

Association of dietary patterns and food allergy in infants during the first year of life

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SUMMARY

Introduction. There is controversy about the effect of dietary patterns during the first year of life and the occurrence of food allergy. The objective of this study was to evaluate the association between family history of allergy, allergic manifestations and dietary patterns during the first year of life in infants with and without food allergy.

Population and methods. We performed a descriptive cross-sectional study in children under 2 years of age (n= 99), sorted in two groups: allergic group (n= 50) and control group (n= 49), matched by socioeconomic status, age and gender. Food allergy was defined by internationally approved clinical criteria, prick and patch tests, and response to diet. Information on diet, clinical data and history of allergy in the parents were collected. The sample size was estimated for logistic regression (Freeman), and Student χ^2 and Mann-Whitney tests were used. The study and consent forms were approved by the Ethics Committee of the Institute of Nutrition and Food Technology (Instituto de Nutrición y Tecnología de los Alimentos, INTA) and the Universidad de Chile.

Results. The allergic group showed a significantly higher prevalence ($p < 0.0001$) of family history of allergy (84%) than the control group (16%). Diarrhea was the symptom most frequently reported by the mothers of allergic infants during the first year of life. Bottle feeding was introduced earlier in the allergic group than in the control group (3 versus 6 months [$p < 0.03$]); no differences regarding the start age for supplementary feeding was found. When performing logistic regression, only the family history of allergy was associated with a higher risk of food allergy (OR: 48.2; CI= 14.2-164; $p < 0.001$).

Conclusions. The early introduction of milk formula could promote the occurrence of food allergy in infants frequently presenting family history of allergy.

Key words: food allergy, breastfeeding, supplementary feeding, family history, infants.

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INTRODUCTION

Food allergy is a failure of the oral tolerance phenomenon in genetically-predisposed individuals, a reaction that may be mediated by antibodies (IgE, IgG, IgA or IgM) or by cells, with wide variety of clinical manifestations.^{1,2}

Genetic predisposition is an important risk factor, with allergy being described in up to 70% of the children of allergic parents.³ The genetic base cannot be modified,⁴ but there are environmental factors to modulate the appearance of food allergy.⁵ In this context, the role of diet during the first year of life could be a determining factor.⁶

Food allergies are more frequent in infants, presumably due to the immaturity of immune and non-immune mechanisms that prevent the entry of antigens through the gastrointestinal barrier.^{7,8} Milk, eggs and peanuts are the most common food allergens in early infancy and childhood. Peanut allergy, though less common than allergy to eggs or milk, is more often associated with serious allergic reactions, including anaphylaxis.⁹

Recent studies indicate that food allergy prevalence has increased in the US and Europe.^{10,11} Currently, this condition affects approximately 2% of the general population and close to 4-8% of American children.¹² According to a meta-analysis conducted predominantly in European countries, the estimated prevalence of food allergy mediated by IgE ranges between 0-3% for milk, 0-1.7% for egg and 0.2-1.6% for peanut.¹³

Recently, the American Academy of Pediatrics¹⁴ and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition¹⁵ published their new guides on nutrition and prevention of allergy in infants and children. Apart from recommending exclusive breastfeeding to 6 months of age, it proposes that supplementary feeding should not be introduced before 17 weeks and all infants should start a solid diet no

later than week 26.¹⁵ Avoiding or delaying the introduction of potentially allergenic food, such as fish or eggs, is not recommended. Additionally, an elimination diet during pregnancy and breastfeeding is not recommended.¹⁶

Dietary practices represent a risk factor potentially modifiable for preventing allergy.¹⁷ Factors related to maternal and infant diet, such as placental transfer, breast milk, baby formulas and supplementary feeding, represent the usual way by which infants come into contact with antigens. The possibility of avoiding the incorporation of food allergens through the manipulation of the diet during pregnancy or early childhood remains controversial.¹⁶

The objective of this study was to evaluate the association between dietary patterns during the first year of life, the family history of allergy and the risk of developing food allergy in a sample of Chilean infants under two years of age.

POPULATION AND METHODS

The sample studied was made up of infants referred to the Immunology, HIV and Allergies Division of the Department of Medicine, Clinical Hospital of the Universidad de Chile (HCUCH), and they were assigned to the allergic group. The sample of infant controls was obtained from Health Centers and Day Care Centers of Santiago, which were matched by age (interval of 15 days), sex and socioeconomic status. There were no differences in terms of the groups' ethnicity, since we worked in the Santiago district and no infants with parents of Mapuche origin (main national ethnic group) were included.

Inclusion criteria: infants aged 6 to 24 months with a birth weight ≥ 2500 g.

