Original Article

Atopic disease presentation in northeastern China: a 10-year retrospective study

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Abstract: This study was designed to investigate the prevalence pattern and characteristics of atopic disease in patients in the second largest allergy clinic in China. All clinical data associated with 103,370 patients treated at our allergy clinic between January 2001 and December 2010 were analyzed. There was a 3.4-fold increase in allergy cases over this 10-year period, with significant increases in hospital visits associated with asthma (43%), rhinitis (31.6%), and urticaria (11.7%), in particular. The highest incidence rates occurred in August, followed by September, and then July. Of 57,887 positive SPT (skin prick test) patients (positive rate of 56%), the main allergens identified were Dermatophagoides pteronyssinus (77.8%), D. farinae (75.1%), Artemisia vulgaris (40.5%), Ambrosia elatior (22.3%), dog dander (10.9%), and Humulus scandens (1.9%). About 65.5% (22,253/33,974) of SPT positive patients responded to at least one type of allergen in serum specific IgE (sIgE) tests. Approximately 18.2% of the patients seen were tested for sIgE reactivity for differential diagnosis purposes although they did not exhibit any signs of atopic disease. Our observations provide allergists with current data for patients in China, which will improve prevention, diagnosis, and treatment of atopic diseases.

Keywords: Allergens, northeastern China, incidence rate, skin prick test, sIgE test

Introduction

A 2004 World Allergy Organization’s (WAO’s) Specialty and Training Council survey of WAO’s 33 member societies conducted to obtain information regarding allergy rates worldwide indicated that approximately 22% of the surveyed populations suffered from some form of allergic disease [1]. Their observations belie an apparent dramatic increase in the prevalence of allergic diseases in both developed and developing countries. Increasing prevalence rates of allergic diseases place a significant burden on health care systems worldwide.

A large regional study indicated that the prevalence of asthma symptoms in children living in Western Europe (57 centers in 12 countries) increased by 2.7% between 1992 and 1996 [2]. In England, cases of allergic rhinitis increased by 43.2% between 2001 and 2005 [3]. In Ontario, Canada, asthma prevalence increased from 8.5% in 1996 to 13.3% in 2005 [4], and in Brazil, the prevalence of asthma in children increased at an annual rate of 1% during the decade of 1998 through 2008 [5]. These relatively focused regional data are consistent with the aforementioned WAO conclusion that atopic disease incidence rates are increasing steadily. Because China does not yet have a nationwide allergy prevalence survey, we set out to establish allergy incidence rates at our hospital, located in northeastern China, where an allergy clinic has been active since 1964.

A relationship between increased rates of children presenting at emergency departments for asthma and seasonal increases in ambient grass pollen levels has been observed, with a pollen level threshold as low as 19 grains/m³ [6]. In addition, the incidence of cases of acute urticaria (AU) presenting to emergency departments in Norwich (UK) and Heraklion (Crete,
Greece) have been reported to be inversely associated with temperature. A non-significant seasonal pattern of AU incidence (October, April-May) was observed in Norwich, in contrast to the significant seasonal pattern (December, February-May) of AU described for Heraklion [7]. However, a regression analysis failed to identify a significant relationship between average annual temperatures and the prevalence of hay fever in the National Health Interview Survey conducted in the USA [8], suggesting that seasonal climate changes play a complicated role in the presentation of allergic diseases.

Furthermore, comparing data across different countries suggests that the prevalence of atopic diseases differs greatly between regions. For example, the prevalence of asthma, eczema, and hay fever among Ethiopian women in 2005-2006 was reported to be 1.7%, 0.9% and 3.8%, respectively [9]. Meanwhile, symptoms suggestive of a history of asthma, eczema, and rhinitis were observed in 23.6%, 10.3% and 24.2% of children examined in a study in Madinah, Saudi Arabia [10].

