

weight gain. Eight AM cortisol was 13.2 mcg/dL (normal range for age, 3-15 mcg/dL) after 4 months of therapy.

Patient 2 was a 5-year-old girl with a history of developmental delay, abdominal pain, and RAST positivity for milk, egg, and wheat. EGD showed a normal esophagus, but histopathology of biopsies demonstrated maximal eosinophil counts of 40 per HPF and basal zone hyperplasia. She was placed on a hydrolyzed formula containing milk protein (Peptamen Jr, Nestlé, Glendale, Calif), omeprazole 10 mg twice daily, and oral cromolyn (Gastrocrom, Celltech Pharmaceuticals, Rochester, NY) 100 mg 4 times daily. After 12 months of therapy, repeat EGD demonstrated a pale, furrowed esophagus with maximum eosinophil counts of 94, 65, and 90 per HPF and diffuse basal zone hyperplasia in the distal, mid, and proximal esophagus, respectively. She was referred to the Children's Hospital Eosinophilic Gastrointestinal Disorders clinic for further treatment. Subsequent skin prick testing showed a positive response to her hydrolyzed milk protein-containing formula, and her diet was changed to elemental formula. After 2 months of elemental formula and oral cromolyn sodium, EGD was unchanged, with a pale, furrowed esophagus and maximal eosinophil counts of 100, 90, and 70 per HPF in the distal, mid, and proximal esophagus with diffuse basal zone hyperplasia. Her developmental delay precluded the use of a fluticasone inhaler device with puff and swallow technique. As an alternative, she received oral budesonide 500 µg (Pulmicort) mixed with sucralose (Splenda) twice daily as topical esophageal therapy. After 3 months of budesonide, she had improvement in her abdominal pain, and EGD revealed a normal-appearing esophagus with improved maximum eosinophil counts of 28, 20, and 5 per HPF in the distal, mid, and proximal esophagus and decreased basal zone hyperplasia.

Because long-term systemic steroid therapy can result in significant secondary side effects on growth and bone development, we opted for a topical steroid formulation that is easier to use in young or developmentally delayed children and does not require the use of a MDI inhaler. In one series, 15% of patients with EE had concurrent developmental delay.⁶ Although treatment with anti-IL-5 mAb has been reported to be successful, this therapy is currently not approved for use in children.⁷ In our experience, a viscous oral suspension of budesonide improved symptoms, resolved endoscopic abnormalities, and markedly reduced or eliminated esophageal eosinophils in 2 patients unable to use a MDI inhaler with a puff and swallow technique. As such, oral budesonide suspension warrants further investigation for the treatment of patients with EE.

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The cradle of IgE autoreactivity in atopic eczema lies in early infancy

To the Editor:

Patients with atopic eczema (AE) are frequently sensitized against a multitude of exogenous allergens and mount high levels of total serum IgE. A great variety of factors, among them cutaneous and gastrointestinal allergen exposure or bacterial and viral superinfections, are associated and are able to induce exacerbations of AE. AE and food allergy belong to those allergic manifestations that occur very early in childhood and frequently proceed to respiratory symptoms of allergy.¹ However, in many cases, it is not possible to identify clearly exogenous or endogenous factors that trigger the chronicity of the disease.

The idea that mechanisms of autoimmunity could also play a role in the pathogenesis of AE gained support by the observation that patients with AE display IgE reactivity to a variety of human protein antigens, of which several have been characterized at a molecular level.² The spectrum of IgE-reactive autoantigens seems to be very broad and includes proteins with structural similarities to exogenous allergens such as plant profilins, dog serum albumin, mold-derived manganese, superoxide dismutase, and genuine autoantigens.²⁻⁶ The presence of autoreactivity seems to be associated with the severity of the disease

