

# Coexistence of allergic diseases: Patterns and frequencies

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## ABSTRACT

*The atopic march hypothesis suggests that allergy diseases often progress from atopic dermatitis to allergic asthma, and allergic rhinitis. How often can the classic progression of allergic diseases be observed in the pediatric patient population? This study aimed to observe the pattern of allergic diseases progression, onset age, disease intervals, and frequency of the allergic march. Data from the National Health Insurance Research Database in the period 1996–2008 were used to obtain a cohort of children with allergic disease. Physician's diagnosis was used to confirm the allergic disease based on the international disease coding. The age of disease onset was compared. There were 10,729 children aged <5 years enrolled from the 200,000 individuals randomly sampled in 2000. Of these, 5866 (54.7%) had been diagnosed with at least one allergic disease. The rate of only one of three diseases diagnosed was 29.8% (3195 patients), whereas 18.8% had two allergic diseases and 6.1% had all three allergic diseases. Only 4.2% of cases matched the allergic march. Patients with more than one disease had earlier onset age than those who had only one disease (4.17 versus 2.79 and 2.32 years old;  $p < 0.05$ ). The allergic march accounts for only 4.2% in this study. A patient with only one allergic disease after the age of 4.17 years will not have another allergic disease until the age of 12 years. However, a patient with an allergic disease before 2.79 years old will probably have another allergic disease in 1.96–2.5 years.*

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**A**lthough eczema, asthma (AS), and allergic rhinitis (AR) tend to cluster in the same individuals and families, their patterns, such as age of onset, coexistence, and intervals, remain unclear.<sup>1</sup> Indeed, understanding the natural history of these disorders may clarify the development and prognosis of allergic diseases and provide guidance for children at risk. The notion of atopic march is a popular description of their relationships to each other.<sup>2</sup> A child supposedly progresses from eczema to AS and hay fever as he/she grows older. However, this simple allergic march hypothesis has been questioned recently. In a prospective survey of Italy, none of the 745 children who had allergic AS at baseline and were followed up for 9 years had atopic dermatitis (AD) at age 6–9 years.<sup>3</sup> Because only 20% of the children eventually developed AD after 9 years, the study concluded that the progression of allergic march is not the same in all children and that this progression may lack some of the stages.

From a general point of view, it is well known that AD is a risk factor for developing AS. In the AS prediction index for children with recurrent wheezing, which predicts if they may develop AS later in life, AD is one of the three major criteria.<sup>4</sup> Nonetheless, it is

unclear whether the chronologic course of the disease necessarily evolves from AD to AS or whether a different natural history may exist, *e.g.*, from bronchial AS to AD.

A number of ideas about allergic diseases have been developed in the past 40 years, often based on clinical experience in caring for patients with more severe disease. Most previous surveys are based on questionnaires or telephone contacts, especially in history or in follow-up.<sup>5–7</sup> Thus, recall bias is the most common problem in the study design. On the other hand, allergic diseases such as eczema, AR, or even AS are diagnosed mainly based on clinical symptoms and signs, together with past and family medical history, especially in children under school age. It is therefore important to confirm these diseases *via* caregivers' and physicians' observations. Caregivers will take their children for medical consult if these diseases are bothersome, whereas clinical practitioners will treat diagnosed allergic disorders. As such, medical records are one of the strongest evidences on patients' need and diseases progression.

This retrospective study used data from the National Health Insurance Research Database (NHIRD) to evaluate allergic diseases progression, onset intervals between different diseases, and frequency of allergic march, if it exists.

## MATERIALS AND METHODS

### Data Source

In March 1995, Taiwan developed a unique healthy insurance system based on a single-payer government-

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Table 1 Distribution of allergic diseases by age and gender

| Age (Y/O) in year 2008 | No. of Children | Male/Female Ratio | No. of Patients | Male/Female Ratio | RR Male vs Female |
|------------------------|-----------------|-------------------|-----------------|-------------------|-------------------|
| 8                      | 2226            | 1.11              | 1221            | 1.32              | 1.19              |
| 9                      | 2137            | 1.10              | 1158            | 1.27              | 1.15              |
| 10                     | 1957            | 1.07              | 1023            | 1.34              | 1.26              |
| 11                     | 2188            | 1.24              | 1196            | 1.40              | 1.13              |
| 12                     | 2221            | 1.11              | 1268            | 1.28              | 1.15              |
| Total                  | 10,729          | 1.13              | 5866            | 1.32              | 1.17              |

RR = rate ratio; Y/O = years old.

run National Health Insurance Program. By 2007, 22.60 million of the 22.96 million Taiwanese were enrolled in the program.<sup>8</sup> The large computerized databases that became the NHIRD were derived from this system by the Bureau of National Health Insurance and maintained by the National Health Research Institutes. These databases were used for research purposes. Personal, physicians', and medical care institutions' identities in these databases were scrambled in compliance with the Personal Electronic Data Protection Law.