It has been reported that the most common allergens causing sensitization in southern India are house-dust mite allergens (range, 65-70%), tree pollens (range, 52-56%), and cockroach antigens (range, 39-53%) [11]. In China, overall prevalence of positive skin prick test (SPT) responses have been reported to be 59.0% for Dermatophagoides farina (a dust mite), 57.6% for D. pteronyssinus (a dust mite), 40.7% for Blomia tropicalis, 16.1% for American cockroach antigens, 14.0% for dog allergens, 11.5% for Blatella germanica, 11.3% for Artemisia vulgaris, 10.3% for cat dander, 6.5% for Ambrosia artemisiafolia, 3.5% for mixed grass pollen, and 2.2% for mixed tree pollen [12]. Undoubtedly, these broad-area surveys are important for understanding the regional prevalence of allergies, but they do not provide reliable information about the incidence and characteristics of allergy symptoms in patients at any given hospital within the large regions surveyed. Furthermore, the correspondence between SPT results and serum allergen-specific immunoglobulin-E (sIgE) test results is unclear. Hence, the aim of the current study was to analyze atopic disease incidence data collected over 10 years, including SPT-sIgE correspondence, in a single targeted hospital in northeastern China.

Materials and methods

Subjects

At the end of 2011, we analyzed patient data collected at the Center for Allergy and Immunotherapy in the General Hospital of Shenyang (Liaoning Province, China)-the second largest allergy clinic in China-from January 2001 through December 2010 (the decade following the clinic’s 2011 conversion to an electronic patient database). Following doctor visits, information regarding diagnostic test results and diagnosis was added to the database. Diagnosis and grouping criteria for asthma and allergic rhinitis were conducted according to the Guidelines for the Prevention and Treatment of Asthma published by the Chinese Medical Association in 1997 and 2003 and the Guidelines for the Diagnosis and Treatment of Allergic Rhinitis published by the Chinese Medical Association in 1997 and 2005. The study was approved by the ethical committee of the General Hospital of Shenyang Military Area Command (No: K18 of 2000).

SPT and sIgE tests

Contraindications for SPTs were use of antihistamines, steroids, or other drugs within the last 2 weeks, symptoms of dermatographia, and active skin disorders. The tests were performed according to standard methods with a panel of inhaled common allergens (ALK, Denmark) and food allergens. Histamine dihydrogen chloride and 1% glycerinate solution served as positive and negative controls, respectively. SPTs were read 15 min after antigen administration and a weal that was at least 3 mm larger than the negative control was considered positive. sIgE tests were performed with the UniCAP system and commercial reagent kits (Pharmacia Diagnostics AB, Uppsala, Sweden) in accordance with the manufacturer’s instructions.

Statistical analysis

Simple descriptive statistics, conducted in SPSS 17 software, were used to analyze patient characteristics. The prevalence rates for specific allergic diseases were calculated by dividing the number of cases by the total number of
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outpatients visiting the clinic during the same time period. Nonparametric nominal data were compared between groups with the rank sum test of two independent samples and expressed as medians and ranges. Parametric data were analyzed with the Chi-square test and expressed as percentages. P values < 0.05 were considered statistically significant.

Results

Patient demographics

A relatively steady trend of increasing allergy incidence has been observed worldwide, and as much as a 1% annual increase in the number of allergic patients have been reported [5]. As a result we anticipated similar results in our patient population.

Complete data were available for 103,370 clinic visits. Of these 103,370 visits examined, 54,121 involved male patients and 49,249 involved female patients (ratio of 1:1). The numbers of visits in which patients in the < 14 years, 14-30 years, 30-60 years, and >60 age bands were 31,321 (30.3%), 20,881 (20.2%), 34,836 (33.7%), and 16,332 (15.8%), respectively. The number of allergy patient visits to our clinic in 2010 was 3.4-fold greater than that observed in 2001. However, a steady ascending year-over-year curve was not observed for the entire decade. Rather, following a generally increasing trendline for 8 years, the number of the allergic patients in our clinic then appeared to decrease over the last 2 years of the decade (Figure 1A). As shown in Figure 1B, apart from patients being seen for asthma and rhinitis, the percentage of first-visit patients at the clinic exceeded that of subsequent-visit patients. In particular, patients with acute drug or food allergies were unlikely to return to the clinic for a second visit.

