Food allergy and related risk factors in 2540 preschool children: an epidemiological survey in Guangdong Province, southern China

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Background: **Although the number of studies on allergic diseases in the general population of southern China is increasing, only a few have addressed food allergy (FA) in children in this region. The present study aimed to investigate the prevalence, clinical manifestations, spectrum of allergens, and related risk factors of FA in preschool children in Guangdong Province, southern China.**

Methods: **A random cluster-sampling method was used to select 24 kindergartens from 12 cities in Guangdong Province. The parents or guardians of the children were requested to complete a questionnaire on general information and data regarding FA diagnosis and symptoms in the children and their first-degree relatives. Thereafter, the Chi-square test, multivariate regression analysis, and Spearman's rank-order correlation coefficient analysis were performed to identify statistically significant differences.**

Results: **Analysis of 2540 valid questionnaires revealed an FA prevalence rate of 4%. Adverse food reactions were due to the consumption of shrimp (4.4%), crab (3.2%), mango (2.3%), cow's milk and dairy products (1.9%), and eggs (1.4%). Logistic regression analysis indicated that a history of FA and a history of allergic rhinitis in the first-degree relatives were the major factors leading to FA in children.**

Conclusions: **The incidence of FA in children in Guangdong Province is higher than that commonly believed. An individual's genetic background is an important risk factor for FA. Hence, mitigation of the impact of lifestyle and environmental factors should be carefully considered to reduce the incidence of childhood FA.**

World J Pediatr 2015;11(3):219-225

Key words: **allergic rhinitis;**
eczema;
epidemiology;
food allergy;
questionnaire

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doi: 10.1007/s12519-015-0030-6

Introduction

The incidence of allergies has been increasing worldwide in recent decades.[1] In these allergies, food allergy (FA) in children has become a global health concern in a context of the ever-evolving modern lifestyles and diet.[2] In the United States, about 5.9 million children have a history of FA, representing an increase of 18%[3-6] over the past decade. Of these children, nearly 40% have experienced FA-related events ranging from transient hypotension to life-threatening anaphylaxis.[7,8] Allergic reactions to food are among the common conditions that necessitate immediate medical care in the emergency room visits.[8,9] Given the diversity of foods and scarce options in diagnostics, however, the current understanding of FA remains inadequate.[10] Studies[11,12] have shown that inconsistency between parents' beliefs and expert opinions frequently leads to under-evaluation of childhood FA. Variations in the prevalence of FA across countries may further complicate the scenario. Therefore, a clear epidemiological picture of FA within a geographic region should be important to support evidence-based, local prevention and management of this condition, especially in a large country such as China.

Despite the increasing research into allergic

diseases in the general population of southern China,[13-15] information about FA among children in this region is limited. In the present study, we aimed to investigate the prevalence, clinical manifestations, spectrum of allergens, and related risk factors of FA in preschool children in Guangdong Province.

Fig. Geographical distribution of the surveyed sites in Guangdong Province, southern China.

Methods

Questionnaire design

The International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire is a globally accepted screening tool that has been extensively used to assess childhood asthma, rhinitis, and eczema.[16] Although the ISAAC questionnaire was designed for children aged ≥6 years,[17] it has also been used in children at age of 3 years or below, with reliable results.[18,19] We adopted the ISAAC questionnaire to account for the local epidemiology of allergic diseases in Guangdong Province while considering the format of the questionnaire. After this, a draft version of the modified questionnaire was given to 20 children who visited our clinics where pediatricians and allergists identified any issues encountered during completion of the questionnaire, and proposed further corrections as needed. Meanwhile, we consulted a group of allergists in the province about the draft. The comments from clinicians and allergists contributed to the final version of our questionnaire after 5 rounds of revisions, with information about personal demographics, symptoms of FA and other allergic diseases, allergen distribution, and FA-related risk factors (family history, duration of breastfeeding, and seasonality of FA occurrence). This modified questionnaire was used as the primary instrument in the present study (see supplementary file for details).

