



Risk factors in food allergy

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RESUMEN

La alergia alimentaria o hipersensibilidad alimentaria alérgica es la reacción inmunológica adversa causada por mecanismos inmunológicos mediados o no por IgE. Es una enfermedad compleja, influida no sólo por factores de herencia poligenética sino también medioambientales. Se han implicado factores de riesgo pre y posnatales, con resultados variables y controvertidos; por tanto, es importante basarse en evidencia científica para dilucidar su verdadero papel en esta enfermedad. De los agentes estudiados, los principales factores de riesgo asociados con alergia alimentaria son la herencia atópica, la falta de lactancia materna exclusiva por al menos tres a seis meses y el destete temprano (antes de los cuatro a seis meses de vida).

Palabras clave: alimentos, reacciones adversas, alergia alimentaria, intolerancia a alimentos.

ABSTRACT

Food allergy or allergic food hypersensitivity is defined as an adverse immunologic reaction caused by immunologic mechanisms mediated or not by IgE. It is a complex disease influenced by polygenetic heritage and environmental factors. Many risk factors have been investigated, pre natal and post natal, and variable and controversial results have been obtained. The most important risk factors associated with food allergy are atopy, lack of breast feeding at least three to six months and early weaning (before four-six months).

Key words: adverse food reactions, food allergy, food intolerance.

Food allergy is a complex disease. Not only influenced by polygenic genes but also environmental factors. This has been one of the least studied allergies even though it has been recognized as an important problem within western countries. It as well as other allergies have been increasing; 3.5 to 4% of Americans are considered to have food allergy¹ and 4 to 6% of world child population are believed to be affected by this.

Recently a group of experts (TASK FORCE) from the European Allergy and Immunology Academy published a review with listings of food allergies² which varies with respect to the listings accepted in the US, where side

effects to food or food hypersensitivity are highlighted as any abnormal reaction provoked by the ingestion of certain food and can be the result of intolerance to food (non allergic food hypersensitivity) or allergic food hypersensitivity (food allergy) [figure 1].

Food allergy or allergic food hypersensitivity is defined as the adverse reaction caused by immunologic mechanisms, which may or may not be mediated by immunoglobulin E (IgE).³ It is important to differentiate from food intolerance or non allergic food hypersensitivity, which is an adverse response caused by the host's physiological characteristics,⁴ for example, metabolic disorders (lactase deficiency). Toxic reactions can imitate food hypersensitivity and are provoked by factors pertaining to the food such as toxic pollutant (histamine from shellfish poisoning) or pharmacological substances contained in the food (tyramine in staled cheese). These types of reactions can affect any healthy person when these substances are consumed in large amounts.³

Food allergy or allergic food hypersensitivity manifests clinically in diverse ways, depending on the immunologic causing it (figure 2). The most common are those measured by IgE, which can affect skin (urticaria, angioedema), followed by the gastrointestinal type (oral allergy syndrome, vomit, diarrhea, etc.).

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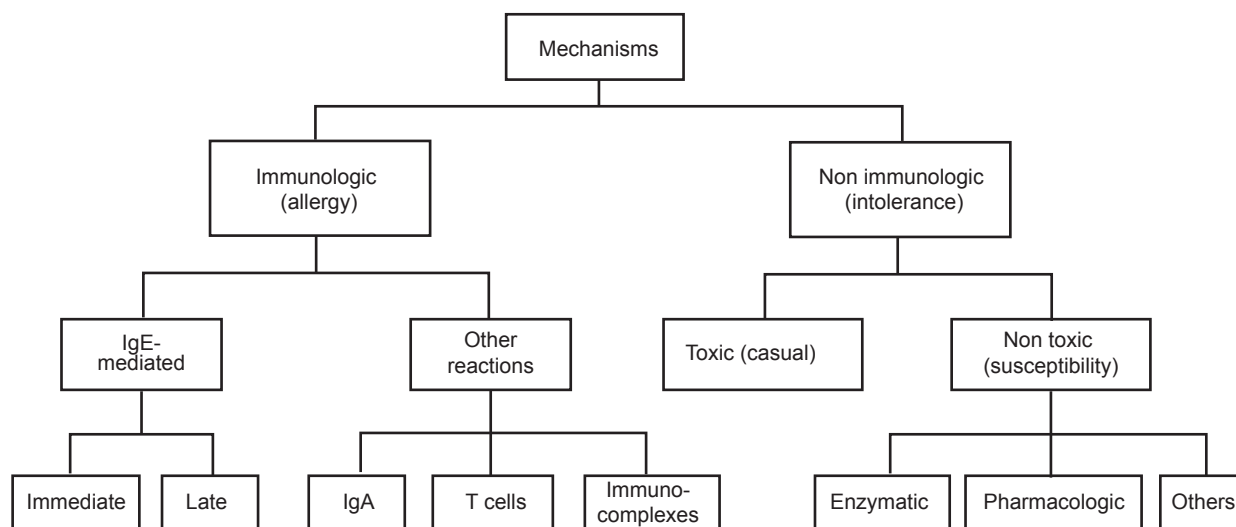


