

The sweat of patients with atopic dermatitis contains specific IgE antibodies to inhalant allergens

K.JUNG, G.SCHLENVOIGT,* K.LADWIG, D.HERRMANN,* C.MOTHES, R.LINSE AND Ch.NEUMANN† *Erfurt Dermatology Clinic, Erfurt, Germany, *Institute of Clinical Immunology, Friedrich Schiller University, Jena, Germany and †Department of Dermatology, Georg August University, Göttingen, Germany*

Accepted for publication 29 July 1996

Summary

We have investigated levels of total and specific IgE against inhalant allergens in the sweat of 15 patients with atopic dermatitis, 10 patients with allergic rhinitis and high levels of specific IgE in the serum, and five patients with psoriasis without atopy as controls, by means of various commercial methods such as fluorescence immunoassay, nephelometry, chemiluminescence assay, enzyme immunoassay and the radioallergosorbent test. Total IgE and specific IgE antibodies were detectable in the sweat of patients with atopic dermatitis as well as of patients with allergic rhinitis alone. These levels of total IgE in the sweat correlated with the severity of the skin disease ($P < 0.05$). By means of the Ciba Corning assay ($P < 0.001$), the fluorescence immunoassay ($P < 0.05$) and the nephelometry assay ($P < 0.05$), positive correlations were then established between the levels of total IgE in the serum and the sweat. Moreover, specific IgE antibodies to birch pollen and *Dermatophagoides pteronyssinus* were detectable in the sweat and correlated positively with these specific IgE levels in the serum ($P < 0.05$). Further, the specific IgE levels against these allergens in the sweat also correlated with the severity of dermatitis ($P < 0.05$). It is suggested that these specific IgE antibodies against certain inhalant allergens in the sweat of patients with atopic dermatitis may play a role in allergen trapping in the skin.

In some patients, exacerbation of atopic dermatitis (AD) seems to be sweat related in that these patients complain of itching during or after sweating.¹ This phenomenon is thought to be one of the diagnostic features of AD.² In addition, the typical eczematous lesions of AD are often localized to the antecubital and politeal fossae and other flexures, sites which are characterized by high numbers of sweat glands.³ These observations suggest that there may be a pathogenic role for sweat in AD.⁴ Sweat

production in patients with AD has been described as increased,⁵ decreased^{6–8} or normal,⁹ different degrees of stimulation perhaps having produced these variable results,^{5,7,10–14} the physical or chemical properties of the sweat of patients with AD did not differ from healthy individuals.^{15,16} Sulzberger *et al.*¹⁷ also demonstrated that sweat injected into the skin of patients with AD produces erythema and infiltration, while other authors have described antisweat-precipitins which, however, are also found in the sweat of healthy persons.¹⁸ Förström *et al.*¹⁹ found higher IgE levels in the sweat of individuals with AD than in controls, a fact which has been recently confirmed.²⁰ Low IgE levels have also been observed in other intercellular fluids,^{21–23} and Adachi and Aoki²⁴ have described IgE antibodies with unknown specificity reacting with sweat of patients with AD.

Since there is an ongoing discussion on the pathogenic role of IgE in AD,²⁵ we have now investigated total IgE levels and specific IgE antibodies to the inhalant allergens grass pollen (*Lolium perenne*), birch pollen (*Betula verrucosa*) and *Dermatophagoides pteronyssinus* (D.pt.) in the serum and sweat of individuals with AD and in patients with allergic rhinitis (AR). High levels of total IgE and specific IgE to two of these allergens were detected in both fluids.

Material and methods

Patients

Fifteen adult patients with AD aged 10–40 years (mean 29 years) were studied. These patients also had allergic rhinitis or bronchial asthma. In addition, 10 adult patients (mean age 25 years) suffering from allergic rhinitis alone but without any symptoms or signs of cutaneous disease were investigated for comparison. Individuals were selected according to their level of serum-IgE antibodies against *Lolium perenne*, *Betula verrucosa* and D.pt. Only patients with a MAST class greater or equal to 3 (see below) to one of these allergens were included. For grading of the severity of AD a score

Correspondence: Dr Kirsten Jung, Hautklinik Erfurt, Arnstädter Strasse 34, PF 565, 99096 Erfurt, Germany.

proposed by Ternowitz and Herlin was used.²⁶ With these criteria 10 patients were found to have mild dermatitis and five to have severe dermatitis. Five patients with psoriasis without atopy were investigated as controls.

