

# Allergy march of Chinese children with infantile allergic symptoms: a prospective multi-center study

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**Background:** Allergy march refers to progression of allergic diseases from infantile food allergy to the development of asthma and allergic rhinitis (AR). Evidence come mostly from studies in European countries. This study aimed to investigate allergy march in Chinese children with infantile food protein allergy (FPA) with a special focus on the effect of different formula interventions.

**Methods:** From 2008 to 2010, 153 infants diagnosed with FPA were recruited in five tertiary hospitals across China. They were randomly treated with amino-acid-based formula or soy-protein-based formula for a period of 3 months. Long-term follow-up was performed when they reached early school age, using questionnaires, physical examinations, and serum-specific immunoglobulin E.

**Results:** The overall follow-up rate was 73.20%. In patients who reached their early school years, the prevalence of physician-diagnosed AR and asthma were 43.75% and 23.21%, respectively. Only 40% of the subjects remained positive for food sensitizations upon follow-up. Twenty-six subjects receiving aeroallergen screening tests in infancy all proved negative, but upon follow-up, 65.57% were sensitized to aeroallergens ( $P=0.005$ ). No significant difference between the effects of amino-acid-based formula and soy-protein-based formula on children's allergy march was observed.

**Conclusions:** A high proportion (47.32%) of Chinese infants with early allergic symptoms developed respiratory allergies by their early school years. Most food-sensitized infants outgrew their condition several years later, but then aeroallergen sensitization often occurred. Amino-acid-based formula showed no advantages over soy protein-based formula with respect to arresting the allergy march.

*World J Pediatr* 2017;13(4):335-340

**Key words:** allergic rhinitis;  
allergy march;  
asthma;  
atopic dermatitis;  
infant

## Introduction

In 1973, Fouchard reported that children with infantile food allergies tend to progress to asthma and allergic rhinitis (AR).<sup>[1]</sup> Early in 1985, a prospective study from New Zealand indicated that early childhood asthma has a complex relationship with other allergic diseases.<sup>[2]</sup> Since the 1990s, the concept of allergy march has generally been accepted, covering the shift in sensitization from food to pollen.<sup>[3]</sup> In recent years, one of the prospective studies from Sweden showed that in children with infantile eczema, 47% of them developed allergic rhinoconjunctivitis while 29% had asthma at the age of ten.<sup>[4]</sup> The aim of the current study was to follow infants with infantile food protein allergy (FPA) in China over time, focusing on the long-term effects of amino-acid-based formula on allergy march and compare them with those of soy-protein-based formula.

## Methods

### Patients

A clinical multi-center study of infants with FPA in China was conducted during the period 2008-2010, in which 153 eligible children were recruited from 5 tertiary hospitals across mainland China and randomly assigned to the amino acid-based formula group or the

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doi: 10.1007/s12519-017-0024-7

Online First March 2017

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soy protein-based formula group to be treated for a period of 3 months with regular follow-ups.<sup>[5]</sup>

### Inclusion criteria

1) Infants were younger than ten months; 2) Infants were diagnosed as FPA by a pediatrician [positive for serum food allergens using a specific immunoglobulin E (IgE) screening test (fx5E), i.e. fx5E as well as manifestation of skin, gastrointestinal or respiratory allergic symptoms, symptoms alleviated with formula intervention]; 3) Breast feeding was not available; 4) Infants has normal liver and renal function; 5) Stable vital signs were exhibited.

### Exclusion criteria

1) Infants were allergic to certain components of the investigated formulas; 2) Infants had positive specific IgE for soy protein; 3) Infants received anti-histamine drugs for a week; 4) Infants received external use of corticosteroids or immunomodulator drugs during a recent two week period; 5) Infants received corticosteroids during the four previous weeks; 6) Infants had severe systemic disease with unstable condition; 7) Infants were immunocompromised or had a history of malignant diseases; 8) Participation in other clinical drug trials during the past 30 days; 9) Reasonable expectation that the subject's compliance would be too poor to complete the study; 10) Infants had been fed an amino-acid- or soy-protein-based formula at a prior point.