Figure 1. Classification of the adverse food reactions.

In the last decade studies have focused on protecting factors that improve the tolerance to causing agents (allergens), still, the ones that help discover predisposing factors to food allergy are very few. The objective of this study is to review the main factors implied in food allergies.

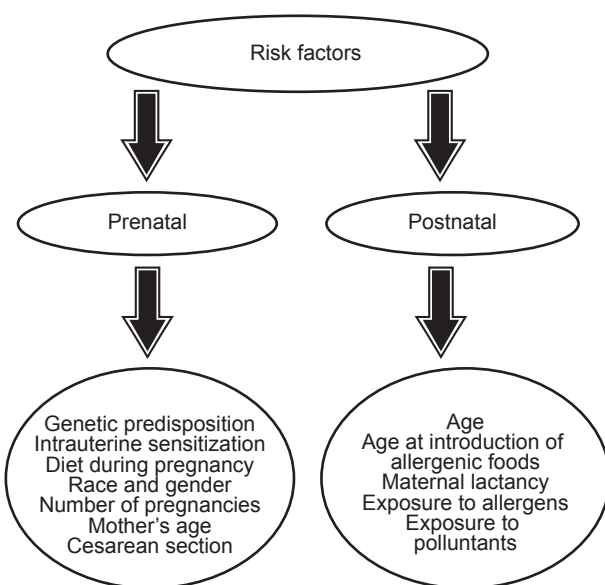


Figure 2. Risk factors associated to food allergy.

FOOD ALLERGY PREVALENCE

Food allergy prevalence is greater during the first few years; it affects nearly 6% of patients under three years of age⁵ and decreases progressively during the person's first decade.

Children with allergic illnesses usually have greater prevalence of food allergy, for instance, 35% of children with moderate to severe atopic dermatitis have food allergy mediated by IgE,⁶ and between 6% to 8% of asthmatic children have wheezes induced by foods (table 1).

Based on recent studies, 3.5% to 4% of American population have food allergy, the prevalence in the Mexican population is not known.²

WHAT SHOULD OUR RECOMMENDATIONS ON RISK FACTORS BE BASED ON?

Numerous risk factors that have been thought to be implied have been researched in food allergies with varying and controversial results; therefore, it is important to have the support with scientific evidence to study these.

The European Academy of Allergies and Clinical Immunology (EAACI) and the World Health Organization

Table 1. Food allergic hypersensitivity

IgE mediated	
Gastrointestinal	Oral allergy syndrome Gastrointestinal anaphylaxis
Cutaneous	Urticaria, angioedema, exanthema morbilliforms and erythema
Respiratory	Acute rhino-conjunctivitis, bronchial spasm
Generalized	Anaphylactic shock
Mixed: IgE and cell mediated	
Gastrointestinal	Eosinophilic allergic oesophagitis, eosinophilic allergic gastroenteritis
Cutaneous	Atopic dermatitis
Respiratory	Asthma
Cell mediated	
Gastrointestinal	Enterocolitis, proctocolitis and food protein-induced enteropathic syndromes; coeliac disease
Cutaneous	Contact dermatitis, herpes-like dermatitis
Respiratory	Food-induced pulmonary haemosiderosis (Heiner syndrome)

(WHO) propose a classification of two categories I or II with evidence level A or B, being the best evidence for recommending their results (table 2).⁷

Then, allergy prevention recommendation should be based mainly in randomized and controlled trials, with high quality conditions, in real life not being ethical or practical, therefore making them inoperable.

