

Allergic Comorbidity of Asthma or Wheezing, Allergic Rhinitis, and Eczema: Result From 333 029 Allergic Children in Shanghai, China

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Abstract

Background: Allergic diseases have become a worldwide public health concern. A defining feature of allergic diseases is they often coexist in children from birth to adolescence.

Objective: To investigate the prevalence of comorbid allergic diseases in allergic children in Shanghai, China.

Methods: A retrospective study of 333 029 children diagnosed with allergic diseases aged 0 to 12 years (mean age: 3.04 years, 59.3% boys) was conducted using the electronic medical records of Shanghai Children's Hospital from January 2013 to July 2018. Comorbidity of allergic diseases is defined as the coexistence of 2 or 3 following diseases in the same child such as asthma (AS)/wheezing, allergic rhinitis (AR), or eczema (EC).

Results: The proportion of children with comorbid allergic diseases was 6.7% (22 351/333 029). Among them, EC + AS/wheezing was the most common (61.3%, 13 711/22 351). Children with a comorbidity had significantly earlier disease onset age than subjects with only 1 disease (2.72 vs 3.06, $P < .05$). The serum total immunoglobulin E (IgE) levels of children with comorbid allergic diseases were higher than those with only 1 disease. In children with a disease onset age of 0 to 9 years, the levels of IgE for children with AS/wheezing + EC were higher than children with AS/wheezing only or EC only; in children with disease onset age of 2 to 5 and 10 to 12 years, the levels of IgE for children with AS/wheezing + AR were higher than children with AS/wheezing only or AR only; in children with a disease onset age of 2 to 5 years, the levels of IgE for children with AR + EC were higher than children with AR only or EC only.

Conclusion: Comorbidity of allergic diseases is common in children in Shanghai, China. The onset age of comorbidity is earlier than that of only 1 disease, and the levels of serum IgE are higher in patients with an allergic comorbidity.

Keywords

comorbidity, asthma, wheezing, allergic rhinitis, eczema

Introduction

Due to their increasing prevalence and complex pathogenic mechanism, allergic diseases have become a worldwide public health concern.¹ Allergic diseases have affected a substantial number of people worldwide, resulting in significant health-care burden and productivity loss.² Notably, a defining feature of allergic diseases is that these diseases often coexist in children from birth to adolescence.³ Recently, a term named “the atopic march” has attempted to explain the extensive comorbidity of atopic diseases, proposing that eczema (EC) precedes the occurrence of allergic rhinitis (AR)

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and asthma (AS).⁴ However, the development of allergic diseases does not simply follow this pattern. An opposing concept, namely, “coexistence” of comorbid allergic diseases, was also proposed.^{3,5} A German Multicenter Allergy Study indicated that the occurrence of only EC in early life would not cause an allergic march but that the coexistence of EC and wheezing would predict AS.⁵ Allergic diseases should not be studied as single⁶ entities, exploring their coexistence with other conditions may be of great help for disease management, especially in children.

The prevalence of allergic comorbidity in European and North American pediatric patients has been reported in the literature.^{3,5} However, a similar study is currently lacking in the Chinese pediatric population. Here, following The Strengthening the Reporting of Observational Studies in Epidemiology statement, we conducted a single-center retrospective study to evaluate the allergic disease comorbidities of children in Shanghai, China, by using the electronic medical records (EMRs) of Shanghai Children’s Hospital from January 2013 to July 2018.

Methods

Selection and Description of Participants

The study subjects were children diagnosed with AS/wheezing, AR, or EC from January 2013 to July 2018 in Shanghai Children’s Hospital, a tertiary care center that recently passed the Healthcare Information and Management Systems Society stage 7 certification.

The diagnosis of allergy was based on the results of positive skin prick tests or specific immunoglobulin E (IgE) levels during patient visits. These cases were diagnosed by clinicians in either outpatient visits or emergency consultations at the hospital. The physicians were all clinically experienced. For children who received treatment before 2015, doctors diagnosed them with AS/wheezing according to the criteria of the Global Initiative for Asthma (GINA) report from 2006.⁷ For children who received treatment after 2015, doctors diagnosed them with AS/wheezing according to the criteria of the GINA report from 2015.⁸ Wheezing arising from bronchiolitis and other comorbid conditions (eg, cardiac disorders, anatomical malformations, or other pulmonary diseases) were specifically excluded. For children who received treatment before 2016, doctors diagnosed them with AR according to the criteria of the ARIA report from 2010.⁹ For children who received treatment after 2016, doctors diagnosed them with AR according to the criteria of the Allergic Rhinitis and its Impact on Asthma (ARIA) report from 2016.¹⁰ For children who received treatment before 2014, doctors diagnosed them with EC according to the criteria published in 2003.¹¹ For children who received treatment after 2014, doctors diagnosed them with EC according to

the criteria published in 2014.^{12–15} In our study, comorbidity was defined as the coexistence of 2 or 3 of the following diseases in the same child: AS/wheezing, AR, or EC.^{16–18}