Exclusion criteria: presence of medical conditions such as genetic, autoimmune and metabolic diseases.

Elimination criteria: presence of medical conditions during the study period or parents who rejected to participate after protocol entry.

Collection of information: a semistructured interview was conducted, in which an *ad-hoc* form was given to the mother. Clinical history, skin tests performed and information needed to confirm the diagnosis by the disappearance of symptoms after the elimination diet were recorded.

Socioeconomic status (SES): categorized by the classification proposed by ESOMAR Chile. This method, originated in Europe, has been previously validated in Chile; it is based on two outcome variables:¹⁸ level of education and occupational category of the main supporter of the home. Both

outcome variables are combined in a "Socioeconomic classification matrix", to determine the SES of the family

Allergic manifestations were used as dependent variable (see below).

The independent variables were: i) family history (family history of allergy, appearance or absence of allergy history in the father and/or mother and/or sibling(s)); ii) dietary pattern (described as duration of breastfeeding and start age of supplementary feeding, categorized in breastfeeding ≥ 4 m and supplementary feeding at ≥ 6 m; breastfeeding ≥ 4 m and supplementary feeding at < 6 m; breastfeeding < 4 m and supplementary feeding at ≥ 6 m; breastfeeding < 4 m and supplementary feeding at < 6 m); iii) interaction of outcome variables.

Nutritional status: based on the ministerial technical standard for the assessment of nutritional status in children under 6 years (instrument referring to the growth standards of the World Health Organization [WHO] 2007), we assessed the nutritional status based on the weight for height indicator, according to weight and height for the age.¹⁹

Operational definitions

Diagnosis of allergy in children: it was based on: i) allergic manifestations described by the primary care physician that referred the infant to the Immunology Service, from where the cases were collected; ii) the positive result of certain foods prick and patch tests; and, iii) the improvement of symptoms after eliminating the allergen.

The clinical diagnosis of allergy required the fulfillment of the three criteria described above and was performed in infants in the allergic group. Infants in the control group were recruited in primary health centers, nurseries and kindergartens of the same geographic area (Metropolitan Area). For control infants, information was obtained from the child's medical record, the health control card and by the survey given during the semistructured interview.

Allergic manifestations: the symptoms that motivated the initial consultation were the cause for a presumptive diagnosis of allergy by the doctor who referred the patient to the specialist. Symptoms were defined operationally: 1) skin: recurrent pruritus, atopy, exanthema or urticaria, eczema, rash; 2) respiratory: wheezing, obstructive signs for more than 24 h responding to bronchodilators, allergic rhinitis; 3) digestive: vomiting, diarrhea, rectal bleeding, moderate to severe esophageal reflux or constipation without proven cause, colic pain making the child cry for

more than an hour a day, two or three times per week; 4) others: the child slept less than 6 h a day (greater insomnia and sleep fragmentation has been described in allergic infants).²⁰

Family history: it was considered positive when at least the father/mother and/or a sibling had a history of asthma: when the diagnosis for allergic asthma was performed in a hospital service and/or the family member used bronchodilators.

- *Rhinoconjunctivitis:* history of one or more of the following symptoms: cluster sneezing, nasal congestion and itching and transparent mucous secretion, along with eye redness, pruritus and tearing, with droopy eyelids.
- *Atopic eczema:* diagnosed by a doctor, including chronic pruritic dermatitis or chronic relapses; or having a history of eczema with typical occurrence and location (diagnosis conducted by the treating specialists).
- *Food allergy:* history of pruritus in skin and/or rash and/or lip inflammation and/or lip pain and edematous tongue and/or vomiting and/or diarrhea after eating certain type of food, having had a positive retest (reaction to the consumption of a food antigen).

Taking into consideration feeding, operational definitions were:

Dietary pattern: the sequence and time for introduction of food to the infant, including the presence and duration of breast or bottle feeding, and the inclusion date of supplementary feeding and its components.

Exclusive breastfeeding: administration of breast milk as the only food to cover the nutritional needs, not requiring any other foods or aggregates.²¹

Supplementary feeding: administration of any food other than milk.²¹

Ethical considerations. Prior to the interview, the mother and/or father received detailed information about the study, and those who agreed to participate signed the informed consent. The study and informed consent were evaluated and approved in March 2007 by the Ethics Committee for human research of INTA and HCUCH.