Types of allergic diseases

It has long been recognized that allergic rhinitis, asthma, and urticaria represent the three major clinical allergic diseases. However, it seems likely that the ratio between each of these varies between populations. For instance, the prevalence of asthma, eczema, and hay fever was 1.7%, 0.9% and 3.8%, respectively, in an Ethiopian population [9], but in Madinah, Saudi Arabia the rates respectively were 23.6%, 10.3% and 24.2% [10].

Asthma (N = 44,492, 43.04%), rhinitis (N = 32,670, 31.60%), and urticaria (N = 12,065, 11.67%) were the three most common atopic diseases observed in patients in our clinic. Together, these three diseases accounted for 86.3% (N = 89,227) of all patient visits to the clinic (Table 1). A detailed profile of the disease diagnoses of our patients by year is shown in Figure 2.

Seasonal distribution

A non-significant seasonal trend in AU incidence (October, April-May) was observed in
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Norwich, in contrast to a significant seasonal impact (December, February-May) of AU described in Heraklion [7], suggesting that the influence of climate on allergic disease presentation varies between geographic areas.

A summary of allergy patients visits to our clinic by month is shown in Figure 3. The highest numbers of patients sought treatment in August, followed by September and July. January and February had the fewest patient seen. In particular, patients presenting with asthma increased between July and September, and peaked in August. Rhinitis cases also peaked in August, and decreased between May and July. Urticaria cases started to increase in June and peaked in September.

Identification of allergens using the SPT

SPT is a common and relatively reliable means for determining allergic responses to specific allergens.

Among the 103,370 patient visits for which cases files were examined in this study, 57,887 (56%) yielded a positive SPT result. The main allergens eliciting positive SPT results were dust mite allergens (D. pteronyssinus, 45,036 cases, 77.8%; and D. farinae 43,473 cases, 75.1%), Ambrosia elatior (12,908 cases, 22.3%), dog dander (6,310 cases, 10.9%), cat dander (4,920 cases, 8.5%), tree pollen (2,373 cases, 4.1%), and H. scandens (1,099 cases, 1.9%) (Table 2).

SPT versus serum sIgE tests

A previous study of 138 school children (age 6-8 years) showed that the majority of subjects with positive SPT reactions to respective allergens also had increased sIgE levels. A significant correlation between the SPT and sIgE levels was found for Dpt, birch pollens, and grass pollens [13]. It was also demonstrated that 98% of 104 patients with allergic rhinoconjunctivitis presented with a positive skin test reaction that correlated with the presence of sIgE specific for timothy grass pollen [14].

However, the relationship between clinical manifestations and SPT (or sIgE) in a large scale remains unclear.

About a third of the 103,370 patients (N = 33,974; 32.9%), constituting a majority (58.7%) of the 57,887 patients with positive SPT responses, had corresponding sIgE responses to allergens in our analysis. About two thirds of the patients with sIgE responses (22,253/33,974; 65.5%) showed a positive SPT response to at least one allergen.

The number of patients with positive SPT and positive serum sIgE test results for particular allergens are reported in Table 2 together with the portion of SPT-positive patients who also had corresponding positive serum sIgE test results for particular allergens. Notably, only 17.5% of the patients with positive D. farinae SPT results also showed corresponding positive sIgE results. Meanwhile, 46.4% of the patients with positive H. scandens SPT results also showed corresponding sIgE results. The numbers of the patients with positive sIgE results varied from year to year. Generally speaking, many more patients with positive sIgE results were observed in 2005 and 2010 than in 2001. Notably, H. scandens represented a novel allergen in 2005 and a surge of patients with positive sIgE against H. scandens was observed in 2010 (Figure 4A).