A 2-step approach was used to identify our subjects. First, all patients with AS/wheezing, AR, or EC were identified by using a coding framework composed of International Classification of Diseases-10 (ICD-10) disease codes. Second, for patients with multiple visits, we chose the record from the first visit for the same disease. For patients with different allergic diseases, we combined their clinical records. The onset age of the diseases and the patient’s sex were collected from the patients’ first set of EMR.

Measurement of Serum Total IgE Concentrations

Serum total IgE (tIgE) concentrations were tested by using a Siemens BNIII-specific protein analyzer in the clinical laboratory of Shanghai Children’s Hospital. According to the diagnostic standards of the clinical laboratory, serum tIgE concentrations below 15 IU/mL are negative at an onset age of 0 to 1 year old, below 60 IU/mL are negative at an onset age of 2 to 5 years old, below 90 IU/mL are negative at an onset age of 6 to 9 years old, and below 200 IU/mL are negative at an onset age of 10 to 12 years old. Thus, our study population was divided into 4 groups corresponding to the different diagnostic standards for serum tIgE concentrations. We also excluded other diseases that can lead to an increase in tIgE level such as parasite diseases and so on.¹⁹

Our study protocol was approved by the Institutional Review Board of Shanghai Children’s Hospital (No. 2018R049-E01). Considering that the present study did not recruit any subjects and objectively could not obtain informed consent from the previous subjects, this study was exempt from obtaining informed consent by the Institutional Review Board of Shanghai Children’s Hospital.

Statistics

Continuous variables were described using means and standard deviations (SDs) for normally distributed data or using medians and interquartile ranges (IQRs) for nonnormally distributed data. Categorical variables were described using frequency. A normality skewness and kurtosis test were performed, and it showed that the distribution of age was normal and the distribution of tIgE at different age groups was skewed. A *t* test was used to compare the difference in the children’s onset age between comorbidity and 1 allergic disease only. Nonparametric tests were used to compare the differences in serum tIgE concentrations between comorbidity

and 1 allergic disease only. Two-tailed P values $< .05$ were regarded as statistically significant. All of the data processing and statistical analyses were performed with SAS version 9.4 software (SAS Institute, Cary, NC).

Results

In total, 333 029 children who were diagnosed with AS/wheezing, AR, or EC in Shanghai Children's Hospital from January 2013 to July 2018 were included in our study, and 59.3% were boys. The mean age was 3.04 years (SD, 2.79 years). The prevalence of children with 1 allergic disease, 2 comorbid diseases, and 3 comorbid diseases was 93.3% ($n=310\ 678$), 6.3% ($n=21\ 057$), and 0.4% ($n=1\ 294$), respectively. When there was only 1 allergic disease, EC was the most common disease (63.1%, $n=196\ 080$), followed by AS/wheezing (29.9%, $n=92\ 937$) and AR (7.0%, $n=21\ 661$). When there was comorbidity, AS/wheezing plus EC (AS/wheezing + EC) was the most common comorbidity (61.3%, $n=13\ 711$, Table 1). The distribution of allergic diseases in our study population is presented in Figure 1. In addition, the distribution of allergic diseases in different onset age groups was also calculated (Figure 2). The EC was the most common allergic disease in children with an onset age of 0 to 1 years old; AR was the most common allergic disease in children with an onset age of 2 to 5 years old. The proportion of AS/wheezing only, AR only, or EC only changed greatly in different onset age groups, but the percentage of children with a comorbidity was relatively stable among groups, merely varying from 4.6% (onset age-group of 2–5 years old) to 8.4% (onset age-group of 10–12 years old).

Differences in the onset age between children with comorbidity and children with only 1 allergic disease were assessed (Table 2). We found that children with comorbidity had a mean onset age of 2.72 years (SD, 2.53 years), which was significantly earlier than those with only 1 allergic disease (3.06 years old, SD, 2.80 years, $P < .05$).

