

REVIEW ARTICLE

Atopic Dermatitis: Summary of the 1st Georg Rajka Symposium 1998 and a Literature Review

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Atopic dermatitis (atopic eczema) was the subject of the 1st Georg Rajka Symposium in Davos, on September 6–9, 1998. This summary and critical review of present knowledge of atopic dermatitis, the most common chronic inflammatory disease of children in industrialized countries, is aimed at physicians and nurses, researchers or students who want a brief introduction to atopic dermatitis to enable them to give optimal service to patients and parents and to make decisions about the direction of future research. It is a subjective review and cannot fully cover all aspects of the subject. However, it focuses on important issues concerning atopic dermatitis in 1998, just a century after it was first described by Besnier (1).

PATIENTS AND COMPLIANCE

Dr Kazuya Yamamoto, Tokyo, summarized 30 years' experience with atopic dermatitis. As in other countries the incidence of atopic dermatitis in Japan has risen, whilst the number of children in families has reduced significantly. Older mothers may be more concerned about their children's skin condition and often demand a cure for the disease. He stressed the importance of the physician in charge explaining carefully the present state of knowledge of disease mechanisms and giving specific advice on therapy, including emollients, anti-inflammatory therapy and behavioural advice.

Is atopic dermatitis "curable" or "controllable"? Many participants felt it important not to discourage the patient or parents by saying that atopic dermatitis is "a life sentence", but rather to convince them that today we have many possible ways of controlling disease activity and that most children will outgrow the symptoms. However, the course of atopic dermatitis cannot easily be predicted. Also, the later development of respiratory atopic diseases is difficult to forecast for the individual child. It is a fact that 35–40% of eczema patients later develop hand eczema in adulthood (2). Hand eczema is the most common occupational disease in adults under the age of 25 years (3), and it often has an atopic dermatitis background (2)¹.

DISEASE DEFINITION

There are several sets of criteria used for the diagnosis of atopic dermatitis. Hanifin & Rajka's 1980 criteria (4) have been followed by the UK Working Group on atopic eczema

and validated questionnaires are available (5, 6). A new "millennium criteria" was suggested for atopic dermatitis, whereby the presence of allergen-specific IgE is mandatory, together with 2 of 3 findings of (a) eczema in typical locations, (b) pruritus, and/or (c) a chronic course². This suggestion was met with scepticism, because almost half of children do not have specific IgE antibodies, but have atopic dermatitis according to the criteria of Hanifin & Rajka (4). The "millennium criteria" suggest that the major abnormality is the production of allergen-specific IgE. This issue has been dealt with previously by the suggestion of dividing atopic dermatitis into an "extrinsic" form, in which specific IgE is present and/or total serum IgE is elevated, and an "intrinsic" form, comprising between 10 and 50%, in which allergies are not found (7).

It is still possible that a better disease definition will arise. Thus far, clinical evaluation is most important, but all studies show a large variation (see below). We still have difficulty in agreeing on disease definition. Also, there is no biochemical parameter that may help us to measure the degree of atopic dermatitis or which is unique to this disorder, not even IgE.

EPIDEMIOLOGY

The difficulties of delineating and diagnosing atopic dermatitis were demonstrated in a recent Swedish study by Broberg, in Gothenburg and Svensson in Kristianstad, dermatologists with lifelong experience in the field³. They performed a questionnaire study of 1,957 parents with 5-year-old children seen at a compulsory child welfare clinic visit from October 1997 to April 1998. The response rate was 89%. All children with ongoing eczema were examined by 1 of the investigators, who validated their clinical investigation and used SCORAD and Rajka & Langeland's protocol for severity scoring of atopic dermatitis. Thirty-five percent stated that their child had past or present eczema. The Schultz-Larsen et al. questionnaire for atopic eczema was fulfilled by 19.5% in Gothenburg and 22.7% in Kristianstad (6). A total of 182 children (9.2%) currently had eczema, as documented by clinical examination. However, the incidence was 6.1% in Gothenburg and 14.5% in Kristianstad. One explanation for

¹Jung K, Bieback C, Linse R. The role of atopy for contact dermatitis. 1st Georg Rajka – Symposium, Davos, 1998

²Bos JD, van Leent EJM, Sillevs Smitt JJ. The millennium criteria for the diagnosis of atopic dermatitis. 1st Georg Rajka – Symposium, Davos, 1998.