Study population and data collection

From June 2013 to December 2013, we conducted an epidemiological survey in 24 kindergartens in Guangdong Province. The selection of these kindergartens was based on considerations of an adequate geographic coverage of urban and rural regions throughout the province. As such, we randomly selected one urban kindergarten and one rural kindergarten as survey sites from each of the following 12 cities (Fig.): Shaoguan and Qingyuan (northern Guangdong), Shaoxing (northwestern Guangdong), Enping and Maoming (western Guangdong), Zhanjiang (southwestern Guangdong), Guangzhou and Dongguan (central Guangdong), Zhuhai (southern Guangdong), Shanwei (southeastern Guangdong), Shantou (eastern Guangdong) and Meizhou (northeastern Guangdong). Overall, these kindergartens were attended by a total of 2761 children aged 1-7 years. During the annual health checkup for these children, which was jointly organized by the kindergartens and our institution, the teachers were given finalized copies of the questionnaire and were trained well on how to complete the questionnaire items. The teachers then distributed the questionnaires, with adequate instructions, to the parents or guardians of the children, and collected them on the following day. To ensure that the parents understood all the medical terms on the questionnaire, a fieldwork investigator (LJY) delivered a 40-minute presentation on the meaning of all questions. Before the survey, this investigator had been accredited on her accuracy, efficiency, and consistency in conveying the delivered message. When necessary, the users of the questionnaire were encouraged to consult the fieldwork investigator for any problems, either over the phone or face-to-face. Before the data analysis, a few of the parents or guardians were followed up on the telephone by the study investigators if their responses to the questionnaires needed to be reconfirmed. Despite these efforts, questionnaires that remained incomplete or with unclear responses were deemed invalid and were not included in the final analysis.

A diagnosis of allergic disease in children had to be confirmed by a clinician. Therefore, the prevalence of FA was estimated by positive responses to the items that recorded the findings of a food sensitization or oral food challenge test by the clinician.[20,21] The manner in which asthma and other atopic disorders were identified has been described elsewhere.[19] Briefly, if the response to the question "Has your child ever had asthma?" was "yes," then the child was considered to have been diagnosed with asthma. The prevalence of other atopic disorders, including drug allergy, allergic rhinitis, allergic conjunctivitis, and anaphylactic enteritis, was determined in the same manner. "Current symptoms" referred to symptoms occurring within the past 12 months. We excluded children with skin rash and/

or gastrointestinal reactions that were associated with bacterial or viral infections.

Ethical statement

The study protocol was approved by the Ethics Committee of First Affiliated Hospital, Guangzhou Medical University (No. GYFYY-2013-02-20). Written informed consent was obtained from parents or guardians of all children before they participated in this study.

Statistical analysis

All data were recorded using Epidata Ver. 2.0 software (EpiData Association, Odense, Denmark) with the use of a double-entry system, after which they were verified and analyzed using Statistical Package for the Social Sciences Ver. 16.0 software (SPSS Inc., Chicago, IL, USA). Numerical data, such as number of subjects, age, body height, and weight were analyzed using the Chi-square test. Logistic regression was performed to analyze the effects of family history on FA in children and to identify the risk factors for FA. Spearman's rank-order correlation coefficient was used to analyze the correlation between FA and history of allergies in the children. P values <0.05 were considered statistically significant.

