Journal of Pediatric Gastroenterology and Nutrition
39:101–102 © July 2004 Lippincott Williams & Wilkins, Philadelphia

Selected Summary

Selected Summaries Editors:
ESPGHAN
Christian Braegger, M.D.

NASPGHAN
Warren P. Bishop, M.D.
Joel R. Rosh
Steven N. Lichtman, M.D.
Jonathan E. Teitlebaum

A Consistent Pattern of Minor Immunodeficiency and Subtle Enteropathy in Children With Multiple Food Allergy Latcham F, Merino F, Lang A, Garvey J, Thomson MA, Walker-Simth JA, Davies SE, Phillips AD, Murch SH. J Pediatr 2003;143:39–47.

Summary: Latcham et al. retrospectively studied 121 children with multiple food allergies collecting clinical, histologic and immunologic information in an attempt to find common patterns that might identify the child at risk. The children were divided into immediate hypersensitivty responders (group 1, n = 44) and delayed responders (group 2, n = 77).

The most common foods inducing immediate responses were milk, eggs and nuts. The most frequently recorded symptoms were urticaria, lip swelling and skin rash (86%). Delayed responses were also present in group 1. In fact, only three children (7%) had no delayed symptoms. The delayed responses in Group 1 were diet-responsive eczema, diarrhea, vomiting, wheezing and failure to thrive. The symptoms in group 2 were mainly eczema, failure to thrive and diarrhea and were induced most commonly by milk, soy, wheat, hydrolysates, eggs, meat and rice. Fourteen children in group 1 and 27 in group 2 had symptoms while exclusively breast fed. A family history of atopy was present in 90% of the children, particularly on the maternal side, as was a history of autoimmunity.

High immunoglobulin (Ig) E concentration, positive skin-prick tests and positive radioallergosorbent tests were more frequent in group 1 than group 2 (50%, 70% and 75% vs. 18%, 27% and 25%, respectively). Both groups tended to have low-normal levels of IgA (45% of cases had IgA $\leq$0.3 g/L), skewing of IgG subclasses with increased IgG_1 and decreased IgG_2 and IgG_4, and skewing of lymphocyte subsets with increased CD4 and CD19 and decreased CD8 and natural killer cells. There was also subtle evidence of enteropathy with focal lymphocyte or eosinophile infiltrate, villous blunting and reduced crypt/villus ratios.

Considering the difficulty in establishing a diagnosis of non–IgE-mediated food allergy, the authors propose that in a child with compatible symptoms, a family history of atopy or autoimmunity and the above described immunologic and histologic pattern might be helpful in supporting this diagnosis.

Comment: The prevalence of food allergy seems to be increasing in parallel with an increased prevalence of extrinsic asthma and environmental allergies. It is thought that these changes reflect changes in living conditions in western countries but also may reflect an increased awareness by medical personnel and parents. Unlike other allergic diseases, there is no specific therapy except avoidance of the offending food. If there were immediate symptoms associated with food allergy or reliable diagnostic tests (radioallergosorbent test or skin-prick test) no one would be reading this commentary! Our problem is to care properly for children with symptoms for which multiple antigens are implicated but in whom routine tests are negative. These children experience vomiting, failure to thrive, wheezing and pruritis from eczema. Given that restricted diets in children with multiple food allergy may result in unbalanced nutritional status and that oral food challenges may involve substantial risks, an accurate diagnosis is of utmost importance.

The article by Latcham et al. suggests possible additional clues to the diagnosis. Besides the immediate responses associated with increased IgE, the authors identified delayed symptoms as well. There were immunologic characteristics shared by both groups which raises the question of whether these characteristics might be more directly associated with the predisposition to sensitization than is the IgE concentration.