Nonparametric tests were used to compare the differences between serum tIgE concentrations of children with an allergic comorbidity and those with only 1 disease (Table 3). In children with onset age of 0 to 1, 2 to 5, and 6 to 9 years, serum tIgE levels for those with AS/wheezing + EC were significantly higher than those of children with AS/wheezing only or EC only ($P = .036$ in 0–1, $P = .041$ in 2–5, $P = .028$ in 6–9). In children with onset age of 2 to 5 and 10 to 12 years, serum tIgE concentrations of children with AS/wheezing + AR were found to be significantly higher than those of children with AS/wheezing only or AR only ($P = .047$ in 2–5, $P = .039$ in 10–12). In children with an onset age of 2 to 5 years, serum tIgE levels of children with AR + EC were significantly higher than those of children with AR

Table 1. Characteristics of our Study Subjects.

	AS/Wheezing Only			AR Only			EC Only			AS/Wheezing + AR			AS/Wheezing + EC			AR + EC			AR + AS/Wheezing + EC		
	Mean (SD) or Median (IQR) or No. (%)			Mean (SD) or Median (IQR) or No. (%)			Mean (SD) or Median (IQR) or No. (%)			Mean (SD) or Median (IQR) or No. (%)			Mean (SD) or Median (IQR) or No. (%)			Mean (SD) or Median (IQR) or No. (%)			Mean (SD) or Median (IQR) or No. (%)		
Sex																					
Boys	62 094 (66.8)			14 065 (64.9)			109 995 (56.1)			2 549 (67.1)			5 937 (43.3)			2 068 (58.3)			889 (68.7)		
Girls	30 843 (33.2)			7 596 (35.1)			86 085 (43.9)			1 248 (32.9)			7 774 (56.7)			1 481 (41.7)			405 (31.3)		
Onset age, years ^a																					
Continuous	4.23 (2.59)			5.89 (2.61)			2.20 (2.65)			4.76 (2.43)			2.14 (2.12)			2.97 (2.80)			2.20 (2.21)		
0–1	28 434 (30.6)			495 (2.3)			115 003 (58.6)			187 (5.0)			7 111 (51.9)			775 (21.8)			297 (23.0)		
2–5	48 658 (52.4)			10 290 (47.5)			55 821 (28.5)			2 456 (64.7)			5 506 (40.1)			1 806 (50.9)			824 (63.6)		
6–9	12 313 (13.2)			8 386 (38.7)			19 391 (9.9)			914 (24.1)			958 (7.0)			803 (22.6)			147 (11.4)		
10–12	3 532 (3.8)			2 490 (11.5)			5 865 (3.0)			240 (6.2)			136 (1.0)			165 (4.7)			26 (2.0)		

Abbreviations: AR, allergic rhinitis; AS, asthma; EC, eczema; IgE, immunoglobulin E; IQR, interquartile range; SD, standard deviation.

^aOur subjects were classified into 4 groups according to their onset ages because the diagnostic criteria of serum total IgE concentrations are different among different onset age groups.

only or EC only ($P = .019$). However, no significant differences in serum tIgE concentrations of children with 3 comorbid diseases (AS/wheezing + AR + EC) were observed in any onset age-group.

Discussion

Our study attempted to explore the prevalence of allergic comorbidity in Chinese allergic children. Several studies have been conducted in some of the other cities in China previously, focusing on the incidence and risk factors of a single allergic disease (AS, AR, and EC).^{20–22} For example, previous studies conducted in China found that the prevalence of AS was between 2.9% and 7.5%, the prevalence of AR was between 9.8% and 31.1%, and the prevalence of EC was between 2.0% and 20.6% among children.^{20–22} In a study conducted by Zhao et al., the coexistence of AS, AR, and EC was observed in the same

child.²¹ In our study, we found that the prevalence of allergic comorbidity was 6.7%. Our research suggests that in children with AS/wheezing, AR, or EC, 6.7% of children have more than 2 allergic diseases. Our study is of great significance for understanding the prevalence of allergic comorbidity in allergic children in China.

In this study, the onset age of comorbidity in children (ie, the age of their first diagnosed allergic disease) was significantly earlier than those with only 1 allergic disease. This phenomenon has already been indicated by several studies.^{23,24} Sun et al. found that patients with more than 1 disease had an earlier onset age than those with only 1 disease, suggesting that an earlier onset age for allergic diseases could increase the risk of developing comorbid allergic diseases. In addition, we noticed that different allergic diseases had different onset ages (Figure 2). For example, EC was the most common allergic disease in children with an onset age of 0 to 1 years old. The percentages of children with AS/wheezing in the different onset age groups varied considerably, ranging from 0.3% (onset age of 0–1 year old) to 20.0% (onset age of 10–12 years old). These phenomena are also consistent with the pathogenetic characters of allergic diseases, that is, there is variation in the allergic manifestations over time, suggesting that EC occurs at