STUDIED RISK FACTORS

Prenatal and postnatal factors have been studied (figure 2).

Prenatal factors

Genetic predisposition

It is believed that in the same way there are genetic factors related to elevated risk of suffering other allergic diseases, there are also genetic factors that predispose to food allergy in individuals.

In the case of peanut allergy, a child has seven times more risk when having a parent or older brother with the

Table 2. Levels and grades in scientific studies

<i>Evidence level</i>	
Ia	Evidence obtained from meta-analysis and randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trial
IIa	Evidence obtained from at least one well designed controlled non randomized trial
IIb	Evidence obtained from at least one trial from another sort, well designed and almost experimental
<i>Grade evidence</i>	
A	Requires at least one controlled trial, randomized as part of the bibliography, of good quality and with recommendation level Ia or Ib
B	Requires the disposition of well conducted clinical trials, without randomization (evidence level IIa or IIb)

same allergy.⁸ A 64% greater risk is present in the case of monozygotic twins when a sibling or parent suffers this alteration.⁹ The influence of genes HLA class II and an elevated rate of coincidence in monozygotic twins have been shown (64%), in comparison with dizygotic (7%) which indicate a strong genetic contribution in peanut allergy.

A study showed association between nut allergy and polymorphism 6 in a signal transducer and a transcript activator.¹⁰ Besides, the risk of food allergy being four times greater in children with asthmatic parents has been proved, this in comparison to normal population.¹¹⁻¹³ This supports it being an inherit trait with a dominant genetic pattern, whether it be recessive or polygenetic, that is as pattern with variable expression.

The risk of food allergy is greater in children born from parents with a strong family background of atopy. In the case of only one parent this corresponds to 50%, in both parents this is 70%. In brothers the risk of being affected is 10 times greater than the general public.¹¹

Japanese population trial showed association between gene IL-10 polymorphism and food allergy.¹⁴ Another trial conducted in German population identified IL-13 polymorphism associated to this condition.¹⁵⁻¹⁶

Intrauterine sensitization

From week 11 in pregnancy small amounts of IgE are produced. In some cases an elevated number of IgE in

the umbilical chord at the moment of birth (> 0.8 UI/mL) and have been associated to a greater risk of allergies during their life.

Protein caused intrauterine sensitization is suggested in the amniotic fluid, which pass through the baby's skin and in a lesser degree through aspiration.^{17,18}

A trial conducted in Vancouver¹⁹ with high-risk children, identified before birth by having at least one parent with allergic disease, determined the concentration of IgE in the umbilical chord at moment of birth, with a followthrough of 12 months. The authors found that the concentration of IgE is a significant predicting factor for food allergy urticaria.

Diet during pregnancy

The option of offering a low allergen diet in pregnant women is still under discussion. There are different postures and recommendations made by the American Pediatric Academy (AAP) and the European Society of Clinical Pediatric Allergy and Immunology (ESPACI).⁸ The AAP does not recommend a diet during pregnancy with the only exception of excluding peanuts, while the ESPACI and the European Pediatric Gastroenterology Society, in a consensus review of prospective studies in children with high risk (at least one sibling –parent or sibling– with allergy), proved the protective effect different dietary programs have in the prevention of allergies in food allergy incidence, specially in milk protein.²⁰

Birth through Cesarean section

This could be a food allergy risk factor, due to the colonization delay in the baby's intestines. In a sample of 2,803 live babies this factor was studied and what was observed was that those born from allergic mothers had seven times greater risk of allergy to egg, fish and nuts,²¹ according to the observations by parents ($p = 0.005$) and four times greater risk of allergies from the same foods, based on the doctor's observations. In non-allergic mothers no significant differences were found between a Cesarean and a vaginal birth.

Male gender

Different studies have pointed out male gender being a risk factor in allergic diseases in general, but few assess the specific relation with food allergy.