Clinical diseases associated with positive serum sIgE results

Based on the current definition of allergy, a group of diseases largely driven by IgE mediat-
ed mechanisms [15], sIgE tests play a pivotal role in the diagnosis of allergy, particularly in the identification of specific allergens resulting in the presentation of respective atopic diseases. Since allergy symptoms are not unique to allergic diseases, clinicians could mistakenly use sIgE tests in patients without atopic diseases. The percentage of patients presenting with particular diseases who were subjected to serum sIgE tests are summarized in Figure 4B. Approximately 18.2% of non-allergy patients seen during the study period were submitted to

Figure 2. Disease profiles of patients diagnosed at the clinic between 2001 and 2010.
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Discussion

In the present study, we observed an upward trend in allergy case visits between 2001 and 2010. Specifically, we observed a 3.4-fold increase in allergy clinic visits over this 10-year period, which indicates that the increase in our area far exceeds increases seen elsewhere, such as the 1% yearly increase reported in Brazil [5]. The upward trend in visits can be attributed to a roughly steady increase in the first 8 years of the decade, followed year-over-year reductions for the last 2 years. The reasons for the decreased hospital visit rates observed at our clinic in the last couple years of the study period are not known. However, it should be noted that the decrease was certainly not due to limited capacity.

Regional differences may be due, at least in part, to the fact that our analysis included both first and second visits. Thus, some of the cases included in our analysis were not new cases. In addition, Chinese patients tend to visit large regional hospitals or clinics straight away without visiting local district clinics first.

Allergic manifestations requiring subsequent visits to the clinic varied. For example, subsequent visits for asthma or rhinitis were more frequent since standardized treatments for asthma and rhinitis require regular scheduled follow-up visits. In contrast, most patients with food and drug allergy were less likely to return the clinic for further treatment.

Patients with and without atopic disease visited our clinic because some allergic diseases are difficult to differentiate from other illnesses based only on clinical symptoms. To our knowledge, this is the first report describing visits of non-allergy patients to an allergy clinic in China. Although variations on the types of allergic diseases observed varied from year to year over the 10-year period analyzed, asthma and allergic rhinitis were consistently the two most commonly observed atopic diseases observed throughout the study. Skin allergy cases were relatively low, likely due to some skin allergy patients being treated by the dermatology department.

Data provided in this report may help others understand the numbers and varieties of atopic diseases presenting in northern China. Demographically, the 30-60-year age band exhibited the highest allergy rates. This observation is consistent with a previous study reporting that the prevalence of positive SPTs and mean total serum IgE levels in asthmatics did not decline with advancing age in California [16]. Further consistent with this result is the finding that the age of adult-onset asthma appears to be increasing among females in Japan [17].

The increases in clinic visits over the summer months may be attributable to similarly timed zeniths in the grass pollen and fungi seasons.

Figure 3. Variation in monthly outpatient visits. Odds ratios of allergic disease relative to the number of cases seen in January are shown.

Table 2. Summary and relation of positive skin prick test (SPT) and specific IgE (sIgE) test results

<table>
<thead>
<tr>
<th>Specific allergen source</th>
<th>Positive SPT</th>
<th>Positive sIgE</th>
<th>Positive sIgE/SPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>D. pteronyssinus</td>
<td>45036</td>
<td>11580</td>
<td>0.257128</td>
</tr>
<tr>
<td>D. farinae</td>
<td>43473</td>
<td>7600</td>
<td>0.174821</td>
</tr>
<tr>
<td>Artemisia vulgaris</td>
<td>23444</td>
<td>6900</td>
<td>0.294318</td>
</tr>
<tr>
<td>Ambrosia elatior</td>
<td>12908</td>
<td>2360</td>
<td>0.182832</td>
</tr>
<tr>
<td>Dog dander</td>
<td>6310</td>
<td>2840</td>
<td>0.450079</td>
</tr>
<tr>
<td>Cat dander</td>
<td>4920</td>
<td>1270</td>
<td>0.258130</td>
</tr>
<tr>
<td>Tree pollen</td>
<td>2373</td>
<td>780</td>
<td>0.328698</td>
</tr>
<tr>
<td><em>Humulus scandens</em></td>
<td>1099</td>
<td>510</td>
<td>0.464058</td>
</tr>
</tbody>
</table>

*D. pteronyssinus* = *Dermatophagoides pteronyssinus*, *D. farinae* = *Dermatophagoides farinae*.
Researchers in Ecuador observed a similar allergy peak in August [19]. Notwithstanding, allergy case trends do not always follow environmental allergen trends. For example, it is unclear why visits from patients with urticaria in our study peaked in September. In this regard, in 1956, Kaufmann and Mayer [18] observed a surprising dissociation between allergy clinic visits and tree pollen peaks.

