

Editorial

Is Soy Allergy Overestimated?

Adverse reactions to foods occur in up to 8% of children, and they are most common in infancy.⁽¹⁾ An elegant prospective survey showed that cow's milk allergy (CMA) afflicts 2% of an unselected population of children in the first 3 years of life.⁽²⁾ Data on the prevalence of allergy to other foods, including soy, in unselected populations of children are not available.⁽³⁾ Food allergy (FA) is defined as an adverse reaction to food due to an immunologic mechanism. Several immunologic mechanisms have been suggested to be involved in the clinical expression of FA. However, the only immunologic reaction that can be evaluated routinely is the IgE-mediated reaction.⁽³⁾ Although skin test response to the offending food and detection of food-specific IgE antibodies are usually positive in children with IgE-mediated FA, there is no reliable laboratory test for the diagnosis of FA. Skin prick tests to foods have a good negative predictive value but a poor positive predictive value.⁽⁴⁾ The methods for detecting food-specific IgE antibodies suffer from the same limits as skin tests.⁽⁴⁻⁶⁾ Double-blind placebo-control oral food challenge (DBPCOFC) is considered the ideal method for confirming histories of adverse reactions to foods, and although in some patients open food challenges are useful, DBPCOFC is imperative for the diagnosis of FA for research purposes or in clinical trials.^(4,7)

Soy allergy has been emphasized in the last decade,⁽⁸⁾ but as stated by Johnstone and Roghmann in this issue,⁽⁹⁾ "Statements in the pediatric and gastroenterology literature to the effect that use of soybean formula should be avoided because of its high "allergenicity" seem to be unfounded." This conclusion is not surprising, since in most studies reported in the literature (excepting four studies), the diagnosis of soy allergy was based on clinical evaluation or anecdotal case histories reported by parents and was not substantiated by scientific diagnostic criteria. No challenge test to soy was made, nor were data on specific IgE to soy available (skin test or RAST or both).⁽⁸⁾

Despite reports that children with CMA commonly have soy allergy, Bock and Atkins showed that only 4 of 54 children (7%) with CMA had symptoms after DBPCOFC with soy.⁽¹⁰⁾ A recent prospective survey on the natural history of CMA showed that only 2 of 39 children with CMA had adverse reactions to soy.⁽²⁾ In addition, it was shown that these 2 children tolerated soy by the age of 3 years, indicating that the soy intolerance was a transient phenomenon.⁽²⁾ The same natural history of soy allergy was shown in another prospective study.⁽¹¹⁾ Sampson found that only 5% of 204 patients with atopic dermatitis showed soy sensitivity, as demonstrated by DBPCFC.⁽¹¹⁾ We have shown that only 4% of 143 children with atopic dermatitis showed a positive challenge test to soy.⁽⁶⁾ In a multicenter study on the use of DBPCOFC, performed on a selected population of 710 patients with a history of FA, only 32 (5%) had a positive response to DBPCDFC to soy, and 170 (24%) reacted to peanuts, 159 (22%) to egg, and 87 (12%) to cow's milk.⁽⁴⁾ Thus, soy appears to be less allergenic than cow's milk (5% vs 12%). No reactions have been reported in a group of children highly allergic to cow's milk who underwent DBPCOC with a soy protein formula. However, 45% of these children reacted to a partially hydrolysed formula and 10% and 18%, respectively, to an extensively casein and whey hydrolysed formula.⁽¹²⁾

Recently, a large group of 900 children with a history of FA were investigated with DBPCOFC, and no case of positive response was reported (C. Magnolfi, personal communication). The incorrect definition of soy allergy and inappropriate diagnostic criteria have led to a large discrepancy in the prevalence of soy allergy, ranging from 3% up to 80%.⁽⁸⁾ Despite these serious flaws, there is general agreement that soy is very allergenic. Pediatricians interviewed by Johnstone⁽⁹⁾ told him that "they were taught either by the head of their pediatric departments or by pediatric gastroenterologists in their training periods that soy was very allergenic".

In addition to the incorrect definition of soy allergy, a common bias of most studies is incorrect quotation of previous studies, as pointed out by Johnstone and Roghmann.⁽⁹⁾ Surprisingly, even position papers by prestigious societies do not support their recommendation against the use of soy protein formulas with quotations from appropriate studies.^(13,14) For example, no references were provided that cow's milk protein hydrolysate formulas were superior to soy protein formulas in children with CMA, and no references were provided against the use of soy protein formulas for management of CMA in two position papers.^(13,14) The study by Gerrard et al.⁽¹⁵⁾ is commonly quoted to support the theory that soy allergy is very common in children with CMA. These authors showed that 10 of 50 children with CMA, all of them fed a soy protein formula, had symptoms caused by soy allergy. Although 5 of the 10 children had undefined symptoms, such as rhinorrhea, bronchiolitis, and vomiting, no challenge test to soy or skin test to soy was performed.⁽¹⁵⁾ Strangely, 5 of the 10 soy-allergic children tolerated another soy protein formula, strongly indicating that the diagnosis of soy allergy was not correct.⁽¹⁵⁾ Another common bias is the use of incorrect quotations of conclusions of previous studies to support the assumption that soy proteins are allergenic. As stressed by Johnstone and Roghmann,⁽⁹⁾ one of the most incorrect quotations is the study by Eastham et al.,⁽¹⁶⁾ which showed that soy proteins are antigenic and not allergenic, as are cow's milk proteins.