A prospective cohort study²² made in With island (UK) included patients in prenatal period and followed the babies from birth to the age of four years looking for environmental and genetic influence in the appearance of allergic manifestations, they conducted cutaneous tests positive to food allergies at the age of four with an incidence of 3.7 for boys and 1.9 for girls.

Postnatal factors

Maternal lactation

Prospective observational trials report that exclusively maternal lactation, for a period of three to six months, decreases the risk of allergy to milk protein and food allergy by the age of three.²³

Saarinen and collaborators²⁴ conducted a prospective trial with followthrough to the age of three without intervention in non-selected children. They found that maternal lactation for a period of at least six months contributes to protection against food allergy. There is no doubt about the nutritional and immunologic importance of maternal lactation, however, the time it should be offered and the exclusiveness in breast-feeding the baby are the factors that influence in the appearance of allergies.

Diverse studies indicate that maternal lactation has a preventative effect compared to cow milk formula feeding.²⁵ Different metanalysis have shown that maternal lactation for a period of at least three months in babies with atopy inheritance is a protective factor against dermatitis atopy (OR 0.58) and recurrent wheezes in the first five years of age (OR 0.52).²⁶

The only random prospective trial compared maternal milk formula to cow milk formula in a sample of premature patients, and found that the cow milk diet increased the risk of atopic dermatitis and allergy to milk protein by the age of 18 months, this specially in the group that had atopic inheritance.²⁷

Other trial in children with atopic risk exclusively breast-fed for more than four months, with a delayed weans, had a significant allergic incidence reduction to cow milk and atopic dermatitis for the first four years of their life.²⁸

This sustains that the introduction of milk formulas before weaning is related to a greater incidence of developing allergy to cow milk protein.²⁹

The American Pediatric Society recommends that children with a high risk of allergy, identified by a strong family background of allergies (both or one parent and sibling), can benefit exclusively from maternal lactation or a highly hydrolyzed hypoallergenic formula.

Even though there are no conclusive studies with regard the nutrition committee of this association recommends the following:

- Children with high risk of atopy should continue with mother lactation during their first year of life; hypoallergenic formulas may be prescribed to complement feeding.
- Mother should remove peanuts and nuts from her diet as well as avoid egg, cow milk and fish.
- Mothers with a diet during their lactation should consider supplements with minerals (calcium) and vitamins.

Meanwhile the European Society of Clinical Pediatric Allergy and Immunology recommends the following:

- Maternal lactation during the first four to six months of life can reduce the incidence of allergic manifestations and is highly recommended.
- Supplementary food should not be administered before five months of life.
- Children with atopy risk (parents or sibling) and fed with formula should take confirmed low allergenic formula, this reduces food and milk protein allergy incidence.

Weaning

Beginning weaning between four and six months of life has been related to a greater incidence of cow milk and food allergy, this based on prospective observational trials.

These being backed up by the European Society of Clinical Pediatric Allergy and Immunology and the American Pediatric Academy based on a weaning guideline that sustains the introduction of solid meals at a short age is associated with the induction of food allergy.³⁰

Independently, the American Pediatric Association suggests:

Maternal feeding during the first year of life; weaning should not be started until the age of six months and introduction of milk until the age of twelve months, eggs and peanuts until two years, nuts and fish until three years.

While the European Society of Clinical Pediatric Allergy and Immunology only suggests maternal lactation for four to six months, with weaning after five months of age.

Kajosaari and Saarinen¹⁸ observed that introducing meal before six months old is related to the increase of food allergies and atopic dermatitis during the first year of life.

Fergusson and collaborators proved in a group of 1,210 children with a follow of ten years that weaning before six months of age is more frequently related to atopic dermatitis.³¹ Wilson and his group observed in a group of 674 children with a follow up of one year that wheeze incidence are of greater incidence in children weaned before 15 weeks of age.³²

Some authors indicate variations as to when begin weaning: some indicate that after four months, others after six, which has demonstrated a similar reduction to cow milk and other food allergy by the first 18 months of life.

Underweight at birth

Diverse studies have pointed out that underweight at birth is a high risk factor in developing allergies, but there are no studies that relate this to food allergy in particular.³⁴

Exposure to intra and extra-home allergens

Different tests have been made in order to know the effect of early age exposure to allergens associated to respiratory allergies, intra and extra-home^{35,36} (asthma, rhinitis); however, no data exist that relate them with food allergies.

