

Atopic Eczema Could Be a Cause and Not an Effect of Cow's Milk Protein Allergy

To the Editor: We read with interest the article published in the August 2012 issue of the *Journal of Pediatric Gastroenterology and Nutrition* entitled Diagnostic Approach and Management of Cow's-Milk Protein Allergy in Infants and Children: ESPGHAN GI Committee Practical Guidelines (1). The authors considered atopic eczema (AE) as a possible skin symptom of cow's milk protein allergy (CMPA) and affirmed that in the children with AE are present positive tests for cow's milk protein-specific immunoglobulin E. We disagree in considering the AE as an expression of CMPA, because, there is an evidence that the AE is a cause, and it is not an effect of food allergy (2–4). A primary alteration of the epidermal barrier leads to increased permeability to food allergens and secondary sensitization mediated by dendritic cell that enhances T_H2 polarization (5). In fact, early-onset atopic dermatitis usually emerges in the absence of detectable immunoglobulin E-mediated allergic sensitization (6).

We write this letter to emphasize this interesting evidence that could lead, in the future, to a “Copernican Revolution”: CMPA, in the future, may no longer be considered among the causes of AE with important changes in the management of the patients with atopic eczema.

Pierluigi Marzuillo, Stefano Guarino, and Laura Perrone
Dipartimento della donna, del bambino e di chirurgia generale e specialistica, Seconda Università degli Studi di Napoli, Naples, Italy

REFERENCES

1. Koletzko S, Niggemann B, Arato A, et al. Diagnostic approach and management of cow's-milk protein allergy in infants and children: ESPGHAN GI Committee Practical Guidelines. *J Pediatr Gastroenterol Nutr* 2012;55:221–9.
2. Strid J, Hourihane J, Kimber I, et al. Disruption of the stratum corneum allows potent epicutaneous immunization with protein antigens resulting in a dominant systemic T_H2 response. *Eur J Immunol* 2004;34:2100–9.
3. Lack G. Epidemiologic risks for food allergy. *J Allergy Clin Immunol* 2008;121:1331–6.
4. Badina L, Barbi E, Berti I, et al. The dietary paradox in food allergy: yesterday's mistakes, today's evidence and lessons for tomorrow. *Curr Pharm Des* 2012;18:5782–7.
5. Bieber T. Atopic dermatitis. *N Engl J Med* 2008;358:1483–94.
6. Illi S, von Mutius E, Lau S, et al. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. *J Allergy Clin Immunol* 2004;113:925–31.

Authors' Reply

To the Editor: In the letter to the editor, Marzuillo et al questioned our categorization of atopic eczema as a symptom of cow's-milk protein allergy (CMPA) (1). Rather, Marzuillo et al

suggested that eczema is the cause of sensitization and CMPA, and that this may alter the management of affected children. We thank the authors for highlighting this complex relation and for creating an opportunity for clarification.

Atopic dermatitis is a complex genetic disease influenced by many gene–gene and gene–environment interactions (2). Genetic effects appear particularly important for early-onset eczema as indicated by the high concordance in monozygotic compared with dizygotic twins and the high prevalence of mutations in the filaggrin (*FLG*) gene, which encodes a key protein involved in epidermal differentiation. Loss-of-function *FLG* mutations lead to a disturbed epidermal-barrier function and are the strongest risk factors for early-onset and persistent eczema with allergic sensitization, and later, asthma (3,4). Interestingly, eczema without sensitization (intrinsic eczema) does not appear to be associated with *FLG* mutations (3). Therefore, the association between early-onset eczema and the presence of food-specific immunoglobulin E may be explained by the genetic factors.

We agree that the disorders in the skin barrier function associated with atopic dermatitis may facilitate sensitization via skin in predisposed infants; however, subjects sensitized to certain food allergens do not always show clinical symptoms when exposed to these foods (5). Furthermore, a high proportion of infants with symptomatic CMPA proved by a double-blind food challenge tested negative against specific immunoglobulin E (6). It is, in fact, clear that the infants with CMPA and eczema experienced increased skin inflammation when exposed to CMP and that their eczema improved or sometimes even resolved when dairy products were eliminated from the diet. As such, even if early-onset atopic eczema was not a symptom of CMPA in these children, but rather a genetically linked disorder, eliminating cow's milk from the diet was beneficial regardless of the sensitization status. These findings may have implications for primary or secondary prevention, which was not the topic of our position paper.

*Sibylle Koletzko and †Bodo Niggemann

*Dr von Haunersches Kinderspital,

Ludwig-Maximilians-University, Munich

†Division of Pediatric Pneumology and Immunology, Charité, Campus Virchow, Berlin, Germany

REFERENCES

1. Koletzko S, Niggemann B, Arato A, et al. Diagnostic approach and management of cow's-milk protein allergy in infants and children: ESPGHAN GI Committee practical guidelines. *J Pediatr Gastroenterol Nutr* 2012;55:221–9.
2. Bieber T. Atopic dermatitis. *N Engl J Med* 2008;358:1483–94.
3. Weidinger S, Illig T, Baurecht H, et al. Loss-of-function variations within the filaggrin gene predispose for atopic dermatitis with allergic sensitizations. *J Allergy Clin Immunol* 2006;118:214–9.
4. Filipiak-Pittroff B, Schnopp C, Berdel D, et al. Predictive value of food sensitization and filaggrin mutations in children with eczema. *J Allergy Clin Immunol* 2011;128:1235–41.
5. Eller E, Kjaer HF, Host A, et al. Food allergy and food sensitization in early childhood: results from the DARC cohort. *Allergy* 2009;64:1023–9.
6. Klemola T, Vanto T, Juntunen-Backman K, et al. Allergy to soy formula and to extensively hydrolyzed whey formula in infants with cow's milk allergy: a prospective, randomized study with a follow-up to the age of 2 years. *J Pediatr* 2002;140:219–24.