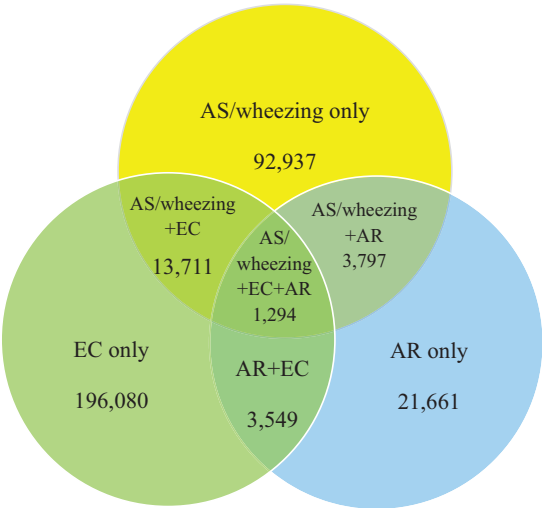


Figure 1. The distribution of allergic diseases in our study subjects. AR, allergic rhinitis; AS/wheezing, asthma/wheezing; EC, eczema.

Table 2. The Differences in Onset Age Between Children With a Comorbidity and Children With Only 1 Allergic Disease.

Disease Status	No. of Children	The Onset Age of the First Allergic Disease, Years ^a
		Mean (SD)
One disease only	310 678	3.06 (2.80)
Comorbidity	22 351	2.72 (2.53)
		$P < .05$

Abbreviation: SD, standard deviation.

^aA *t* test was used to compare the differences between the onset age of 1 disease and onset age of the comorbidity.

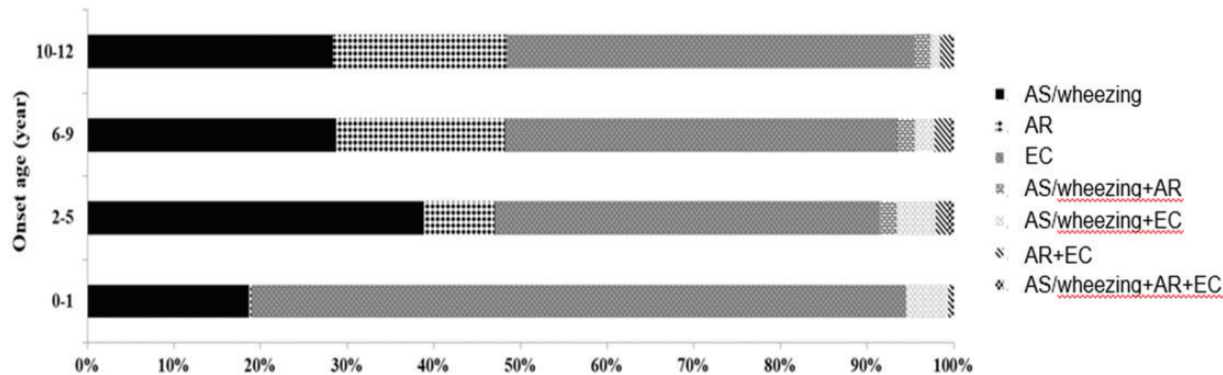


Figure 2. The percentages of allergic diseases in different onset age groups. AR, allergic rhinitis; AS/wheezing, asthma/wheezing; EC, eczema.

Table 3. Serum Total IgE Concentrations in Children With a Comorbidity and Children With Only 1 Allergic Disease.

Onset Age, Years ^a	IgE (IU/mL)					
	AS/Wheezing Only	AR Only	EC Only	AS/Wheezing + AR ^b	AS/Wheezing + EC ^b	AR + AS or Wheezing + EC ^b
0–1 year	19.2 (58.6–7.4)	12.7 (40.4–4.3)	27.0 (73.2–9.8)	29.3 (242.0–12.3)	38.0 (303.6–16.8)*	46.0 (372.0–14.3)
2–5 years	127.0 (342.0–46.0)	153.0 (348.0–51.4)	65.0 (174.0–22.5)	191.5 (708.5–68.5)*	88.0 (402.0–62.3)*	182.0 (756.0–70.2)
6–9 years	199.0 (530.0–68.4)	190.0 (446.0–88.4)	56.5 (182.5–17.7)	252.1 (625.0–76.0)	244.0 (610.0–89.0)*	257.0 (760.0–83.4)
10–12 years	368.0 (610.0–131.0)	297.0 (568.0–131.0)	88.3 (281.0–29.8)	432.0 (840.0–167.0)*	412.0 (720.0–147.0)	354.0 (830.2–277.0)

Abbreviations: AR, allergic rhinitis; AS/wheezing, asthma/wheezing; EC, eczema; IgE, immunoglobulin E.