There is no doubt that a number of gastrointestinal disorders, such as colitis, enterocolitis, and malabsorption, have been shown in infants fed soy protein formulas.⁽¹⁷⁻²³⁾ These adverse reactions to soy are more common in infants under 6 months of age suffering from cow's milk-induced enteropathy. The immunopathogenetic mechanism(s) involved in these reactions is not known. The negative response to the skin test to soy and the absence of serum IgE to soy in the affected infants support the hypothesis that IgE-mediated hypersensitivity does not play a role in soy-induced enteropathy. An interesting observation was made by Donovan and Torres-Pinedo,⁽²⁴⁾ which showed that infants under age 6 months with chronic diarrhea secondary to acute gastroenteritis and with multiple protein intolerance, including soy protein, tolerate a soy protein formula containing lactose much better than the conventional lactose-free soy products, thus suggesting that the clinical intolerance to soy was not related to the proteins but to the carbohydrate components. However, because of the rather common adverse reactions to soy formulas in infants with cow's milk enteropathy, soy protein formulas should be used with caution in this population of high-risk infants. We speculate that the common prejudice to the use of soy protein formulas in children with CMA may be due to the rather common adverse reactions to soy formulas described in infants with cow's milk enteropathy.

According to our wide experience in the use of soy protein formulas for the prevention of CMA, these products are safe in high-risk babies.⁽²⁵⁻²⁸⁾ Although soy protein formulas can induce adverse reactions in infants with cow's milk enteropathy, according to recent studies that used DBPCOC for diagnosis of soy allergy, such products are safe in the majority of babies with IgE-mediated CMA,^(1,2,4,6,12) whereas cow's milk protein hydrolysate formulas always should be given with caution due to the possible allergenicity in an already sensitized individual.⁽²⁹⁻³³⁾ Such reactions are more common with whey partly hydrolysate formulas,^(12,29,34) which contain a significant amount of intact cow's milk proteins.^(29,31-35) Extensively hydrolysate formulas are safer, as shown by studies performed in children with CMA using DBPCOFC.^(12,34) Other advantages of soy protein formulas are their acceptable palatability and lower cost when compared with cow's milk protein hydrolysate formulas.

In conclusion, several biases of previous studies have led to overestimation of soy allergy and to the common prejudice that soy protein formulas are not safe in children with CMA. All the previous published studies on soy allergy should be critically reevaluated. According to a few studies that used DBPCOFC, the prevalence of soy allergy in children with CMA seems to be lower than usually reported. Further studies using DBPCOFC are necessary to definitely establish the true prevalence of soy allergy in children with CMA and in the general pediatric population.

