

Letter to the Editor

Severe refractory atopic dermatitis in adults is highly atopic

To the Editor:

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease affecting both children and adults. Most children have a substantial reduction in the severity of their AD over time or outgrow it altogether. Others continue to have severe disease as teenagers and adults, or experience a relapse during adulthood. The factors that contribute to the persistent severe skin inflammation in these individuals are unknown.

We performed a retrospective chart review of all patients older than 18 years who were treated for AD at National Jewish Medical and Research Center in Denver between 2000 and 2006. Patients were assigned a severity score based on the Rajka and Langeland Criteria¹ evaluating the extent of involvement, the amount of time of remission per year, and the intensity of itch.

Forty adults were found to have severe AD by these criteria. These patients had poorly controlled eczema despite the use of topical and oral corticosteroids, topical calcineurin inhibitors, antibiotics, and antihistamines. They were compared with adults in 2 other groups: those with quiescent AD or moderate AD. The quiescent AD group consisted of patients with a history of AD in the past, but no recent skin disease. The moderate AD group had active disease responsive to topical treatment.

As shown in Table I, the median serum IgE value in the severe AD group was 3922 IU/mL, compared with 44 IU/mL for quiescent AD and 358 IU/mL for moderate AD ($P < .0001$ and $.005$, respectively.)

As shown in Table II, the severe AD group had increased perennial allergen sensitivity compared with the moderate AD group (dust mite, $P = .005$; molds, $P = .004$). The majority of patients in the severe AD group lived outside Colorado (28/38), most frequently in humid climates such as Florida (6/38), Texas, Oklahoma, California, and Massachusetts (each 2/38). The majority of patients with moderate AD lived in Colorado (16/19). There was also a significantly higher rate of food allergen sensitization by skin testing in the severe AD group compared with the moderate AD group ($P = .007$). The most common positive foods, by skin prick testing, in the severe AD group were peanut (11/35), egg (9/35), shellfish (7/35), soy (7/35), and milk (6/35).

Of the patients in the severe refractory AD group, 25 of 36 (69%) reported a history of asthma, compared with 16 of 23 (70%) in the moderate AD group ($P = 1.0$). In addition, 34 of 37 (92%) in the severe AD group had a history of allergic rhinitis, as did 22 of 23 (97%) in the moderate AD group ($P = 1.0$). There was no difference in family history of atopic disease ($P = .74$) between these 2 groups. The age of onset of AD was not significantly different in the 2 groups, with most having early childhood onset. Of the severe AD group, 4 of 38 (10%) had onset of AD

TABLE I. Refractory AD is associated with elevated serum IgE

	N	Average age (y)	Female/male ratio	Median IgE (IU/mL)
Severe refractory AD	38	39	2.3:1	3922*
Moderate AD	23	35	2.4:1	358
Quiescent AD	12	34	1.4:1	44

* $P < .0001$ compared with quiescent AD and $P = .005$ compared with moderate AD.

TABLE II. Skin prick testing sensitivity to allergens

	Dust mite	Animal dander	Molds	Grass	Weeds	Trees	Foods
Severe refractory AD	30/36	30/36	27/35	26/35	23/35	22/35	23/35
Moderate AD	9/20	16/20	7/20	12/20	11/20	12/20	4/17
<i>P</i> value	.005	.73	.004	.36	.57	1.0	.007

during adolescence or adulthood, compared with 4 of 23 (17%) in the moderate group ($P = .46$).

In our population, severe refractory AD is primarily an atopic disease characterized by increased levels of total serum IgE and positive skin tests to dust mites, molds, and food allergens, compared with patients with more moderate disease. Further studies are needed to determine whether severe, poorly controlled AD may be a result of polyallergen sensitivities, and the inability of these individuals to remove allergenic triggers from their indoor environment and diets. The severe AD group may have had increased exposure to dust mites and molds in comparison with the moderate AD group because they lived in climates more conducive to the presence of these allergens in the environment. In addition to exposure, skin barrier defects that are found in AD may lead to this increased allergen sensitization.² Recent studies have found that loss-of-function mutations in the gene for filaggrin, a protein involved in skin barrier function, are associated with severe AD, as well as increased allergen sensitivity, elevated total IgE, and asthma.³⁻⁵ Furthermore, it has been observed that asthma and allergic rhinitis are associated with filaggrin mutations only in the presence of AD.⁶ These studies suggest that skin barrier dysfunction in AD could lead to allergen absorption through the skin and increased allergen sensitization. Alternatively, another recent article suggests that T_H2 immune responses may also contribute to acquired defects in the skin barrier. The authors hypothesize that chronic allergen exposure could contribute to reduced filaggrin expression in AD.⁷ A prospective controlled clinical trial is needed to determine whether effective food elimination diets or indoor avoidance of dust mite and molds will enhance management of refractory AD.

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Supported by National Institutes of Health grant AR41256, General Clinical Research Center grant MO1 RR00051 from the Division of Research Resources, the Edelstein Family Chair in Pediatric Allergy and Immunology, and the University of Colorado Cancer Center.

Disclosure of potential conflict of interest: B. H. Salt owns stock in Novartis, Qiagen, and Roche. The other authors have declared that they have no conflict of interest.

REFERENCES

1. Rajka G, Langeland T. Grading of the severity of atopic dermatitis. *Acta Derm Venereol Suppl (Stockh)* 1989;144:13-4.
2. Cork MJ, Robinson DA, Vasilopoulos Y, Ferguson A, Moustafa M, MacGowan A, et al. New perspectives on epidermal barrier dysfunction in atopic dermatitis: gene-environment interactions. *J Allergy Clin Immunol* 2006;118:3-21.
3. Barker JN, Palmer CN, Zhao Y, Liao H, Hull PR, Lee SP, et al. Null mutations in the filaggrin gene (FLG) determine major susceptibility to early-onset atopic dermatitis that persists into adulthood. *J Invest Dermatol* 2006; Sep 21 [Epub ahead of print].
4. Weidinger S, Illig T, Baurecht H, Irvine AD, Rodriguez E, Diaz-Lacava A, 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.
5. Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006;38:441-6.
6. Marenholz I, Nickel R, Ruschendorf F, Schulz F, Esparza-Gordillo J, Kersch T, et al. Filaggrin loss-of-function mutations predispose to phenotypes involved in the atopic march. *J Allergy Clin Immunol* 2006;118: 866-71.
7. Howell MD, Kim BE, Boguniewicz M, Leung DYM. Modulation of filaggrin by T_H2 cytokines in the skin of atopic dermatitis (AD). *J Allergy Clin Immunol Abstract* 2007;119(Suppl):S283.

doi:10.1016/j.jaci.2006.11.006