and may be used as a parameter reflecting chronic tissue damage. Furthermore, it has been shown that IgE auto-reactivity decreases after successful treatment. To address the question at which time point of life IgE reactivity to endogenous antigens starts and what factors may influence the development of IgE autoreactivity, we performed a retrospective analysis of clinical and serological parameters in well documented adult patients with AE with and without IgE autoreactivity and a serological survey for IgE autoreactivity in children with AE during their first years of life. A total of 174 adult patients with AE from the Department of Dermatology in Bonn, Germany, have been analyzed regarding atopic status, and the severity of the disease was evaluated according to the Diepgen score, the criteria of Bos, the criteria of Hanifin and Rajka, and the Scoring Atopic Dermatitis system. The occurrence of clinically manifest AE skin lesions has been evaluated and documented retrospectively for each of the adult patients with AE during the following periods of life: 0 to 2 years, 2 to 6 years, 6 to 14 years, 14 to 20 years, and >20 years. The study protocol was approved by the local ethical committee of the University of Bonn and the University of Berlin.

In addition, sera from 102 AE children from the serum bank of the University Children's Charité Berlin were analyzed. The first set of sera ($n = 20$) pulled out of the serum bank fulfilled the following criteria: children with AE with total IgE levels between 1.000 and 9.999 kU/L, and age < 13 years. The second set of sera ($n = 60$) were from children with AE younger than 1 year without limits regarding total IgE. The third set of sera ($n = 40$) were from 20 children with AE (age < 6 years) for whom 2 blood samples taken 1 year apart were available and no limit was set for total IgE levels.

We have searched in a clinically well defined population of 174 adult patients with AE (age, 35.4 ± 14.8 years) for the presence of IgE autoantibodies to nitrocellulose-blotted human epithelial cell-derived antigens.

We found that 23% of the patients with AE mounted IgE reactivity to a variety of human epithelial antigens. This group has been defined as the autoantibody-positive group (AA^+), whereas the remaining 77% of patients with AE without IgE autoantibodies has been defined as the autoantibody-negative group (AA^-). Sera from 26 control individuals (age, 36.5 ± 16.5 years) without any atopic disorders and 10 patients with psoriasis as another chronic inflammatory skin disease showed no IgE auto-reactivity (data not shown).

Xerosis ($P < .001$), dyshidrosis ($P < .001$) and ichthyosis of the skin ($P = .007$) were much more pronounced in AA^+ patients (Table I). In addition, these patients had much more frequent recurrent bacterial ($P = .006$) and viral ($P < .001$) infections of the skin such as impetigo contagiosa or eczema herpeticum during the course of AE (Table I). Furthermore, pruritus was much more pronounced in the AA^+ subgroup ($P = .04$). In addition, significantly more AA^+ patients had a positive history for clinical manifestations of food allergy ($P < .0001$) and a higher total Diepgen score ($P = .036$) than AA^- patients (Table I).

The levels of total serum IgE were significantly higher in the group of AA^+ patients. In addition, IgE levels specific for *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* allergens, cat dander, egg, milk, wheat, codfish, green apple, peanut, hazelnut, *Aspergillus fumigatus*, *Candida albicans*, *Pityrosporum ovale*, birch pollen, and grass pollen allergens were significantly higher in AA^+ patients than in AA^- patients.

To evaluate whether the development of IgE autoreactivity may be associated with an onset of AE in a certain period of life, the course of AE during different periods of life has been evaluated retrospectively for the AA^+ and AA^- groups. Most significant differences have been found for patients with an early onset of AE and manifestation of clinically symptomatic AE between the 2nd and 6th years of life. The prevalence of AE in this particular period of life was significantly higher in the AA^+ compared with the AA^- group ($P < .0001$).

To study whether IgE autoreactivity already occurs early in infancy, sera from AE children were analyzed. First, we analyzed a group of 60 children with AE younger than 1 year for IgE autoreactivity. As exemplified for 20 sera, we found that 15% of the children mounted IgE autoreactivity. These AA^+ children had significantly higher total IgE serum levels (1206 ± 1589 kU/L) than AA^- children (90.3 ± 187 kU/L; $P < .001$). Most of the AA^+ children had already developed sensitizations against nutritive allergens.