Collection of sweat

After the skin had been cleaned with soap and tap water patients were exposed to a sauna for 5–10 min. Sweat was collected into tubes from the face, sternal area and back (total of 2–4 ml).

Assessment of total IgE

Total IgE in serum and sweat was determined with four different commercial kits: a fluorescence immunoassay Fluoro-FAST (IF) (MAST Diagnostica, Hamburg, Germany), a nephelometric assay IgE Behring (N) (Behring, Germany), a chemiluminescence immunoassay IgE-extended range (CL) (Ciba Corning Diagnostics, Farnwald, Germany) and an enzyme immunoassay (EI) (Kallestad-Sanofi/Pasteur, Freiburg, Germany).

Assessment of specific IgE antibodies

Specific serum-IgE antibodies to *Lolium perenne*, *Betula verrucosa* and D.pt. were determined by means of a commercial fluorescence immunoassay IgE-FAST Plus (IF-Plus) (MAST Diagnostica, Hamburg, Germany).

Specific IgE in the sweat of our patients was determined by the radioallergosorbent test RAST (Pharmacia, Sweden), the fluorescence immunoassay IgE-FAST Plus (IF-Plus) (MAST Diagnostica, Germany), the enzyme immunoassay Allergocoat EAST (EAST) (Kallestad, Sanofi/Pasteur, Germany) and the chemiluminescence immunoassay Magic Lite SQ IgE specific (CL-SQ) (Ciba Corning Diagnostics, Germany).

Statistical methods

Student's *t*-tests (paired and unpaired) were performed and the correlation coefficients *r* (paired and unpaired) calculated.

Results

Levels of total IgE in serum and sweat

The four methods used to measure total serum- and sweat-IgE showed a correlation. Only patients with severe AD had significant levels of IgE in their sweat and in the serum as well ($P < 0.05$) (Fig. 1). This was confirmed in all four assay systems employed. Most

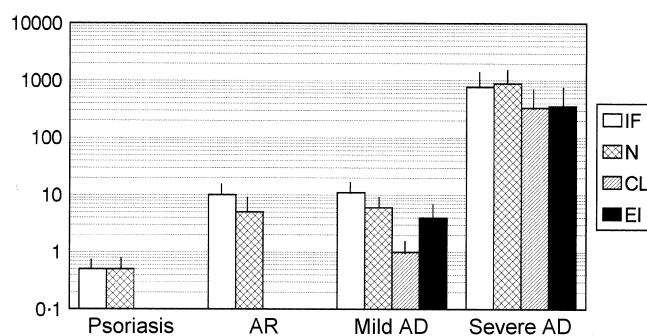


Figure 1. Levels of total IgE in the sweat of patients with psoriasis, allergic rhinitis (AR), mild AD and severe AD. Bars represent mean values of IgE (IU/ml) measured in the sweat of individuals with psoriasis ($n=5$), AR ($n=10$), mild AD ($n=10$) and severe AD ($n=5$). Results which were obtained by different methods are represented by different types of bars. IF, fluorescence immunoassay; N, nephelometry; CL, chemiluminescence immunoassay; EI, enzyme immunoassay.

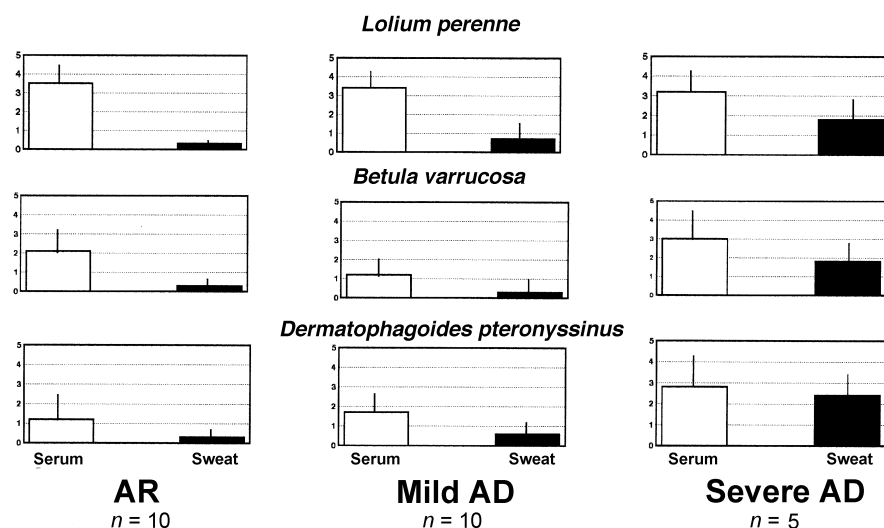
individuals had lower sweat- than serum-IgE levels. Only in one patient with severe AD was the sweat-IgE level higher than the serum level. A statistically significant correlation between serum-IgE levels and sweat-IgE levels was established with the CL assay ($r=0.76$; $P < 0.001$), N assay ($r=0.582$; $P < 0.05$) and IF assay ($r=0.542$; $P < 0.05$).