Determination of what allergens are responsible for atopic disease presentation is critical for the development of efficacious treatment plans for allergic disease patients. Using standardized protocols for the identification of allergens, we found that the top five allergens eliciting positive SPT responses in our clinic were from *D. pteronyssinus*, *D. farinae*, *Artemisia vulgaris*, *Ambrosia elatior*, and dog dander. Tree pollen was only responsible for 4.1% of atopy cases, which is not sufficient to have caused the major rise in allergy cases observed between July and September. Given that the top two allergen sources among our studied population were two dust mite species, surges in dust mite populations may underlie the summer increases in allergy visits. A prior study of dust mite allergen concentrations in beds indicated that these allergens peak in late autumn in Sydney [20]. In addition, a study in Turkey showed that sensitization to pollens, house dust, and molds was 59.7%, 20.5% and 2%, respectively, and that grass pollen sensitivity was 3-fold more common than tree pollen allergies [21], supporting our observation that the major rise in allergy cases occurred in autumn.

It should be noted that a severe IgE-mediated response to aeroallergens and airway inflammation could account for the increasing prevalence of allergic respiratory diseases in polluted urban areas. The most abundant components of urban air pollution in urban areas with high levels of vehicle traffic are airborne particulate matter, nitrogen dioxide, and ozone [22].

The correlation between SPT and slgE results has been variable across studies. Most studies have involved relatively small populations of perhaps several hundred subjects. In our large sample, only 65.5% of SPT-positive patients had corresponding slgE results. The correspondence was particularly poor for *D. farina* allergens (only 17.5%), and moderately better for *H. scandens* allergens (46.4%). Better SPT/IgE correspondence has been reported in smaller

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**Figure 4.** A. Numbers of patients with positive slgE results in 2001, 2005, and 2010. Serum slgEs against a panel of allergens were measured. d1 = *Dermatophagoides pteronyssinus*; d2 = *Dermatophagoides farinae*; w6 = *Artemisia vulgaris*; w1 = *Ambrosia elatior*; w22 = *Humulus scandens*. B. Clinical diseases associated with slgE tests. The data were presented as the percentage of total slgE measured.
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studies. For example, Schuetze et al. found that a majority of 138 children (age, 6-8 years) with positive SPT reactions to specific allergens had corresponding increased sIgE responses [13]. In a study of 104 allergic rhinoconjunctivitis patients with positive SPT reactions, Huss-Marp et al. also observed good correlation (98%) with sIgE reactivity for timothy grass pollen, although a dose-response relationship between sIgE level and clinical outcome of timothy allergen exposure could not be established [14]. Conversely, poor relationships between SPT and sIgE results have been described for children with dairy allergens, regardless of whether the children presented with the relevant food allergies [23].

The yearly shifting trend of positive serum sIgEs against novel allergens such as *H. scandens* in our area is of interest because it is reasonable to expect that people will encounter more novel allergens over time. Given this expectation, efforts need to be made to better understand environmental allergen patterns, particularly with respect to the presentation of atopic diseases in the industrialized world.

Although 33,974 patients were given sIgE tests in our clinic over the 10-year period examined, we are still not sure which atopic diseases should be screened in this manner due to the cost of the test and the variability of results. For example, 77%, 94%, and 68% of Finnish children, and 43%, 67%, and 41% of Russian children with asthma, hay fever, and eczema, respectively, were found to be sIgE positive in the same study [24]. Our results with sIgE tests may provide a useful guide for allergists given that this is the first large scale study describing the use of these tests.

In conclusion, we analyzed data collected over a 10-year period at the second largest allergy clinic in China. To our knowledge, this is one of only a few large-scale studies conducted at a single allergy clinic. This study provides a host of useful datasets for clinicians, researchers, and patients, including a 3.4-fold increase in annual allergy case visits over a 10-year period, monthly clinic visitation patterns, and allergy incidence seasonality, and identifies the top allergens associated with atopic disease in our area. Moreover, our observation that *H. scandens* represents an emergent allergen source in our area may be a key to elucidating the current landscape of allergens in our region.

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Disclosure of conflict of interest

None.

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