Sample size and statistical analysis. The sample size was calculated according to criteria by Freeman et al.,²² proposing ten events of interest by analyzed outcome variable; considering the variables family history of allergy, dietary pattern, their interaction and allergic manifestation, a sample of 50 children was calculated for each group. Data were validated and

normality was evaluated by the Shapiro-Wilk test. We used the Student t test, the chi-square test and the Mann-Whitney test for differences between the groups according to their normality and type of variable. Subsequently, to evaluate the risk of allergy we used a logistic regression model that included three independent outcome variables: family history (2 categories), dietary pattern (4 categories) and interaction, being the allergic manifestation (allergic/control group) the dependent variable. A significance level with a *p*-value <0.05 was used and the data analysis was performed using the software SPSS® v.15.0.

RESULTS

A total of 100 children, 50 cases and 50 consecutive controls were included in this study, collected between May 2007 and February 2008. The final sample analyzed was formed by 99 infants, 50 allergic children and 49 healthy controls; one infant from the control group whose mother decided to withdraw from the study was discontinued. The characteristics of infants are shown in Table 1.

Diarrhea was the symptom most frequently reported by mothers of the allergic infants during the first year of life (Figure 1). The frequency of broncho-obstructive syndrome did not differ between both groups.

In the allergic group, a family history of allergy was significantly more frequent (84% versus 16% in controls, *p* < 0.001) and the current height/age indicator was significantly lower (71 ± 7.2 versus 74.3 ± 7 cm) in comparison to the control group (*p* < 0.03).

We found no differences between dietary patterns of both groups. Almost all children (96%) were breastfed infants and the median (interquartile range) duration of exclusive breastfeeding was of 4 (2-6) and 5 (2.5-6) months in the allergy group and control group, respectively, with no significant differences. Similarly, the median (interquartile range) starting age for supplementary feeding was of 6 (5-6) months in both groups. On the contrary, introduction of bottle feeding occurred earlier in the allergic group: 3 (1.4-16) versus 6 (2.75-12) months, respectively, *p* < 0.03) as well as the inclusion of foods other than milk before 8 months of age, being earlier in the allergic group (*p* < 0.02). Finally, there were no differences in the time for inclusion of cereals, fish/shellfish, seeds (peanuts, nuts or almonds), meats (red or white) or legumes during the first year of life.

The univariate logistics regression analysis re-

vealed that family history of allergy (OR: 48.29, [CI: 14.22-164.04], $p < 0.001$) –not the dietary pattern– determined the greater risk for presenting allergic manifestations. By categorizing the outcome duration of exclusive breastfeeding (≤ 4 months or >4 months) and supplementary feeding (<6 months or ≥ 6 months), we found no significant differences between the groups.

DISCUSSION

This study shows that the presence of allergic manifestations in infants under 2 years is mainly associated to the family history of allergy and to the early incorporation of milk formulas. The frequency of allergy in infants with a family history of allergy in our sample (84%) is greater than what was reported for inheritance of atopic syndrome, since some reports indicate that 66% of newborn infants with a history of atopy develop the allergic disease.^{23,24}

Our results show that bottle feeding was introduced earlier to the diet of allergic infants, with no differences in the age of introduction or duration of breastfeeding. The first is consistent with studies showing that early introduction of cow milk is associated with greater sensitivity to its protein;²⁵ it is suggested that incorporating a milk formula early in this high risk group would favor the appearance of symptoms in the infants.²⁶ On the

other hand, the beneficial effects of breastfeeding have been historically described in children with genetic predisposition to allergy.²⁷ Despite this, the protecting role of breastfeeding has been recently questioned;²⁸ various studies have reported an association between duration of breastfeeding with a greater risk of developing asthma, atopy and atopic dermatitis.²⁹ However, in a critical review of the subject, Muraro et al.³⁰ concluded that exclusive breastfeeding for at least 4 months in infants with a high risk of developing atopic syndrome, is associated with a lower cumulative incidence for developing allergy to cow milk protein at 18 months of age.

Gastrointestinal and skin symptoms turned out to be the most frequent cause that led to suspecting an allergic disorder. Among the first, diarrhea, colic, gastroesophageal reflux, constipation and bloody stools are all frequent symptoms in the evaluated age group. The results are consistent with those reported by Sicherer,³¹ who reviewed the spectrum of clinical gastrointestinal allergic manifestations in infants and children concluding that these symptoms would be associated to allergic phenomena in the early stages of life.³¹

It could be suggested that the symptoms described above are as “expected” because they are frequent symptoms in the first year of life, usually explained by the physiological limitations existing at this age; but it should be noted that these