REFERENCES

1. Bock SA. Prospective appraisal of complaints of adverse reactions to foods in children during the first 3 years of life. *Pediatrics* 1987;79:683-688.
2. Host A, Halken S. A prospective study of cow milk allergy in Danish infants during the first 3 years of life. *Allergy* 1990;45:587-596.
3. Businco L, Benincori N, Cantani A. Epidemiology, incidence and clinical aspects of food allergy. *Ann Allergy* 1984;53:615-622.
4. Bock SA, Sampson HA, Atkins FM, et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: A manual. *J Allergy Clin Immunol* 1988;82:986-997.
5. Benincori N, Novarino D, Cantani A, et al. On the reability of RAST in childhood food allergy. *Allergol Immunopathol* 1983;11:255-260.
6. Giampietro PG, Ragno V, Daniele S, et al. Soy hypersensitivity in children with food allergy. *Ann Allergy* 1992;69:143-146.
7. European Society of Pediatric Gastroenterology Working Group for the Diagnostic Criteria for Food Allergy. Diagnostic criteria for food allergy with predominantly intestinal symptoms. *J Pediatr Gastroenterol Nutr* 1992;14:108-112.
8. Businco L, Bruno G, Giampietro PG, Cantani A. Allergenicity and nutritional adequacy of soy protein formulas. *J Pediatr* 1992;121:21-41.
9. Johnstone DE, Roghmann KJ. Recommendations for soy infant formula: A review of the literature and a survey of pediatric allergists. *Pediatr Asthma Allergy Immunol* 1993;7:77-88.
10. Bock SA, Atkins FM. Patterns of food hypersensitivity during sixteen years of double-blind, placebo-controlled food challenges. *J Pediatr* 1990;4:561-567.
11. Sampson HA. The role of food allergy and mediator release in atopic dermatitis. *J Allergy Clin Immunol* 1988;81:635-645.
12. Ragno V, Giampietro PG, Bruno G, Businco L. Allergenicity of milk protein hydrolysate formulae in children with cow's milk allergy. *Eur J Pediatr* (in press), 1993.
13. Committee on Nutrition. Soy-protein formulas: Recommendation for the use of infant feeding. *Pediatrics* 1983;72:359-363.
14. European Society of Pediatric Gastroenterology and Nutrition. Committee on Nutrition. Comment on the composition of soy-protein based infant and follow-up formulas. *Acta Paediatr Scand* 1990;79:1001-1005.
15. Gerrard JW, Mackenzie JWA, Goluboff N, et al. Cow's milk allergy: Prevalence and manifestations in an unselected series of newborns. *Acta Paediatr Scand* 1973;234(Suppl):1-21.
16. Eastham EJ, Lichauco T, Grady MI, Walker WA. Antigenicity of infant formulas: Role of immature intestine on protein permeability. *J Pediatr* 1978;93:561-564.
17. Ament ME, Rubin CE. Soy protein: Another cause of the flat intestinal lesion. *Gastroenterology* 1972;62:227-234.
18. Halpin TC, Byrne WJ, Ament ME. Colitis, persistent diarrhea, and soy protein intolerance. *J Pediatr* 1977;91:404-407.
19. Powell GK. Milk and soy-induced enterocolitis of infancy: Clinical features and standardization of challenge. *J Pediatr* 1978;93:553-560.
20. Berezin S, Schwarz SM, Glassman M, et al. Gastrointestinal milk intolerance of infancy. *Am J Dis Child* 1989;143:361-362.
21. Butler HL, Byrne WJ, Marmer DJ. Depressed neutrophil chemotaxis in infants with cow's milk and/or soy protein intolerance. *Pediatrics* 1981;67:264-268.
22. Van Sickle GJ, Powell GK, McDonald P, Goldblum RM. Milk- and soy protein-induced enterocolitis: Evidence for lymphocyte sensitization to specific food proteins. *Gastroenterology* 1983;88:1915-1921.
23. Alvarez JR, Torres-Pinedo R. Interactions of soybean lectin, soysaponins, and glycine with rabbit jejunal mucosa in vitro. *Pediatr Res* 1982;16:728-731.

EDITORIAL

24. Donovan GK, Torres-Pinedo R. Chronic diarrhea and soy formulas. Inhibition of diarrhea by lactose. *Am J Dis Child* 1987;141:1069–1071.
25. Businco L, Marchetti F, Pellegrini G, Perlini R. Predictive value of cord blood IgE levels in “at risk” newborn babies and influence of type of feeding. *Clin Allergy* 1983;1:503–508.
26. Businco L, Cantani A, Meglio P, Gruno G. Prevention of atopy: Results of a long-term (7 months to 8 years) follow-up. *Ann Allergy* 1987;59:183–186.
27. Businco L, Bruno G, Grandolfo ME, et al. Response to poliovirus immunization and type of feeding in babies of atopic families. *Pediatr Allergy Immunol* 1990;1:60–63.
28. Businco L, Cantani A. Prevention of childhood allergy by dietary manipulation. *Clin Exper Allergy* 1990;3:9–14.
29. Businco L, Cantani A, Longhi MA, Giampietro PG. Anaphylactic reactions to a cow’s milk whey protein hydrolysate (Alfaré, Nestlé) in infants with cow’s milk allergy. *Ann Allergy* 1989;62:333–335.
30. Schwartz RH, Keefe MW, Harris N, Witherby S. The spectrum of IgE-mediated acute allergic reactions to cow’s milk in children as determined by skin testing with cow’s milk protein hydrolysate formulas. *Pediatr Asthma Allergy Immunol* 1989;3:207–215.
31. Businco L, Cantani A. Hypoallergenic formulae. *Allergy Today* 1990;3:9–11.
32. Kleinman RE, Bahana S, Powel GF, Sampson HA. Use of infant formula in infants with cow milk allergy. A review and recommendations. *Pediatr Allergy Immunol* 1991;4:146–155.
33. Oldaeus G, Bjorkstén B, Einarsson R, Kjellman N-IM. Antigenicity and allergenicity of cow milk hydrolysates intended for infant feeding. *Pediatr Allergy Immunol* 1991;4:156–164.
34. Businco L, Dreborg S, Einarsson R, et al. Hypoallergenic formulae: Allergenicity and use for treatment and prevention. A Position Paper of ESPACI. *Pediatr Allergy Immunol* (in press).
35. Sampson HA, Bernhisel-Broadbent J, Yang E, Scanlon SM. Safety of casein hydrolysate formula in children with cow milk allergy. *J Pediatr* 1991;118:520–525.

Address reprint requests to:
Luisa Businco, M.D.
Allergy and Clinical
Immunology Division
Department of Pediatrics
University “La Sapienza”
Viale Regina Elena, 324
00161 Rome, Italy