This Longitudinal Health Insurance Database contained all of the original claim data of 200,000 individuals randomly sampled from the Registry for Beneficiaries unique personal identification number (ID) of the NHIRD in 2000, which maintained the registration data of every National Health Insurance Program beneficiary during the period 1996–2000. This registry contained 3.72 million individuals. All registration and claim data of the 200,000 individuals collected and constituted the Longitudinal Health Insurance Database. There was no significant difference in gender and age distribution ( $\chi^2 = 1.74$ ;  $df = 1$ ;  $p = 0.187$ ) between the patients in the Longitudinal Health Insurance Database and the original NHIRD. The National Health Research Institutes followed all of the aforementioned randomly sampled patients to the year 2008.<sup>9</sup>

### Data Collection

Each computerized claim form in the Longitudinal Health Insurance Database included the patients' personal identification number (scrambled ID), age, gender, visit dates, medical care institutions, primary physicians, and the diagnosis relevant to the visit. Each visit (including the well-baby for checkup, ambulatory, emergency, and hospitalizations) were all linked by personal scrambled ID since 1996–2008. All children <5 years old by the year 2000 were checked for their earliest visit since birth (if he/she had used the healthy insurance even once, including well-baby visit and vaccination in the randomly sampled patients).

### Patient Subgroups

Asthmatic patients were selected based on the diagnosis of AS (International Classification of Diseases [ICD], Ninth Revision, Clinical Modification [ICD-9-CM] code 493.xx) because one of the conditions for an outpatient visit at least three times during the cohort period, or any emergency consult or hospitalization for such a diagnosis. AR was defined by codes for ICD-9 code 477.x at least three times in outpatient visits or any emergency consults or hospitalizations.

AD was defined by codes for ICD code 691.xx (excluding 691.0x) or 692.xx (excluding 692.0x–692.8x) in any visit or emergency consult and hospitalization. A maximum of three outpatient and five inpatient diagnoses were listed per encounter. The age at disease onset was based on the first record with the aforementioned code.

### Statistical Analysis

All analyses were performed using SAS Version 9.1.3 for Windows (SAS Institute, Inc., Cary, NC). LIFETEST component of the SAS software was used to model the age distribution of incident allergic diseases. The first diagnostic date of any specific allergic disease was used to calculate and determine their age at onset.

Standard methods for analyzing contingency tables were used. For  $r \times c$  tables,  $p$  values of chi-square test were provided and  $p < 0.05$  indicated statistical significance. ANOVA and Student's  $t$ -test were applied for disease-onset interval comparison of among three allergic disease groups.

### RESULTS

In 2000, there were 10,729 children <5 years old enrolled from 200,000 individuals randomly sampled. Their age and sex distribution is shown in Table 1. There were 5866 (54.7%) children who had been diagnosed with at least one of the allergic diseases of AS, AR, or AD in the period of 1996–2008. The rate of only one of the three diseases diagnosed was 29.8% (3,195 patients), with AR (14.4%) as the most common disease, followed by AS

Table 2 Pattern of allergic diseases

| Kinds of Allergic Disease | Total No. | Case Nos. Who Were Unable to Identify Their First-Onset Allergic Disease | Case No. Who Were Able to Identify Their First-Onset Allergic Disease | AD First   | AS First   | AR First     |
|---------------------------|-----------|--------------------------------------------------------------------------|-----------------------------------------------------------------------|------------|------------|--------------|
| 0                         | 4863      | 0                                                                        |                                                                       |            |            |              |
| 1                         | 3195      | 0                                                                        | 3195                                                                  | 723 (6.7%) | 927 (8.6%) | 1545 (14.4%) |
| 2                         | 2015      | 287                                                                      | 1728                                                                  | 275 (2.6%) | 866 (8.1%) | 587 (5.5%)   |
| 3                         | 656       | 130                                                                      | 526                                                                   | 176 (1.6%) | 223 (2.1%) | 127 (1.2%)   |

AD = atopic dermatitis; AR = allergic rhinitis; AS = asthma.

Table 3 Time intervals among the onset of three diseases

| Disease Status                   | Time to First Disease Onset | Time Interval between First and Second Disease Onset | Time Interval between Second and Third Disease Onset |
|----------------------------------|-----------------------------|------------------------------------------------------|------------------------------------------------------|
| One*                             | 4.17 yr                     | —                                                    | —                                                    |
| Two#                             | 2.79 yr                     | 2.50 yr                                              | —                                                    |
| Three§                           | 2.32 yr                     | 1.96 yr                                              | 2.31 yr                                              |
| Significance of group comparison | *, *§, #§: $p < 0.0001$     | #§: $p < 0.0001$                                     |                                                      |

(8.6%) and AD (6.7%). In the longitudinal study, 18.8% had two diseases of allergy (Table 1).

The onset of AD before AR or AS was observed only in 4.2% (451 patients) of cases. The other patients had onset of AS (10.1%) or AR (6.7%) before AD. Moreover, 6.1% (656) of cases had all three allergic diseases diagnosed during the study period (Table 2). Of these, 1.6% (176 patients) had AD as the first diagnosis, and then AS or AR.