Results

Of the 2761 questionnaires distributed, 2540 were retrieved with valid responses and 221 could not be retrieved or had invalid data, or were not included because of parent refusal, thus yielding a valid response rate of 92.0%. Of the valid questionnaires, 1331 were from boys (52.4%) and 1209 from girls (47.6%). The mean age of the study population was 4.6±1.1 years (Table 1). In these subjects, FA had been diagnosed in 4.0% of the children, whereas either anaphylactic enteritis or purpura was diagnosed in only 0.2% of the subjects (Table 2). The results of the Chi-square test indicated that sex was not a statistically significant factor in the prevalence of FA (χ^2=0.065, P=0.968). Consumption of shrimp (4.4%), crab (3.2%), mango (2.3%), cow's milk and dairy products (1.9%), and eggs (1.4%) were the leading causes of adverse reactions related to FA (Table 3). However, 22.4% of the parents reported uncertainty on which food would lead to allergic reactions in their children.

Overall, the FA-related adverse reactions included skin (33%), facial (11.7%), gastrointestinal (10.3%), systemic (5.1%), and respiratory (2.9%) symptoms in the children (Table 4). Moreover, we further analyzed the reactions of the children to cow's milk and dairy products as well as eggs (these food allergens are most common in young children) to identify the associated symptoms (Table 5). Analysis of FA prevalence revealed that these symptoms appeared 5- to 10-fold less frequently in children of 4 years old or over compared with younger children. Although the overall frequency of symptoms by age was comparable between children allergic to cow's milk and dairy and those allergic to eggs (χ^2=0.085, P=0.782), significant differences were noted in the frequency of individual symptoms between

Table 1. Demographics and physical characteristics of children (n=2540)

Variables	n (%)
Subjects	2540 (100)
Boys	1331 (52.4)
Girls	1209 (47.6)
Age (y), mean±SD	4.6±1.1
1 to 3	368 (14.5)
>3 to 4	785 (30.9)
>4 to 5	749 (29.5)
>5 to 6	554 (21.8)
>6 to 7	84 (3.3)
Height (cm), mean±SD	107.4±8.6
Weight (kg), mean±SD	18.6±3.8

SD: standard deviation.

Table 2. History of allergy and allergic reactions in children and their families (n=2540)

History of allergic diseases	Children, n (%)	Father, n (%)	Mother, n (%)	Siblings, n (%)
Food allergy	102 (4.0)	76 (3.0)	81 (3.2)	15 (0.6)
Drug allergy	132 (5.2)	74 (2.9)	119 (4.7)	15 (0.6)
Allergic purpura	5 (0.2)	72 (2.8)	79 (3.1)	13 (0.5)
Allergic dermatitis	127 (5.0)	264 (10.4)	224 (8.8)	43 (1.7)
Bronchial asthma	107 (4.2)	15 (0.6)	18 (0.7)	8 (0.3)
Allergic conjunctivitis	33 (1.3)	8 (0.3)	25 (1.0)	5 (0.2)
Allergic rhinitis	351 (13.8)	3 (0.1)	8 (0.3)	15 (0.6)
Anaphylactic enteritis	5 (0.2)	76 (3.0)	79 (3.1)	15 (0.6)

Table 3. Prevalence of allergy to common food allergens in children (n=2540)

Food	n (%)
Eggs	36 (1.4)
Cow's milk and dairy products	48 (1.9)
Fish	15 (0.6)
Shrimp	112 (4.4)
Beef	18 (0.7)
Wheat	3 (0.1)
Cashew nuts, hazelnuts, almonds, and other nuts	3 (0.1)
Potato	3 (0.1)
Chocolate	3 (0.1)
Peanut	10 (0.4)
Soybeans	5 (0.2)
Crab	81 (3.2)
Mango	58 (2.3)

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Table 4. Prevalence of symptoms due to food allergy in children (*n*=2540)