³Broberg A, Svensson A. Prevalence and severity scoring of atopic dermatitis. 1st Georg Rajka – Symposium, Davos, 1998.

such a significant difference could be different treatment principles of eczema among the different groups of children. This study underlines the difficulties of performing population-based epidemiological studies of atopic dermatitis. The disease is fluctuating and is influenced by treatment. In addition, the Swedish study demonstrate that approximately 80% of the children had less than 10% of body surface involvement, indicating that the majority of children with atopic dermatitis have mild disease. This was confirmed in their scoring results, in which only 4% were scored to have severe disease.

New detailed data were presented on studies of 5–6-year-old pre-school children in different locations in Germany, based on dermatological examinations in 1991, 1994 and 1997 of 4,012 children with a response rate of around 70% (8). The overall prevalence was 10.4%, but significant differences were observed, as were differences between cities. Thus, the prevalence of atopic eczema ranged in former East Germany between 7.1 and 13.8%, with a mean of 11.2%, whereas in former West Germany the prevalence ranged between 3.4 and 6.2%, with a mean of 4.6%. These figures are from 1997. A total of 43% of children had at least 1 positive prick test (“extrinsic atopic eczema”), 38.1% among children in former East Germany compared with 50.7% among children in former West Germany, which is significantly higher. It will be interesting to study the different prevalence rates of atopic dermatitis regarding its “intrinsic” and “extrinsic” variants. Again, disease fluctuation may vary significantly, although the German studies were conducted in the same time period.

Children developing atopic dermatitis have increased gestational age and birth weight (9). These observations show that even before disease expression, unknown *in utero* signals are already present and will influence gestation. The “older mother” theory, whereby increased age of the mother may influence disease expression has, however, not been further substantiated (10).

PATHOPHYSIOLOGICAL MECHANISMS

Amongst the many papers on disease mechanisms, 3 major topics were discussed: cells in atopic eczema; mediators and their receptors; and adhesion molecules.

Lymphocytes

Atopic dermatitis cannot develop if T-lymphocytes are not present in the skin. The skin-homing T-lymphocytes are for the most part activated as defined by their HLA-DR expression. The number of allergen-specific T-lymphocytes is small and difficult to evaluate, but cloning experiments have clearly demonstrated their presence in atopy patch test reactions. They can also be found in peripheral blood, but have so far not been looked for in non-tested, but active eczematous skin. Positive patch tests towards environmental allergens do always have fewer T-lymphocytes than active eczema lesions. Skin-homing T-lymphocytes can be grown *in*

vitro after addition of IL-2 and IL-4 without further stimulation⁴. Such cell lines show polyclonal growth, express an immature phenotype and have increased telomerase activity, perhaps as signs of “immaturity”⁵. Their significance in disease development requires further study (11, 12).

Since the discovery of cutaneous lymphocyte antigen (CLA) and the finding that CLA+ T-cells have special capacities for skin-homing via binding to E-selectin, they have been intensely studied in atopic dermatitis. CLA is an activation marker that is down-regulated during *in vitro* growth. CLA is found on 5–20% of peripheral blood T-cells, but on approximately 50% of skin-homing T-cells in an atopen patch test. Approximately half of CLA+ cells also express CD25 receptors (IL-2 receptor) and one-quarter express HLA-DR as a marker for “activation”. When isolated *in vitro* they show spontaneous proliferation, and their cytokine profile is high in IL-5 and IL-13, IL-10 may be high, IL-4 is negative or low and IFN- γ is negative. Thus, apart from lacking IL-4, they express a Th-2 pattern. CLA+ T-cells from non-atopic patients do, however, show a Th-0 profile⁶. CLA+ T-cells from atopic patients also augment eosinophil survival. When CLA+ T-cells are quantitated in an atopen patch test, the percentage of CLA+ cells does not increase during the development of the reaction, but shows no change or a slight fall^{7,8} (13). Also, it is not certain whether the antigen-specific reacting T-lymphocytes are all CLA+, although cloning experiments indicate this.