### Measurements

Long-term follow-up was conducted when the subjects were 4 to 7.5 year-old. A questionnaire was used to collect information since infancy. It included symptoms of the skin and of the upper and lower respiratory tract. Questions about the skin symptoms were designed according to the Williams diagnostic criteria for atopic dermatitis (AD)<sup>[6]</sup> and those for the upper respiratory tract symptoms focused mainly on the manifestations of AR.<sup>[7]</sup> The core questions in the questionnaire of the International Study of Asthma and Allergies in Childhood were used to inquire about the lower respiratory tract symptoms.<sup>[8]</sup> AD, AR, and asthma were defined in subjects using a doctor's diagnosis.

Physical examinations were performed, including standardized evaluation for AD using "The Severity Scoring of Atopic Dermatitis" (SCORAD),<sup>[9]</sup> anterior rhinoscopy, and examination of the respiratory system.

Serum-specific IgE was measured for six food allergens, including egg white, cow's milk, codfish, wheat, peanuts, soybeans, and eight aeroallergens, including house dust mite (*dermatophagoides pteronyssinus*, and *dermatophagoides farinae*), molds, cat and dog hair, cockroaches, pollen, and grass using

the ImmunoCAP system (ThermoFisher Scientific/Phadia, Uppsala, Sweden). The s-IgE was considered positive if  $\geq 0.35$  KUA/L. For subjects in the main study center, skin prick tests (SPT) for aeroallergens were also performed (Allergopharma, Germany). Airway resistance was tested using the method of impulse oscillometry for children aged less than 6 years old and for those who had poor cooperation; and for those over 6 years old, forced expiratory flow volume curve was used (MasterScreen, Jaeger). For subjects who did not manage to complete follow-up in the clinic, information from a questionnaire was delivered through the phone.

### Statistical analysis

Data were processed with SPSS20.0 software. Means/medians and proportions were used in description. Probable influence factors for allergy march were analyzed using logistic regression model. Chi-square test and rank sum test were also used in data analysis.

### Ethics statement

Written informed consent was obtained from parents of all subjects. The study was approved by the Ethics Committee of Beijing Children's Hospital, Capital Medical University.

### Results

In infancy, among the 153 recruited FPA subjects, 114 (74.51%) manifested skin symptoms like AD or urticaria, 28 (18.30%) presented with early respiratory symptoms, i.e. wheezing or nasal obstruction but did not have any diagnosis of AR or asthma, and 10 (6.54%) had gastrointestinal disorder, such as diarrhea. The latest follow-up period started in Nov 2013 and continued through Sep 2015, during which 112 subjects (73.20%) were followed. Their ages ranged from 4-7.5 years old, with a mean age of  $5.68 \pm 0.98$  years old. There were no significant differences in sex composition, mean age, or SCORAD index in infancy between the participants who completed follow-up and those who dropped out.

### Prevalence of development of respiratory allergic disease

Upon the latest follow up, when the children were 4-7.5 years old, 47.32% (53/112) of them developed physicians diagnosed AR or asthma.

### Serum-specific IgE test results

In infancy, the participants were all fx5E. Twenty-six of them had also been screened for aeroallergens (phadiatop) and all showed negative results.

A total of 61 subjects accepted serum specific IgE test upon the latest follow up, in which 40 (65.57%)

were positive for aeroallergens (Table 1). Sixteen children had serum aeroallergen s-IgE results both in infancy and during early school years, with 13 proved positive upon follow-up, while all were negative in infancy. Of the 40 subjects who were tested positive for aeroallergens s-IgE, 36 (90%) presented as multiple sensitization, comprising 59.02% of the total 61 tested subjects, with as many as 7 aeroallergens sensitized simultaneously. A total of 60 subjects were tested for food sensitization; among them, only 24 (40%) remained positive for food allergens at early school age (Table 2). The rate of sensitization to aeroallergens was significantly higher than to food allergens at 4-7.5 years of age ( $P=0.005$ ).

Total serum IgE levels of the 60 tested subjects ranged from 2.00 KUA/L to 1980.00 KUA/L. Among these subjects, 35 (58.33%) developed respiratory allergic diseases (i.e. AR or asthma). The median total IgE level of

the subjects who developed respiratory allergies was 120 (quartile range: 210.6) KUA/L, and it was 87.4 (quartile range: 346.6) KUA/L in those who had not. However, no significant difference was found in total IgE level between these two groups of subjects ( $P=0.388$ ).