Levels of specific IgE antibodies in serum and sweat

With each of the four methods (IF-Plus, RAST, CL-SQ, EAST) specific IgE antibodies to *Lolium perenne* and *Betula verrucosa* pollen as well as D.pt. were detected in the sweat of individuals with AD as well as AR without dermatitis, but not in the sweat of patients with psoriasis. Levels of specific IgE antibodies to these allergens were high (MAST/RAST/allergy classes 3 and 4) (Fig. 2). With the IF-Plus assay a positive correlation between specific IgE levels in serum and sweat was found for birch pollen ($r=0.76$; $P < 0.01$) and D.pt. ($r=0.73$; $P < 0.01$). With the IF-Plus assay, the sweat of individuals with severe AD showed significantly higher specific IgE levels to *Betula verrucosa* and D.pt. than the sweat of those with mild AD or with AR alone ($P < 0.05$) (Fig. 2). For D.pt. this was also confirmed by the RAST ($P < 0.001$) and EAST ($P < 0.005$) tests (results not shown). For IgE to *Lolium perenne*-antigen the difference between mild and severe AD reached statistical significance only with the RAST method ($P < 0.05$) (results not shown).

Also in the serum, specific IgE levels to *Betula verrucosa* and D.pt. were significantly higher in patients with severe AD ($P < 0.05$) (Fig. 2). For *Lolium perenne* we found no statistical differences between the levels of serum-IgE antibodies in patients with AR, mild AD and severe AD.

Figure 2. Specific IgE antibodies in serum and sweat of patients with AR ($n=10$), mild AD ($n=10$) and severe AD ($n=5$). Bars represent mean values $\pm$ standard deviations of MAST classes obtained by IF-Plus assay. IgE levels for *Betula verrucosa* ($P < 0.05$) and *Dermatophagoides pteronyssinus* ($P < 0.05$) differed significantly in the serum and sweat of individuals with AR, mild AD and severe AD. For *Lolium perenne* the differences in IgE levels did not reach statistical significance.



Discussion

While secretion of IgA by human skin glands has been repeatedly described,²⁷ information on IgE excretion is rare. IgE, however, has been implicated in the pathogenesis of AD in recent years.^{25,28,29} It is therefore interesting that high levels of total IgE and specific IgE to inhalant allergens were detectable in the sweat of patients with severe AD. Sweat-IgE levels as detected by the CL assay, the N assay and the IF assay correlated positively with serum-IgE levels indicating that passive diffusion of IgE from serum into sweat may occur. We confirmed that serum-IgE levels increase with disease severity.^{28,30} Patients with high disease activity and high serum-IgE levels showed higher concentrations of total IgE in their sweat than patients with low disease activity^{19,20} or patients with AR alone. A new finding was that part of this IgE consisted of specific antibodies to inhalant allergens, the quantity of specific IgE in the sweat correlating positively with disease activity. This was significant for the allergens D.pt. and *Betula verrucosa*.

The implications of these findings for the exacerbation of AD is presently unclear. It has, however, been shown that Langerhans cells in the skin of AD bind IgE through Fc receptors.^{29,31,32} There is also preliminary evidence that autologous specific IgE bound to the Langerhans cells of these patients facilitates the presentation of inhalant allergens to sensitized T cells.³³ Allergen-sensitized T cells occur in the skin of AD.^{34–37} As inhalant allergens appear to be capable of penetrating the skin of individuals with AD,³⁸ specific IgE on Langerhans cells may facilitate a specific immune response to these allergens in the skin. Although the exact pathway of penetration of IgE as far as the Langerhans cells has not been demonstrated, it is suggested that it may diffuse through the epithelium of sweat glands into

the epidermis. Transport of IgE to the epidermis by sweating may thus be an important mechanism to enhance allergen trapping at that site.