Exposure to environmental pollutants

Exposure to tobacco fumes (main indoor pollutant) has been studied as a risk factor in allergic diseases. There is significant association between parents smoking (specially mother), asthma and wheezes during infancy,^{37,38} but they are in no relation with food allergies.

CONCLUSIONS

Based upon the revision of different articles, the main risk factors associated to food allergies are inheritance

(atopy), lack of exclusive maternal lactation during the first three to six months of age and early weaning (before four to six months of age).

The most important recommendations are: exclusive maternal lactation, independently of any atopic inheritance, avoiding exposure to cow milk and solid meals during the first four month of life.

REFERENCES

- Munoz-Furlong A, Sampson HA, Sicherer SH. Prevalence of self reported seafood allergy in the U.S. *J Allergy Clin Immunol* 2004;113(Suppl. 1):S100.
- Johansson S, Hourihane JO, Bousquet J, Brujinzeel-Koomen C, et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001;56:813-24.
- Sampson HA. Update on food Allergy. *J Allergy Clin Immunol* 2004;113:805-19.
- Sampson HA. Food Allergy. Part 1: immunopathogenesis and clinical disorders. *J Allergy Clin Immunol* 1999;103:717-28.
- Bock SA. Prospective appraisal of complaints of adverse reactions to foods in children during the first 3 years of life. *Pediatrics* 1987;79:683-8.
- Eigenmann PA, Sicherer SH, Borkowski TA, Cohen BD, Sampson HA. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics* 1998;101-8.
- Barton S. Which clinical studies provide the best evidence? The best RCT still trumps the best observational study. *BMJ* 2000;321:255-6.
- Hourihane JO, Dean TP, Warner JO. Peanut allergy in relation to heredity, maternal diet, and other atopic diseases: results of a questionnaire survey, skin prick testing, and food challenges. *BMJ* 1996;313:518-21.
- Sicherer SH, Furlong TJ, Maes HH, Desnick RJ, et al. Genetics of peanut allergy: a twin study. *J Allergy Clin Immunol* 2000;106:53-56.
- Amoli MM, Hand S, Hajeer AH, Jones KP, et al. Polymorphism in the STAT6 gene encodes risk for nut allergy. *Genes Immun* 2002;3:220-4.
- American College of Allergy, Asthma, and Immunology. Food allergy a practice parameter. *Ann Allergy Asthma Immunol* 2006(3 Suppl. 2);96:S1-68.
- Wahn U, von Mutius E. Childhood risk factors for atopy and the importance of early intervention. *J Allergy Clin Immunol* 2001;107:567-74.
- Hendrik N, Vibeke B, Celeste P. Environmental factors as a cause for the increase in allergic disease. *Ann Allergy Asthma Immunol* 2001;87(Suppl. 1):7-11.
- Campos-Alberto EJ, Shimojo N, Suzuki Y, Mashimo Y, et al. IL-10 gene polymorphism, but not TGF-beta1 gene polymorphisms, is associated with food allergy in a Japanese population. *Pediatr Allergy Immunol* 2008;19:716-21.
- Liu X, Beaty TH, Deindl P, Huang SK, et al. Associations between specific serum IgE response and 6 variants within the genes IL4, IL13, and IL4RA in German children: the German Multicenter Atopy Study. *J Allergy Clin Immunol* 2004;113:489-95.
- Lack G. Epidemiologic risks for food allergy. *J Allergy Clin Immunol* 2008;121:1331-6.
- Bjorkstén B, Jellman B, Zeiger R. Development and prevention of allergic disease in childhood. In: Middleton E, Reed C, Ellis E, Adkinson F, et al, editors. *Allergy principles and practice*. 5th ed. St Louis: Mosby 2003;pp:816-37.
- Annesi-Maesano I, Pollitt R, King G, Bousquet J, et al. In utero exposure to lead and cord blood total IgE. Is there a connection? *Allergy* 2003;58:589-94.
- Kaan A, Dimich-Ward H, Manfreda J, Becker A, et al. Cord blood IgE: its determinants and prediction of development of asthma and other allergic disorders at 12 months. *Ann Allergy Asthma Immunol* 2000;84:37-42.
- Muraro A, Dreborg S, Halken S, Host A, et al. Dietary prevention of allergic diseases in infants and small children. Part III: Critical review of published prereviewed observational and interventional studies and final recommendations. *Pediatr Allergy Immunol* 2004;15:291-307.
- Eggesbo M, Botten G, Stigum H, Nafstad P, Magnus P. Is delivery by cesarean section a risk factor for food allergy? *J Allergy Clin Immunol* 2003;112:420-6.
- Tariq S, Matthews SM, Hakim EA, Stevens M, et al. The prevalence of and risk factors for atopy in early childhood: a hole population birth cohort study. *J Allergy Clin Immunol* 1998;101:587-93.
- Halken S. Prevention of allergic disease in childhood: clinical and epidemiological aspects of primary and secondary allergy prevention. *Pediatric Allergy Immunol* 2004;15(Suppl. 16):9-32.
- Saarinén UM, Kajosaari M, Backman A, Siimes MA. Prolonged breast-feeding as prophylaxis for atopic disease. *Lancet* 1979;2:163-6.
- Schoetzau A, Filipiak-Pittro B, Koletzko S, von Berg A, et al. Effect of exclusive breast-feeding and early solid food avoidance on the incidence of atopic dermatitis in high-risk infants at 1 year of age. *Pediatr Allergy Immunol* 2002;13:234-42.
- Bloch AM, Mimouni D, Mimouni M, Gdalevich M. Does breastfeeding protect against allergic rhinitis during childhood? A meta-analysis of prospective studies. *Acta Paediatr* 2002;91:275-9.
- Lucas A, Brooke OG, Morley R, Cole TJ, Bamford MF. Early diet of preterm infants and development of allergic or atopic disease: randomized prospective study. *BMJ* 1990;300:837-40.
- Halken S, Hansen KS, Jacobsen HP, Estmann A, et al. Comparison of a partially hydrolyzed infant formula with two extensively hydrolyzed formulas for allergy prevention: a prospective, randomized study. *Pediatr Allergy Immunol* 2000;11:149-61.
- Høst A, Husby S, Østerballe O. A prospective study of cow's milk allergy in exclusively breast-fed infants. *Acta Paediatr Scand* 1988;77:663-70.
- Fiocchi A, Assa'ad A, Bahna S, Adverse Reactions to Foods Committee, et al. Food allergy and the introduction of solid foods to infants: a consensus document. *Ann Allergy Asthma*