Symptoms	*n* (%)
General symptoms	
General malaise and fatigue	38 (1.5)
Fever and loss of appetite	79 (3.1)
Headache	13 (0.5)
Facial symptoms	
Flushed cheeks, nose tip, and earlobe	142 (5.6)
Moist ear canal	8 (0.3)
Dry lips	30 (1.2)
Drooping or swollen eyelids	33 (1.3)
Itching, red, or swollen eyes	79 (3.1)
Earache	5 (0.2)
Gastrointestinal symptoms	
Nausea	43 (1.7)
Vomiting	53 (2.1)
Abdominal pain	53 (2.1)
Abdominal distension and diarrhea	46 (1.8)
Myxoid or thin watery stool	53 (2.1)
Skin symptoms	
Pruritus	292 (11.5)
Angioedema	3 (0.1)
Erythema	109 (4.3)
Purpura or petechia	8 (0.3)
Rashes	147 (5.8)
Eczema	135 (5.3)
Urticaria	145 (5.7)
Respiratory symptoms	
Wheezing	74 (2.9)
Runny nose	310 (12.2)
Sneezing	353 (13.9)
Nasal congestion	295 (11.6)
Cough	292 (11.1)

Table 5. Age at diagnosis and allergic reactions to cow's milk or dairy products (*n*=2540)

Variables	Cow's milk and dairy products, *n* (%)	Eggs, *n* (%)
Age at diagnosis		
0-3 y	150 (5.9)	58 (2.3)
4 y	15 (0.6)	13 (0.5)
Allergic symptom		
Vomiting	28 (1.1)	13 (0.5)
Diarrhea	18 (0.7)	3 (0.1)
Constipation	15 (0.6)	5 (0.2)
Eczema	121 (4.8)	48 (1.9)
General malaise, crying, or irritability	10 (0.4)	10 (0.4)

both the subgroups (χ^2=48.285, P<0.001).

Logistic regression analysis of the effect of other potential factors on FA in the children indicated that the duration of breast-feeding in infancy was not significantly correlated with FA in children (Table 6). Multivariate logistic regression revealed that a history of FA and allergic rhinitis in first-degree relatives was significantly associated with FA in children (P<0.05). Spearman's rank-order correlation coefficient analysis indicated that FA in children was correlated with a history of drug allergy (rs=0.049, P=0.035), allergic dermatitis (rs=0.052, P=0.023), bronchial asthma (rs=0.051, P=0.025), allergic conjunctivitis (rs=0.071, P=0.002), and allergic rhinitis (rs=0.059, P=0.010).

Responses to the questionnaire items on the knowledge of allergic diseases indicated that the parents or guardians had poor awareness of these diseases, with 44.7% reporting that they knew little about the types of allergic disease and related symptoms, and only 3.6% reporting that they knew something about these entities. When the parents or guardians were asked about what they would do if their children presented with allergy-like symptoms, only 11% replied that they would take their children to the hospital for consultation and treatment, 64.8% reported that they would not consult any medical provider, and 65.3% dismissed the need for any attempt to alleviate or treat their children's allergic symptoms.

Discussion

The prevalence of FA is an important consideration in the evaluation of public health. FA may cause severe allergic reactions and even death, but the most reliable treatment remains to be avoidance of allergens.[10] Providing clear food ingredient labels is thus the most essential and effective method to help patients ward off sensitizing food allergens.[22] Unfortunately, current

Table 6. Multivariate analysis of potential risk factors associated with food allergy in the study

Factors	Unadjusted OR (95% CI)	P^*	Adjusted OR (95% CI)	$P^\dagger$
Duration of breastfeeding ≥4 mon	1.06 (0.65-1.71)	0.823	1.339 (0.843-2.126)	0.216
Allergy history of close relatives				
Drug allergy	3.29 (1.84-5.86)	0.000	0.825 (0.381-1.788)	0.626
Allergic dermatitis	2.06 (0.96-4.40)	0.063	0.825 (0.381-1.788)	0.071
Allergic rhinitis	2.22 (1.36-3.63)	0.002	1.958 (1.029-3.727)	0.041
Bronchial asthma	3.30 (1.13-9.62)	0.029	1.652 (0.520-5.246)	0.395
Allergic conjunctivitis	3.06 (0.90-10.41)	0.073	0.655 (0.189-2.267)	0.504
Anaphylactic enteritis	12.22 (2.20-67.80)	0.004	2.561 (0.427-1.547)	0.304
History of allergic diseases in fathers	2.93 (1.80-4.77)	0.000	0.815 (0.429-1.547)	0.532
History of allergic diseases in mothers	2.74 (1.68-4.48)	0.000	0.747 (0.400-1.395)	0.359
History of allergic diseases in siblings	3.24 (1.43-7.38)	0.005	1.294 (0.536-3.122)	0.566