Our results, demonstrating specific IgE to such an important allergen as D.pt. in the sweat of individuals with AD, suggest that sweating possibly facilitates percutaneous sensitization of atopic individuals to this antigen and may lead to an immunologically mediated exacerbation of the dermatitis.

References

1. Hu CH. Sweat-related dermatoses: old concept and new scenario. *Dermatologica* 1991; **182**: 73–6.
2. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol (Stockh)* 1980; Suppl. **92**: 44–7.
3. Stüttgen G, Schaefer HIN. *Funktionelle Dermatologie*. Berlin: Springer-Verlag, 1974: 159–61.
4. Marghescu S. Immunologische Aspekte der Neurodermitis atopica. *Hautarzt* 1993; **44**: 392–3.
5. Warndorff JA, Hamer M. The response of the sweat glands to beta-adrenergic stimulation with isoprenaline. *Br J Dermatol* 1974; **90**: 263–8.
6. Sulzberger MB, Herrmann F, Morill SD *et al.* Studies of sweat, lipids and histopathology in children with dry skin (xerosis). *Int Arch Allergy* 1959; **14**: 129–43.
7. Greene RM, Winkelmann RK, Opfer-Gehrking TL, Low PA. Sweating patterns in atopic dermatitis patients. *Arch Dermatol Res* 1989; **281**: 373–6.
8. Parkkinen MU, Kiistala R, Kiistala U. Sweating response to moderate thermal stress in atopic dermatitis. *Br J Dermatol* 1992; **126**: 346–50.
9. Lobitz WC Jr, Campbell CJ. Physiologic studies in atopic dermatitis (disseminated neurodermatitis). I. The local cutaneous response to intradermally injected acetylcholine and epinephrine. *Arch Dermatol Syphilol* 1953; **67**: 575–89.
10. Rovinsky J, Saxl O. Differences in the dynamics of sweat secretion in atopic children. *J Invest Dermatol* 1964; **43**: 171–6.
11. Murphy GM, Smith SE, Smith SA, Greaves MW. Autonomic function in cholinergic urticaria and atopic eczema. *Br J Dermatol* 1984; **110**: 581–6.