TABLE1. General characteristics of the sample

Outcome variable	Group		p value
	Allergic (n= 50)	Control (n= 49)	
Age (months)**	12.4 $\pm$ 5.2	12.5 $\pm$ 5.6	NS
Male gender (%)	26 (52)	24 (49)	NS
Socioeconomic status (%)			
Very high/high	32	31	NS
Upper-middle/middle	56	45	NS
Middle-low/low	12	24	NS
Presence of family history of allergy (%)	84	16	< 0.001
Weight at birth (g)**	3318 $\pm$ 435	3386 $\pm$ 420	NS
Height at birth (cm)**	49.9 $\pm$ 2.8	50.1 $\pm$ 1.8	NS
Weight at birth (%)			
2500 to 2999 g	30	22.4	NS
3000 to 4000 g	66	69.4	NS
> 4000 g	4	8.2	NS
Current weight (g)*	8460	9840	NS
Current height (cm)**	71 $\pm$ 7.2	74.3 $\pm$ 7	0.03

*Data expressed as medians; **data expressed as mean $\pm$ standard deviation.

Significant differences between groups: $p < 0.05$; Mann-Whitney U test or Student t test as appropriate.

patients were referred to the specialty center for a lack of response to the treatment of these symptoms, conducted at primary care level, and this is precisely one of the criteria internationally agreed at present to suspect that the manifestations may be allergic. On the other hand, the skin is one of the target organs more frequently involved in hypersensitivity reactions, with a wide spectrum of symptoms, such as dermatitis, rash and angioedema, all commonly present in food allergy reactions.³² In our sample, atopic dermatitis was mainly reported among allergic infants and was really infrequent in the controls, which is consistent with that published in the literature.

Overall, the results suggest that in the case of symptoms as those described, in a child with a family history of allergy, it would be appropriate to perform a presumptive diagnosis of allergy and refer the patient to a specialist. Given the high frequency of the symptoms described, identifying the family history would represent a useful tool to decide whether the patient should be referred or kept at the local doctor's office.

Our results also show that allergic children present significant differences in relation to their current height compared to the control group; this

data can be explained by the late diagnosis. This finding is relevant for the nutritional monitoring conducted by mother and child programs, since it is clear that the referral and diagnosis should be done as early as possible, with a specialized diet treatment.

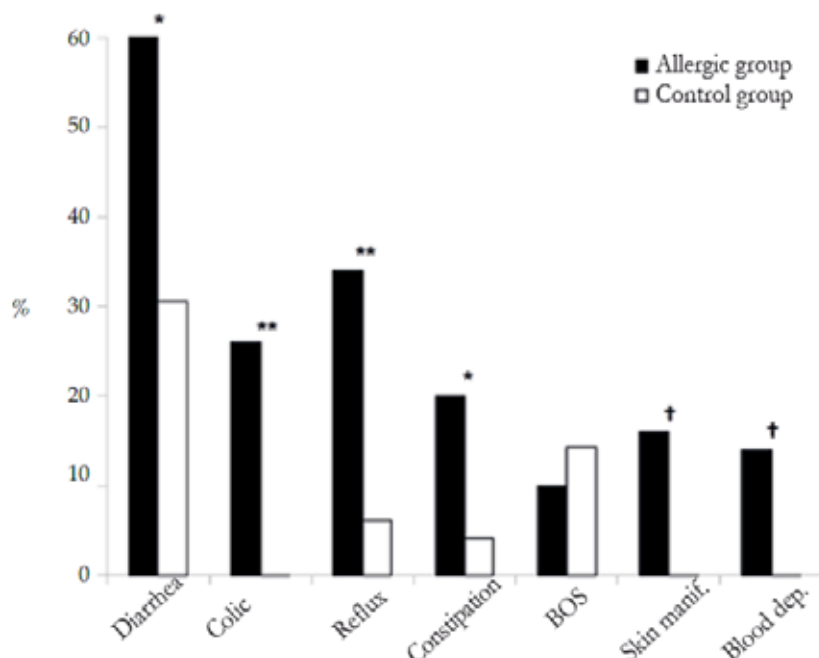
It is important to note that the control subjects were recruited from different centers of the Metropolitan Area, for which it was not possible to control all the environmental variables that could influence the results of the study. Another limitation is related to recall bias, since it were the mothers who described the chronological order of introduction of food to their children and provided the family history.

On the other hand, the main strength of this study was the possibility of having patients diagnosed at a national referral center for the clinical diagnosis of allergy.

CONCLUSIONS

This study shows that, in infants, the early introduction of milk formula is associated with the presence of food allergy and that the most important risk factor for its development is the parents' family history of allergy. It is important to con-

FIGURE 1. Clinical characteristics related to allergic symptoms according to the group



Significant differences between both groups, chi-square test, * $p < 0.003$, ** $p < 0.0003$, † $p < 0.004$. BOS= broncho-obstructive syndrome.

sider these results at the time to indicate the consumption of artificial milk formulas, especially in infants whose parents have a history of allergy.

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