4%)	0.561
Aeroallergens	44/99 (44.4%)*	27/55 (49.1%)*	0.579
Food allergens	14/99 (14.1%)	9/56 (16.1%)	0.745
Other allergic diseases (-)			
Aeroallergens	23/60 (38.3%)*	16/35 (45.7%)*	0.481
Food allergens	8/60 (13.3%)	4/36 (11.1%)	0.750
Other allergic diseases (+)			
Aeroallergens	20/39 (51.3%)*	11/20 (55%)	0.787
Food allergens	7/39 (17.9%)	5/20 (25%)	0.524
Elevated eosinophil percentage	12/84 (14.3%)	7/54 (13.0%)	0.826

\*  $p < 0.05$  compared with food allergens.

genders also reflects a complex and diverse pathogenic role of IgE expression.

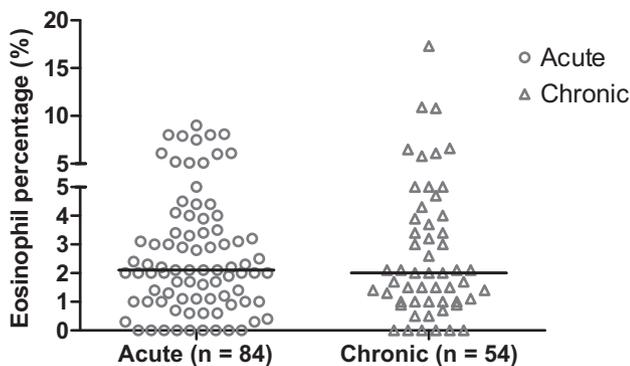
Few data are available concerning the relationship of sensitization prevalence to common allergens with the disease duration of urticaria. We tried to identify their association but failed to detect significant differences between the two groups. There were also no differences with regards to the proportion of sensitization to inhaled and food allergens between the acute and chronic groups, which reflects the lack of tendency of sensitization to ingested or aeroallergens in both groups. Although several studies have obtained significant correlations between the results of the MAST and CAP systems, the CAP test tended to have better sensitivity.<sup>24-26</sup> The lower ratio of the CAP/MAST tests in the chronic group than that of the acute group may result in underestimation of the sensitization rates of the chronic group.

Urticaria is regarded to be induced by ingested allergens much more frequently than inhalants, and IgE-mediated allergies to food are the most common cause of the acute form. This study showed discordant results in that there

was a significantly higher prevalence of sensitization to aeroallergens than food allergens both in the acute and chronic group. Previous studies have shown that various infections, especially viruses or mycoplasma related respiratory infections, were most the frequently documented etiologies of acute urticaria in children,<sup>10,27,28</sup> and suggested to perform a detailed survey for infectious agents in urticaria patients with febrile episodes, respiratory tract symptoms or poor responses to antihistamine treatment. Numerous studies also reported that several viral and mycoplasma infections may promote allergic respiratory inflammation in children.<sup>29,30</sup> Therefore, we can suppose that the results of a significantly higher sensitization rate to aeroallergens than food allergens in both the acute and chronic groups could be the outcome of airway allergic sensitization evoked by those respiratory infections, which also trigger urticaria occurrence. It further implies that routine laboratory screening for common allergens to discover the cause leading to urticaria is not appropriate. It might be more feasible to consider the test results as an index of atopy when respiratory infections are associated with urticaria occurrence.

Eosinophils have been suggested to be implicated in urticaria,<sup>31-35</sup> and a definite rise in eosinophil counts during the acute stage of urticaria has been illustrated.<sup>36</sup> However, a lack of peripheral blood eosinophilia and a total absence of eosinophils in patients with chronic urticaria have also been reported.<sup>37-39</sup> These conflicting results demonstrate the complex role of eosinophils in urticaria. We did not find a statistical difference in eosinophil percentage between the acute and chronic groups, and the proportion of patients with an elevated eosinophil percentage also did not differ significantly between the two groups. Our results are different from a previous study in which the percentage of cytoplasmic vacuolation of circulating eosinophils was significantly increased in the long-duration group compared with the short-duration group in urticaria.<sup>40</sup> Another study also revealed that up-regulation of chemoattractant receptor-homologous molecules (CRTH2) on eosinophils was observed in chronic but not acute urticaria patients.<sup>41</sup> Leiferman et al<sup>42</sup> reported that the deposition of localized eosinophil granule proteins is greatly out of proportion to the number of identifiable cells in dermatologic diseases, and suggested that eosinophil involvement in cutaneous diseases can not be judged by the number of intact eosinophils in the tissue. They further suggested that exploring the granule constituents liberated from infiltrating eosinophils or surface molecules expressed as an indicator of eosinophil activation might be a better marker of eosinophil involvement.

In conclusion, boys potentially have a higher serum IgE expression than girls with urticaria. IgE levels and eosinophil percentages are not good indicators for a prolonged course of urticaria. A higher prevalence of sensitization to aeroallergens than food allergens was found in children with urticaria. The prevalence of sensitization to aeroallergens was significantly higher than that of food allergens in children with urticaria. Routine laboratory analysis for common allergens is not appropriate, and it could be a feasible approach to detect a predilection for atopy when respiratory infections are the causative factors of urticaria occurrence.



**Figure 4.** Eosinophil percentage in the acute (○) and chronic (△) groups. Bars show the median.

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