OR: odds ratio; CI: confidence interval. *: univariate logistic regression model; †: multivariate logistic regression model, adjusted for all the variables listed in the table.

efforts in this area are yet to be reinforced in light of the concerning food safety issues over the recent years in China. A great number of FA patients experience lowered life quality owing to the considerable stress involved in self-deciding their daily diets.[23] For children, the problem can be even greater because unguided, overdone avoidance of foods would result in physical underdevelopment. This may be part of clinical relevance in the present epidemiological study.

The double-blind placebo control food challenge (DBPCFC) is the gold standard for the diagnosis of FA, as it has the highest specificity among all the currently relevant tests.[2,24] However, DBPCFC is time consuming, costly, and inconvenient to use; in addition, there has been no globally recognized uniform protocol for DBPCFC or for interpreting the DBPCFC results. Skin prick test and serum-specific immunoglobulin E test represent the two methods most frequently used in clinical practice. Unfortunately, the lack of standardization in commercially available products of food allergen extracts used in these tests may, at least in part, account for the inconsistency between test findings and clinical symptoms. Owing to these difficulties, laboratory data are limited in reflecting the incidence of FA in the real world. Because of this, epidemiological surveys have been widely used in studying FA over these years.[12,13,15]

In the present study, responses to the questionnaire indicated that 4.0% of the children had a history of physician-diagnosed FA, which was close to the rate of 4.6% reported by Leung and colleagues.[25] Moreover, 22.4% of the parents or guardians in the present study believed that their children had FA but were uncertain of its cause, as compared with 8.1% reported by Leung et al[25] and the rate was similar to 25.0% reported by Asero et al.[26] However, a comparison of these findings may be difficult as the causes of FA may differ across the geographical regions under survey. The study population in Leung et al's survey[25] comprised preschool children in Hong Kong whose parents reported full awareness of allergic diseases, whereas 44.7% of the parents in the present study had little knowledge about allergic diseases. Therefore, the parents in the present study were likely to confuse FA with food intolerance.[27] Moreover, since only 11% of the parents reported that they would seek medical attention after onset of a probable allergic reaction in their children, the incidence of FA in Guangdong Province may not have been properly estimated as expected, rendering the need for proactive actions for patient education.

According to the parents in the present study, the foods that most frequently induced FA symptoms in their children were shrimp (4.4%), crab (3.2%), mango (2.3%), cow's milk and dairy products (1.9%), eggs (1.4%), and beef (0.7%). Our findings regarding shrimp and crab were consistent with those of Leung and colleagues who reported crustacean seafood as the most common food in Hong Kong leading to FA.[25] In Singapore, crustacean seafood and cubilose have been identified as the foods most likely to cause allergic reactions, and these account for up to 40% of childhood FA.[28,29] However, our findings regarding the remaining food allergens in terms of their relation to allergic reactions differed from those reported in the Hong Kong study. In particular, while peanuts have been identified as one of the major allergens in developed countries, with the incidence of peanut allergy being 1.1% in the United States[30] and 1.4% in Switzerland,[31] the incidence rate has been reported to be as high as 8.1% in Hong Kong.[25] We speculated that this difference may be attributed to the geographical diversity in genetics, lifestyle, and/or dietary habits. In addition, these findings also shed light on the importance of clear labeling of food package ingredients to help patients with FA avoid consumption of offending food allergens.[32]

In the present study, a history of physician-diagnosed FA was found in 3.0% of fathers and 3.2% of mothers (Table 2), which was comparable to the data from Europe and America.[2,21,33,34] The results also suggested that a history of FA, allergic rhinitis, and anaphylactic enteritis in first-degree relatives (father, mother, and siblings) and a history of drug allergy, allergic dermatitis, bronchial asthma, and allergic rhinitis in children may be associated with a higher risk of childhood FA.