### SPT results

A total of 29 subjects in Beijing Children's Hospital underwent SPT for aeroallergens, and 24 (82.76%) showed positive results (Table 3). In view of positive test results, SPT was considered more sensitive than s-IgE testing. However, in general, these two kinds of test methods did have reasonably good consistency.

### Airway resistance

Pulmonary function tests were performed on 60 subjects, with 15 (25%) showing abnormal results. Among

**Table 1.** Distribution of aeroallergens specific IgE ( $n=61$ )

Aeroallergens	Amount of sensitized cases						Total (%)
	Class 1	Class 2	Class 3	Class 4	Class 5	Class 6	
Dpt	1	3	10	9	3	6	32 (52.46)
Df	1	6	3	9	7	7	33 (54.10)
Cat hair	1	2	5	2	0	0	10 (16.39)
Dog hair	2	5	2	0	0	0	9 (14.75)
Cockroach	1	5	0	0	0	0	6 (9.84)
Molds	3	5	4	1	0	0	13 (21.31)
Pollen	2	0	3	0	0	0	5 (8.20)
Grass	1	3	1	0	1	0	6 (9.84)

Dpt: dermatophagoides pteronyssinus; Df: dermatophagoides farinae.

**Table 2.** Distribution of food specific IgE ( $n=60$ )

Food allergens	Amount of sensitized cases						Total (%)
	Class 1	Class 2	Class 3	Class 4	Class 5	Class 6	
Egg white	5	11	0	0	0	0	16 (26.67)
Cow's milk	6	7	0	0	0	0	13 (21.67)
Codfish	4	1	1	0	0	0	6 (10.00)
Wheat	7	4	2	1	0	0	14 (23.33)
Peanut	4	2	1	0	0	0	7 (11.67)
Soybean	3	3	0	0	0	0	6 (10.00)

**Table 3.** Distribution of aeroallergens SPT results ( $n=29$ )

Aeroallergens	Amount of sensitized cases				Total (%)
	+	++	+++	++++	
Dpt	1	4	8	4	17 (58.62)
Df	0	6	10	2	18 (62.07)
Hay dust	8	0	0	0	8 (27.59)
Cat hair	2	0	2	3	7 (24.14)
Dog hair	1	4	0	0	5 (17.24)
Humulus	1	0	0	0	1 (3.45)
Alternaria	4	2	0	1	7 (24.14)
Mixed molds	1	0	0	0	1 (3.45)
Pollen I*	0	1	0	0	1 (3.45)
Pollen II†	0	1	2	0	3 (10.34)
Grass	0	0	1	4	5 (17.24)
Mugwort	0	0	1	4	5 (17.24)
Ragweed	1	0	2	0	3 (10.34)
Goosefoot	2	1	0	0	3 (10.34)
Poaceae/frumentum	0	0	0	0	0 (0)

Dpt: dermatophagoides pteronyssinus; Df: dermatophagoides farinae; SPT: skin prick test. \*: alder, hazel, poplar, elm, willow; †: birch, beech, sycamore. The ratio of the wheal diameter of the tested allergen to that of the positive control was represented by the following symbols. "+": the ratio of 25%-49%; "++": the ratio of 50%-99%; "+++": the ratio of 100%-199%; "++++": the ratio  $\geq 200\%$ .

**Table 4.** Analysis of risk factors of allergy march

Influence factors	Total amount of cases		$\chi^2$	P value
	Developed airway allergies	Without airway allergies		
Sex				
Male	39	43	0.007	0.933
Female	14	16		
Family history of allergy				
Positive	46	30	11.902	0.001
Negative	7	23		
Phenotype of AD				
Persistent	31	15	21.487	0.000
Transient	8	35		
Recurrent respiratory tract infection				
With	16	5	7.185	0.007
Without	37	48		
Different infant formula				
Amino acid based	29	24	1.433	0.231
Soy protein based	21	28		

AD: atopic dermatitis.

these 15 subjects, one showed a good reaction to the bronchodilator, while four showed positive results for the bronchial challenge test. Here, 10 of the 15 children with an abnormal airway resistance turned out to have developed respiratory allergic diseases.