One of the predisposing factors for allergy is immune deficiency, particularly IgA deficiency (1). These children had strong family histories of autoimmunity and low or low-normal levels of IgA. Knowing that the shift of B cells toward IgA is mediated by transforming growth factor β, the authors looked for and demonstrated a reduction in the expression of transforming growth factor β by mucosal lymphocytes in children with food allergy (2). Transforming growth factor β is a potent immunosuppressive cytokine, induced by mucosal inflammation after exposure to enteric bacteria. Given the importance of the normal gut flora to both the local and the systemic immune repertoire, it is tempting to speculate that these children might have a genetically programmed tendency to reduced response, leading to inadequate induction of tolerogenic lymphocytes. That is, rather than the classic Th1/Th2 imbalance, they might have an insufficient Th3 response.

Decreased exposure to bacteria in developed countries is thought to be a cause of the insufficient Th3 response. This change might also explain the results of preliminary studies which have shown a reduction of atopic dermatitis in children whose mothers receive probiotics during pregnancy (3) and a decreased severity of atopic dermatitis in children with cow's milk hypersensitivity treated with probiotics and an elimination diet (4). This mechanism may be common to allergy in general when one considers that a person's exposure to environmental endotoxin may have a role in the development of tolerance to allergens found in natural environments (5). Again, the evi-

dence is compelling: allergies increase as material conditions improve.

Many studies indicate that there is a critical time early in infancy, possibly even during fetal life, when the genetically programmed atopic infant is at higher risk of becoming sensitized to food allergens. This might also be true with autoimmunity. This article raises the question of whether children with a strong family history of atopy and autoimmunity are also at increased risk of later autoimmunity. There are examples suggesting that this is indeed the case. Exposure to gluten before the age of 3 months in children genetically predisposed to diabetes type 1 (those with HLA DR3/DR4–DQ8 genotype, born of parents with type 1 diabetes) carries a fivefold higher risk for the development of islet autoantibodies (6). First exposure at the age of 7 months or older may also increase the risk for islet autoimmunity, possibly related to the larger amount of exposure at initial introduction (7). The timing of first exposure may influence immune tolerance to food antigens, and there may be an exposure time window that best allows tolerance to be achieved. Early introduction may lead to inflammation in the gut, altering the immune cell repertoire or leading to changes in islet β cells that may still be immature (6). MacFarlane et al. describe a wheat storage globulin protein, G1b1, that may be associated with islet cell damage. They also demonstrated that the sera from patients with type 1 diabetes has antibodies to G1b1, in contrast to sera from patients who do not have the disease (8).

Many questions remain unanswered and sometimes a new look at an old problem helps. Searching for other markers of allergy rather than the classic ones may be a productive line of investigation.

*Lucia Gomes
†Jorge Amil Dias
*Hospital Santo António
†Hospital S. João
Porto, Portugal

REFERENCES

1. Stern M. Allergic enteropathy/food allergy. In: Walker A, ed. *Pediatric Gastrointestinal Disease*. Hamilton, Ontario: B.C. Decker; 2000, 746–62.
2. Perez-Machado MA, Ashwood P, Thomson MA, et al. Reduced transforming growth factor-beta1-producing T cells in the duodenal mucosa of children with food allergy. *Eur J Immunol* 2003; 33:2307–15.
3. Kalliomaki M, Salminen S, Arvilommi H, et al. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. *Lancet* 2001;357:1076–9.
4. Majamaa H, Isolauri E. Probiotics: a novel approach in the management of food allergy. *J Allergy Clin Immunol* 1997;99:179–85.
5. Braun-Fahrlander C, Riedler J, Herz U, et al. Environmental exposure to endotoxin and its relation to asthma in school-age children. *N Engl J Med* 2002;347:869–77.
6. Ziegler AG, Schmid S, Huber D, et al. Early infant feeding and risk of developing type 1 diabetes-associated autoantibodies. *JAMA* 2003;290:1721–8.
7. Norris JM, Barriga K, Klingensmith G, et al. Timing of initial cereal exposure in infancy and risk of islet autoimmunity. *JAMA* 2003;290:1713–20.
8. MacFarlane AJ, Burghardt KM, Kelly J, et al. A type 1 diabetes-related protein from wheat (Triticum aestivum): cDNA clone of a wheat storage globulin, Glb1, linked to islet damage. *J Biol Chem* 2003;278:54–63.