12. Szentivanyi A. The beta adrenergic theory of the atopic abnormality in bronchial asthma. *J Allergy* 1968; **42**: 203–32.
13. Hemels HGWM. The effect of propranolol on the acetylcholine-induced sweat gland response in atopic and non-atopic subjects. *Br J Dermatol* 1970; **83**: 312–14.
14. Foster KG, Haspinaall JR, Mollel CL. Effects of propranolol on the response of human eccrine sweat glands to acetylcholine. *Br J Dermatol* 1971; **85**: 363–7.
15. Cotton DWK, Sutorius AHM, Urselmann EJM. The fractionation of sweat from atopic and normal subjects. *Acta Derm Venereol (Stockh)* 1971; **51**: 189–93.
16. Cotton DWK, Van Rossum E. Hexokinase, glucose-6-phosphate dehydrogenase, and malate dehydrogenase in the isolated sweat glands of normal and atopic subjects. *Br J Dermatol* 1973; **89**: 459–65.
17. Sulzberger MB, Herrmann F, Borota A, Strauss MB. Studies of sweating. VI. On the urticariogenic properties of human sweat. *J Invest Dermatol* 1953; **21**: 293–303.
18. Wilkinson RD, Elie JD, Miot MJ *et al.* Autoimmunity to human sweat. I. Demonstration of antigens in sweat reactive with autologous and homologous sera. *J Invest Dermatol* 1971; **57**: 401–7.
19. Förström L, Goldyne ME, Winkelmann RK. IgE in human eccrine sweat. *J Invest Dermatol* 1975; **64**: 156–7.
20. Reck S. Quantitative IgE-Bestimmung im Schweiß von Patienten mit atopischer Dermatitis. Inaugural-Dissertation der Medizinischen Fakultät der Westfälischen Wilhelm, Universität Münster 1990.
21. Jansen CT, Haapalahti J, Hopsu-Havu VK. Immunoglobulin E in the human atopic skin. *Arch Derm Forsch* 1973; **246**: 299–302.
22. Döring HF, Ilgner M, Heinlein E. Vergleich der IgE-Konzentrationen in Hautstanzen aus atopischen Ekzemherden, ekzemfreier Haut und gesunder Haut. *Allergologie* 1988; **11**(4): 162–4.
23. Beck HI, Hagdrup HK, Brandrup F *et al.* IgE in atopic dermatitis: a study of the intercellular fluid. *Acta Derm Venereol (Stockh)* 1987; **67**: 476–80.
24. Adachi K, Aoki T. IgE antibody to sweat in atopic dermatitis. *Acta Derm Venereol (Stockh)* 1989; Suppl. **144**: 83–7.
25. Bruijnzeel-Koomen CAFM, Mudde GC, Bruijnzeel PLB. New aspects in the pathogenesis of atopic dermatitis. *Acta Derm Venereol (Stockh)* 1989; Suppl. **144**: 58–63.
26. Ternowitz T, Herlin T. Defective monocyte and p.m.n. leukocyte chemotaxis and clinical characteristics in atopic dermatitis. *Arch Dermatol Res* 1986; **278**: 454–9.
27. Gebhart W, Metze D, Jurecka W *et al.* Immunoglobulin A in human skin glands. In: Fritsch P, Schuler G, Hintner H eds. *Immunodeficiency and Skin*. Curr Probl Dermatol. Vol. 18 Basel: Karger, 1989: 31–6.
28. Thestrup-Pedersen K. Immunology of atopic dermatitis. *Acta Derm Venereol (Stockh)* 1989; **69** (Suppl. **151**): 77–83.
29. Bruijnzeel-Koomen C, Van Wichen D, Toonstra J *et al.* The presence of IgE molecules on epidermal Langerhans cells from patients with atopic dermatitis. *Arch Dermatol Res* 1986; **278**: 199–205.
30. Jung K, Bittrich A, Klimmek V, Schubert H. Imbalance of CD4+CD29+ and CD4+CD45RA+ T-helper cell subsets in peripheral blood of patients with severe atopic dermatitis. *Arch Dermatol Res* 1993; **285**: 135–9.
31. Bieber T, De La Saller C, Wollenberg A *et al.* Constitutive expression of the high affinity receptor for IgE (Fcε R1) on human Langerhans cells. *Arch Dermatol Res* 1992; **284**: 60 (Abstr.).
32. Bieber T, Prinz JC, Rieger A *et al.* Induction of FcεR2/CD23 on human epidermal Langerhans cells by recombinant interleukin 4 and gamma interferon. *J Exp Med* 1989; **170**: 309–14.
33. Mudde GC, Van Reijssen EC, Boland GJ *et al.* Allergen presentation by epidermal Langerhans cells from patients with atopic dermatitis is mediated by IgE. *Immunology* 1990; **69**: 335–41.
34. Heijden FL, Wierenga EA, Bos JD *et al.* High frequency of IL-4 producing CD4+ allergen specific T lymphocytes in atopic dermatitis lesional skin. *J Invest Dermatol* 1991; **97**: 389–94.
35. Sager N, Feldman A, Schilling G *et al.* House dust mite-specific T cells in the skin of subjects with atopic dermatitis: Frequency and lymphokine profile in the allergen patch test. *J Allergy Clin Immunol* 1992; **89**: 801–10.
36. Ramb-Lindhauer C, Feldmann A, Rotte M *et al.* Characterization of grass pollen reactive T-cell lines derived from lesional atopic skin. *Arch Dermatol Res* 1991; **238**: 71–6.
37. Reijssen FC, Bruijnzeel-Koomen CAFM, Kalthoff FS *et al.* Skin-derived aeroallergen-specific T-cell clones of TH2 phenotype in patients with atopic dermatitis. *J Allergy Clin Immunol* 1992; **90**: 184–92.
38. Tanaka Y, Tanaka M, Anan S *et al.* Immunohistochemical studies on dust mite antigen in positive reaction site of patch test. *Acta Derm Venereol (Stockh)* 1989; Suppl. **144**: 93–6.