### Potential influencing factors of the allergy march

Several factors which were considered to influence allergy march were analyzed (Table 4). No significant differences were found between the effects of amino-acid-based formula and soy-protein-based formula. Multiple logistic regression analysis finally proved that persistent AD and family history of allergies to be independent risk factors for development of respiratory allergic diseases [odds ratio (OR): 3.057 vs. 3.420,  $P < 0.05$ ].

### Discussion

The phenomenon of "allergy march" was first described in 1973.<sup>[1]</sup> It often begins as infantile atopic eczema, usually manifesting in the first 2-3 months of life, often associated with food allergies that can become more pronounced through the first year of life. Asthma usually manifests in the pre-school years, followed by allergic rhinitis in school-aged children. Although eczema and early allergies to milk and eggs tend to resolve, asthma and allergic rhinitis tend to persist through childhood.<sup>[10]</sup>

The prevalence of allergic diseases varies across different countries and regions. A large-scale epidemiological surveys of children's allergic diseases in China showed the rates of AD, AR and asthma were 2.78%, 10%, and 3.02%, respectively.<sup>[7,11,12]</sup> However, the current study showed that children with infantile-FPA-associated allergic symptom history presented much higher rates of respiratory allergic disease during early school years than the contemporary national level. In Sweden, Ekbäck et al<sup>[4]</sup> conducted a prospective study in infants with eczema recently, which showed that, at the age of ten, 64% of the children still had problems with eczema, 47% had allergic rhinoconjunctivitis, 29% had asthma, and only 14% had no symptoms of allergies. In this way, eczema in infancy must be considered a serious warning sign for lasting allergic problems rather than a transient condition, although eczema usually gets less severe over time.<sup>[4,13]</sup> This is the first work supporting the theory of "allergy march" to be conducted in Chinese children with sufficient data and convincing evidence.

In terms of allergen sensitization, results showed that, although all the children tested positive for food allergens in infancy, only 40% remained sensitized to

food allergens by their early school years. The children who had undergone screening for inhalant allergens in infancy all showed negative results, but in early school follow-up, 65.57% of the followed subjects were sensitized to inhalant allergens. Results showed that sensitization to aeroallergens was more prevalent than sensitization to food allergens in these children by early school age. These atopic children subsequently tended to present more severe sensitization to aeroallergens than to food allergens, if they presented any at all. These findings are consistent with those of other studies in this respect.<sup>[14,15]</sup> A cross-sectional study of the IgE repertoire from Italy has indicated that food-related components (in particular those of milk and eggs) were the most frequently recognized at the earliest ages, whereas specific IgE to plant allergens appeared invariably later.<sup>[14]</sup> Similarly, a prospective study in a sample of 276 children from a one-year birth cohort of unselected Danish children followed from birth to 26 years of age proved that sensitization to food allergens was most prevalent in early infancy, whereas sensitization to inhalant allergens dominated later on.<sup>[15]</sup> This is in accordance with the clinical course, where young children suffered mainly from eczema and food allergy, whereas asthma and rhinoconjunctivitis dominate in later childhood and adulthood.

In the current study, 51.69% of the subjects had persistent AD; and the prevalence of respiratory allergic diseases was higher in early school ages than those who outgrew AD after infancy. It is here suggested that persistent AD may predict, to a large extent, the possibility of developing AR or even asthma. Quite a few studies on children's allergy march are from the Europe and the United States.<sup>[4,16-18]</sup> For example, the Swedish Dampness in Building and Health study recruited a total of 3124 children aged 1-2 years, and followed up five years later using a parental questionnaire, which indicated that persistence of eczema [adjusted OR (aOR): 5.16, 2.62-10.18 and aOR: 4.00, 2.53-6.22, respectively] further increased the odds of developing asthma and rhinitis.<sup>[16]</sup> Similarly, in a Canadian cohort of infants at high risk of asthma, Carlsten et al<sup>[17]</sup> demonstrated that early-onset persistent AD, which is closely associated with atopic sensitization, increases the risk of atopic disease in later childhood and so appears to be part of the atopic march. Another relevant study from the United States assessed the atopic profiles of toddler-aged children with frequent wheezing who were at high risk for developing of persistent asthma and had parental histories of asthma, AD, or both. It showed a high prevalence of aeroallergen sensitization (54%) in this high-risk cohort and suggested that aeroallergens might have an important role in the early development of asthma.<sup>[18]</sup> A more recent study from Korea proposed an allergy-