Furthermore, we analyzed a group of 20 children with AE (age, 2-13 years) with moderate to severe AE and total IgE serum levels higher 1000 kU/L for the presence of IgE autoantibodies. We found that 16 of 20 children (80%) displayed IgE autoreactivity.

Finally, we analyzed a group of 20 children with AE (age, 2-6 years) with moderate to severe forms of AE and multiple sensitizations against food allergens and

TABLE I. Factors occurring more often in AA^+ adult patients with AE than in AA^- adult patients with AE

	AE persistent during the 2nd and 6th year of life	Recurrent bacterial infections	Recurrent viral infections	Food allergy	Pruritus	Xerosis	Dyshidrosis	Ichthyosis
P value*	<.0001	.006	<.001	<.0001	.04	<.001	<.001	<.001

* χ^2 Test.

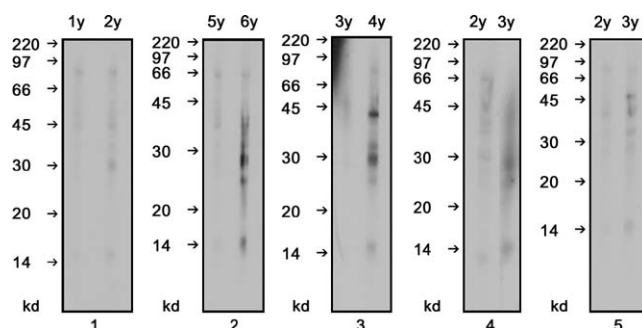


FIG 1. IgE autoreactivity develops in early infancy. Development of IgE autoreactivity revealed in serum samples obtained from 5 children (1-5) at 2 different time points by immunoblotting with protein extracts from the human epithelial cell line A431. The lanes correspond to the age of the children. Molecular weights (kd) are displayed on the left sides of the blots.

aeroallergens. From these children, 2 serum samples that had been taken at 2 different time points within 1 year were available. Fig 1 shows the development of IgE autoreactivity in representative AA⁺ children from this group and documents that IgE autoreactivity develops in the first years of life.

The survey for IgE autoreactivity performed in the adult group of patients with AE confirmed earlier observations that IgE autoreactivity specifically occurs in a subgroup of patients with AE, termed AA⁺, but not in healthy individuals or persons with other inflammatory skin diseases.

It is known that exogenous allergens, in particular food allergens such as milk or egg, can trigger severe aggravations of skin lesions. Positive oral food challenges in children with allergy are accompanied by increased plasma histamine concentrations and activation of eosinophils in combination with clonal expansion of skin-homing food allergen specific T cells. The finding of a significantly higher prevalence of food allergy in the AA⁺ subgroup thus supports the hypothesis that food allergens may act as a first trigger of IgE autoimmunity. In view of the data presented here, it might be speculated that a chronic ingestion of allergenic food led to repetitive tissue damage of the gut and gut epithelial cells.

The other characteristic clinical features of the AA⁺ subgroup of patients (xerosis, dyshidrosis, ichthyosis, bacterial and viral infections, pruritus) may on the one hand contribute to mechanical damage of the skin and perpetuate the release of autoallergens from skin keratinocytes as a primary phenomenon. On the other hand, autoreactivity may be responsible for the development of these manifestations.

The finding that the AA⁺ subgroup had a significantly higher prevalence of clinically symptomatic episodes of AE between the 2nd and 6th year of life compared with the AA⁻ subgroup prompted us to search for IgE autoreactivity in another population of children with AE. This analysis demonstrated that IgE autoreactivity develops in the first years of life, as early as sensitization to food allergens and respiratory allergens have been shown to

occur. In conclusion, these findings identify early infancy as the critical period for IgE autosensitization and emphasize the importance of this period of life for the development of atopic diseases as well as for preventive measures against allergy such as elimination diet in patients with food allergy in early infancy.

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