Eczema appears to be among the common symptoms of allergies early in life.[35] In our study, eczema was the most prevalent allergic symptom among children allergic to cow's milk, and was reported to occur at 2-3 months of age. The immature digestive and immune functions in newborns and young children and the resulting vulnerability of their guts to food allergens may explain the higher rate of allergy to cow's milk, which is usually among the earliest foods given to babies. It has been shown that allergic diseases in humans occur in a sequential manner according to age, such that FA is more common at a younger age, whereas an increasing prevalence of sensitization to inhalant allergens is noted at an older age.[36,37,38] Similarly, some children may grow out of sensitization to certain foods (such as cow's milk, dairy products, and eggs) or experience a switch in the offending allergens from these foods to inhalant allergens (e.g., dust mites, pollen, and pet dander) as they get older.[39] Such a sequence of events may be the result of "allergy march",[40] and in the present study, may underlie the lowered prevalence of allergy to cow's milk and eggs

after the age of 4 years compared with that during ages 0 to 3 years. Knowledge of the evolving prevalence of FA with age would help early diagnosis and intervention of this condition in a large geographical region such as Guangzhou Province, China. Other studies[21,41,42] indicate that the duration of breastfeeding and sex are important factors in the development and occurrence of FA. In contrast to the results of the present study, which identified that a history of FA and a history of allergic rhinitis in the first-degree relatives were the 2 main factors affecting the incidence of FA in children, Leung et al[25] identified that breastfeeding duration and sex were the 2 main factors.

There are several limitations in the present study. First, due to the retrospective design of our survey and many other studies, there would inevitably be a recall bias for the parents when completing the questionnaires, which may compromise the accuracy of the responses. Second, the study questionnaire was designed to investigate the major food allergens in the region under survey; hence, we used a list of the 13 common rather than a full spectrum of food allergens in our analysis. Therefore, further studies focusing on more food allergens in southern China are needed. Third, the parent-reported physician diagnosis of allergy in their children may not have been absolutely reliable. This is a common drawback in many studies based on self-reporting. Even in studies that did not rely on self-reporting, such as the one conducted in the United Kingdom,[43] the incidence of FA was found to be 2.5% when children were examined using the oral food challenge test and/or a combined review of medical history and skin test, but only 1.6% when examined using the DBPCFC. However, the disadvantages of the DBPCFC in terms of safety and operability compromise its use for clinical investigation of large samples.

Nevertheless, the present study provides epidemiological data indicating that the incidence of FA in preschool children in Guangdong Province is similar to that in Europe and the United States, and that the most common food allergens may differ across these regions; moreover, the incidence of childhood FA to crustacean seafood, mango, and cow's milk and dairy products was higher in Guangdong Province. A family history of allergic disease was also found to be associated with higher risk of FA among preschoolers in Guangdong Province, southern China.

Funding: Guangdong Natural Science Foundation (No. S2013010014728), Guangzhou Bureau of Science Technology & Information Project (No. 201400000002), Guangzhou Bureau of Health Project (No. 20151A010094). The funders were not involved in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Ethical approval: The protocol of this study was approved by the Ethics Committee of First Affiliated Hospital, Guangzhou Medical University (No. GYFYY-2013-02-20). Written informed consent was obtained from parents or guardians of all children before they participated in this study.

Competing interest: The authors have no conflicts of interest related to this article.

Contributors: Zeng GQ and Luo JY contributed equally to this study.

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Received November 18, 2014
Accepted after revision March 16, 2015