^aOur subjects were classified into 4 groups according to their onset ages because the diagnostic criteria of serum total IgE concentrations are different among different onset age groups.

^bNonparametric tests were used to compare differences in serum total IgE concentrations between children with a comorbidity and those with only 1 allergic disease (AS/wheezing + AR vs AS/wheezing only or AR only, AS/wheezing + EC vs AS/wheezing only or EC only, AR + AS/wheezing + EC vs AR + AS/wheezing or AS/wheezing + EC or AR + EC).

* $p < .05$. (For AS/wheezing + EC: $P = .036$ in 0–1, $P = .041$ in 2–5, $P = .028$ in 6–9; for AS/wheezing + AR: $P = .047$ in 2–5, $P = .039$ in 10–12, for AR + EC: $P = .019$ in 2–5.)

an earlier age while AR and AS occur at an older age.^{16,25,26} Furthermore, we calculated the distribution of allergic diseases in boys and girls. We did not observe that EC was more prevalent among girls than boys, as other studies have suggested.^{17,27} In our study, we found that there was little difference in the prevalence of comorbidity between boys and girls (data not shown), which was similar to the results of the Swedish birth cohort (BAMSE) birth cohort study.³

Immunoglobulin E is extremely important in the development of allergic diseases.¹⁶ Higher serum tIgE concentrations have frequently been detected in allergic patients as an indicator of atopy,^{23,28} which is obviously associated with the occurrence and development of allergic diseases, especially in early childhood.^{29–32} In allergic diseases, allergic sensitization and comorbidity are 2 different but interrelated aspects.³³ Allergic sensitization, defined as the susceptibility of an individual to produce IgE antibodies in response to allergic antigens, is generally thought to be a common element linking various manifestations of allergic diseases.^{34,35} Individuals with allergic diseases, including common diseases such as AS, AR, and EC, usually show a T-helper 2 (Th2)-skewed immune response. In the Th2 immune response, chronic eosinophilic inflammation and IgE production are involved.^{36–39} The development of chronic eosinophilic inflammation is a risk factor for allergic sensitization,⁴⁰ which could further aggravate IgE antibody production in response to allergic antigens.⁴¹ Therefore, in sensitized subjects, allergen-specific IgE is the initial trigger of a complex inflammatory cascade causing symptoms of allergic diseases.¹⁶ It is reasonable that more IgE is likely to be produced and released in the bloodstream when the allergic reactions take place in a large scope of bodies, for example, the comorbidity of allergic diseases.⁴² Pinart et al. found that compared with children without IgE sensitization, comorbidity was more common in IgE-sensitized children.^{18,23} In a Swedish population-based birth cohort, Ballardini et al. found that there was an association between IgE antibodies and the comorbidity of allergic diseases from birth to adolescence.⁴³

Our study has several strengths. First, our study is an epidemiological survey with a considerable sample size of 333 029 children, thereby allowing for generalizations of the outcomes. In addition, the study of such a large sample size is difficult to perform in practical research. Our study uses the data from EMR, which enabled us to find some useful information from clinical practice in a cost-effective way. Second, instead of parental self-reported allergic diseases, our study used the EMR data from Shanghai Children's Hospital where the diseases were diagnosed by pediatricians, which greatly reduced disease misclassification and minimized recall and selection bias.

Several limitations also need to be acknowledged. First, this is a retrospective study that needs to be extended to more hospitals for further improvement. Second, our study focused only on the children, and our findings might not be suitable for adults who have usually shown different clinical characteristics.^{44,45} Third, the onset age of allergic diseases in children might be underestimated since children with mild symptoms may not seek medical care until their symptoms become serious.⁴⁶

In summary, we found that comorbid allergic diseases are relatively common in Chinese allergic children with an onset age of 0 to 12 years old. The onset age of comorbid allergic diseases was earlier, and the serum tIgE concentrations of allergic comorbidities were higher in children with allergic comorbidities than in children with only 1 disease. Early diagnosis and better understanding of serum tIgE levels would be helpful for improving the prognosis and well-being of allergic pediatric patients.

Author Contributions

Heyu Ji acquired, analyzed, and interpreted the data and wrote the first draft of the manuscript. Yi Hu interpreted the results and revised the manuscript critically for important intellectual content. Ting Zhang and Yizhong Wang revised the manuscript. Li Shen helped to analyze the data. Shu Wang, Min Chen, and Mingyue Wei organized our data. Guangjun Yu conceived the study and gave final approval of the version of the manuscript to be published.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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