- Immunol 2006;97:10-21.
31. Fergusson DM, Horwood LJ, Shannon FT. Early solid food feeding and recurrent childhood eczema: a 10-year longitudinal study. *Pediatrics* 1990;86:541-6.
32. Wilson AC, Forsyth JS, Greene SA, Irvine L, et al. Relation of infant diet to childhood health: seven year follow up of cohort of children in Dundee infant feeding study. *BMJ* 1998;316:21-25.
33. Halken S, Høst A, Jacobsen HP, Hansen LG, Østerballe O. Prevention of food allergy in high-risk infants until the age of 5 years. A prospective dietary intervention study. *Allergy* 1995;26:49-61.
34. O'Connell EJ. Pediatric allergy: a brief review of risk factors associated with developing allergic disease in childhood. *Ann Allergy Asthma Immunol* 2003;90(Suppl. 3):53-58.
35. Melen E, Wickman M, Nordvall SL, Hage-Hamsten M, Lindfors A. Influence of early and current environmental exposure factors on sensitization and outcome of asthma in pre-school children. *Allergy* 2001;56:646-52.
36. Lau S, Illi S, Sommerfeld C, Niggemann B, et al. Early exposure to house-dust mite and cat allergens and development of childhood asthma: a cohort study. *Lancet* 2000;356:1392-7.
37. Strachan DP, Cook DG. Parental smoking and childhood asthma: longitudinal and case-control studies. *Thorax* 1998;53:204-12.
38. Tager IB. Smoking and childhood asthma-where to we stand? *Am J Respir Crit Med* 1998;158:349-51.

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