march-associated AD phenotype, which was characterized by early onset of AD with its persistence, increased serum IL-13 levels, high atopy, and persistently high proportions of blood eosinophils.<sup>[19]</sup> Similarly, the present study proved a family history of allergies and persistent AD to be independent risk factors for allergy march, and they may be used to identify a certain group of high-risk children who need more preventive measures. The vast majority of these participants were classified as having moderate to severe AD according to the SCORAD index, which might prompt their parents to consult a physician. It has been established that severe eczema in infancy can predict AR and asthma development,<sup>[4,18]</sup> which may be reflected, to some extent, in the current study, although no express comparison has been made.

In the current study, the prior FPA infants had been fed amino-acid- or soy protein-based-formula at random. Both formulas relieved their allergic symptoms in infancy, and amino-acid-based formula showed an advantage in weight gain.<sup>[5]</sup> Nonetheless, no differences were found between the two formula groups with respect to the prevalence of respiratory allergic diseases by early school age. Australian guidelines state that three types of infant formulas (soy, extensively hydrolyzed and amino acid) are appropriate for treating cow's milk protein allergy.<sup>[20]</sup> However, with respect to preventing allergy march, the German Infant Nutritional Intervention study investigated the effect of hydrolysate infant formulas on allergic phenotypes in children with family histories of allergies at school age; the results showed several types of hydrolyzed formula interventions had no difference from standard cow's milk formula with respect to preventing asthma and AR.<sup>[21]</sup> A newly published meta-analysis indicated that food sensitization during the first 2 years of life can identify children at high risk of subsequent allergic disease who may benefit from early preventive strategies, this last of which needs further exploration.<sup>[22]</sup> We found that amino-acid-based formula had little long-term effect on the allergy march of previously food-sensitized infants until their early school years.

There are limitations for this study. First, the inclusion criteria for infant participants were based on serum s-IgE test results, which did not include non-IgE-mediated FPA patients. Second, follow-up at early school ages might be more amenable to parents whose children are suffering from subsequent allergic symptoms rather than those who are not, which may result in higher rates of sensitization by early school age.

In conclusion, a considerable proportion (47.32%) of Chinese children with previous infantile FPA-associated allergic symptoms tended to develop AR or

asthma by early school age. Most infants sensitized to common foods will outgrow it four to six years later, but they are likely to develop aeroallergen sensitization, usually after a negative screening test result for that in infancy. Persistent AD and family history of allergies are independent risk factors for the development of respiratory allergies. Amino-acid-based formula showed no advantage over soy-protein-based formula with respect to preventing allergy march in Chinese children.

## Acknowledgements

We would like to express our gratitude to all the children who participated and their parents. We would like to thank all the staffs of Allergy Department of Beijing Children's Hospital (BCH) and Capital Medical University and the staffs of all the other facilities involved in this study. We are especially grateful to Dr. Chun-Ping Shen of the BCH Dermatology Department and Dr. Jun Tai and Dr. Wei-Li Dai from the ENT Department for helping in the physical examinations of the participants. We would also like to thank the participating nurses for collecting blood samples.

**Funding:** This study was supported by 2012 National Science and Technology Supporting Project-research of standardized diagnosis, treatment and prognosis evaluation in pediatric common respiratory diseases, which is part of the project of "Research and demonstration of advanced diagnosis, treatment and appropriate technology in common pediatric diseases".

**Ethical approval:** The study was approved by the Ethics Committee of Beijing Children's Hospital, Capital Medical University, Beijing, China. Written informed consents were obtained from the guardians of the participants.

**Competing interest:** None.

**Contributors:** Gao Q wrote the main body of the article under the supervision of Xiang L and Shen KL. Ma L provided advice on medical aspects. All authors contributed to the intellectual content and approved the final version. Xiang L and Shen KL are the guarantors. Xiang L and Shen KL contributed equally to this work as co-corresponding authors.

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Received March 31, 2016

Accepted after revision July 18, 2016