Patients with more than one disease had earlier onset age than those with only one disease ( $p < 0.05$ ). Patients who had three diseases also had earlier onset age than those with two diseases ( $p < 0.05$ ; Table 3).

## DISCUSSION

Only ~4.2% patients have allergic march in this survey. In patients who had more than one allergic disease before 12 years of age, the onset age is earlier than those who had only one allergic disease. In patients with two diseases, the onset age of the first disease is 2.79 years old. The duration between the first and second disease is 2.5 years. In patients with three diseases, the onset age of the first disease is 2.32 years old and the interval between the first and second disease is 1.96 years, and the interval between the second and third disease is 2.31 years. As such, a patient who has had only one allergic disease up to 4.17 years of age will most likely not have another allergic disease until the end of follow-up or the age of 12 years. On the other hand, a patient with allergic disease before 2.79 years old will perhaps have a second kind of allergic disease in 1.96–2.5 years. Finally, if a patient has

the second kind of allergic disease within a 2-year interval (~1.96 years), he/she will have the third kind of allergic disease.

The clinical manifestations of AD range from mild-to-severe itching and erythrodermic skin rash to lichenification, and prurigo papules in infants and children.<sup>10</sup> Most caregivers may ignore the mild facial symptoms because of its spontaneous remission. However, none of the current definitions of eczema have been validated in children.<sup>11,12</sup> Although the Scoring Atopic Dermatitis Index has been used in infants, it is primarily a tool for assessing eczema severity rather than the diagnosis of eczema itself.<sup>13,14</sup> Thus, for this study, eczema in children is defined as diagnosed by a doctor.

A study by Buffum shows that asthmatic children with coexistent AD have more severe AS than those without AD,<sup>15</sup> and the severity of AD seems to correlate with the severity of asthmatic response. A multicenter German birth cohort study that followed 1314 children from birth to 7 years old shows that early wheeze and a specific sensitization pattern are significant predictors for wheezing at school age, irrespective of early eczema.<sup>16</sup> Early eczema without these cofactors does not confer any increased risk of subsequent AS (adjusted odds ratio, 1.11; 95% CI, 0.56–2.20). A study in Australia also observes that some children with no symptoms of allergic disease at 18 months but with skin test positive to any allergen are more likely to develop symptoms of wheezing or rhinitis, but not AD, at 5 years old.<sup>17</sup> Based on these observations, the development of a particular allergic disease does not necessarily follow the classic paradigm

of atopic march, which may explain why <5% of patients in the current survey have allergic march. Patients with mild AD may not seek medical consultation, so these patients are not included in the health care database but exist in caregivers' recall.

On the other hand, some researches had mentioned early childhood eczema had different phenotypes (atopy or nonatopy). A systemic review of the literature further found that up to two-thirds of persons with eczema are not atopic.<sup>18</sup> Current evidence also suggests that eczema alone may not be the first most predictive phenotype in the atopic march.<sup>19</sup> The resulting 4.2% rate of allergic march in our survey may reflect the real world with different phenotypes of allergic diseases.

From the general survey here, if patients have any allergic disease (*i.e.*, AD, AS, or AR) before 2.79 years old, he/she will have another allergic disease after 2.5 years. If these patients have the second allergic disease within <2 years later, he/she would have the third allergic disease after 2.3 years. In short, if a child has an allergic disease by 4.17 years old, the allergic disease will not progress to another before 12 years of age. The earlier the onset age of disease, the more allergic diseases may develop in the future.

Epidemiological birth cohort studies have shown that sensitization is a dynamic process.<sup>20</sup> Various phenotypes of allergic diseases have been described, making it reasonably clear that allergic sensitization in early childhood is a very strong determinant of the development of different kinds allergic disease later in childhood. It means that the earlier onset of allergic disease causes earlier sensitization in children, which is compatible with the findings here. Early prevention of sensitization under 3 years old may delay or block the allergic disease progression.

There are some limitations in this study. First, children with mild symptoms may not be brought to the outpatient department, thereby underestimating the actual onset time of the disease. However, the exact time of disease onset really bothers caregivers, because most allergic diseases have been treated symptomatically. From the patients' viewpoint, disease severity becomes a concern only when it affects their life. So, the time of disease diagnosis and treatment may be a more suitable onset time. Second, the results here are based entirely on computerized data from a heterogeneous population. Despite including recorded ICD-9 CM coding in the medical claims data, it is hard to know the severity of allergic disease. It is also difficult to determine if the enrolled patients received appropriate treatment for their allergic disease at any given point. Whether this influences disease progression remains unclear.

In conclusion, allergic march, or the progression of allergic diseases, is not the same in all children and may be lacking in some stages. In this study, only ~4.2% of patients have the classic march. The earlier the onset of

allergic disease correlates with the more allergic diseases the patients will have. The strength of this study is its large size, its population-based design, and the relatively small loss of study subjects during follow-up, thereby allowing for generalizations of the findings.

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