Dendritic cells

Inflammatory dendritic epidermal cells (IDECs) are dendritic cells with the CD1a⁺/CD11b⁺⁺⁺ phenotype in contrast to the usual CD1a⁺⁺⁺/CD11b⁻ Langerhans' cells. IDECs are present in inflammatory diseases and are not unique for atopic dermatitis⁹ (14). The trombospondin receptor (CD36) is increased on IDECs, but never expressed in normal skin. CD23 (Fc \cdot RI) expression correlates with total serum IgE level. IDECs disappear within 7–14 days of topical treatment with FK506.

The question is whether IDECs are a new type of dendritic cells coming from the CD34+ cell compartment in the blood and ultimately from the bone marrow, or whether they are phenotypically changed Langerhans' cells because of the inflammatory processes occurring in the skin. However,

⁴Bang K, Lund M, Volke A, Thestrup-Pedersen K. Skin-homing T lymphocytes from atopic dermatitis exhibit different growth potential and phenotype than T lymphocytes from blood. 1st Georg Rajka – Symposium, Davos, 1998.

⁵Wu K, Lund M, Bang K, Thestrup-Pedersen K. Telomerase activity and telomere length of lymphocytes from patients with atopic dermatitis. 1st Georg Rajka – Symposium, Davos, 1998.

⁶Akdis CA, Akdis M, Weigl L, Disch R, Santamaria Babi LF, Simon HU, Blaser K. Regulation of allergic inflammation by skin homing T-cells in atopic eczema. 1st Georg Rajka – Symposium, Davos, 1998.

⁷Akdis M, Simon HU, Weigl L, Blaser K, Akdis CA. In vivo activated skin homing T-cells in atopic eczema induce IgE and regulate eosinophil survival and apoptosis. 1st Georg Rajka – Symposium, Davos, 1998.

⁸Bruijnzeel-Koomen C. The atopy patch test as a model for allergic inflammation in atopic dermatitis. 1st Georg Rajka – Symposium, Davos, 1998.

⁹Wollenberg A. Inflammatory dendritic epidermal cells (IDEC) – characterization of an inflammation-associated epidermal cell population from atopic dermatitis in their relationship to Langerhans cells. 1st Georg Rajka – Symposium, Davos, 1998.

IDECs are not unique for atopic dermatitis, but are found in other inflammatory skin diseases, although their number is highest in atopic eczema⁹.

Eosinophils

New studies have shown that patients with atopic dermatitis have long-lived eosinophils, because the cells *in vitro* have a prolonged life and are less likely to go into apoptosis (15). The prolonged *in vitro* culture is promoted by IL-5 and GM-CSF; both mediators are increased in atopic dermatitis. The long-lived eosinophils may be characteristic for atopic dermatitis, because eosinophils from patients with the hyper-eosinophilic syndrome (Churg-Strauss syndrome) did not exhibit similar *in vitro* characteristics (15).

Mediators and receptors

This area has become complex and confusing. When analysing the results it is of utmost importance to consider which model was studied (e.g. cloned antigen-specific T-cells vs. polyclonal T lymphocytes from blood or from skin biopsies) and how the cytokines were measured (on the transcriptional level (mRNA), on FACS analysis, immunohistology, *in situ* hybridization, or as secreted proteins).

When allergen-specific, cloned T lymphocytes from positive patch tests are studied they have for the major part a Th-2 profile, although CLA+ allergen-reactive cells do not express IL-4⁶. However, when T lymphocytes are studied from chronic active, eczematous lesions or from skin-homing, polyclonal T-cells, then the picture shows either a Th-0 profile or a Th-1 profile with a high up-regulation of IFN- γ . This has been found in *in situ* studies, on immunohistology and when studying skin-homing T-cell lines (16)¹⁰.

When studying other cytokines, IL-16 has been found¹¹. Eotaxin and MIP-1 α mRNA were up-regulated in a late phase allergic reaction in mice¹² and in humans, whereas RANTES and IL-8 were not up-regulated¹³.

It seems fair to conclude that our knowledge of cytokines has not helped us better to understand atopic dermatitis. There is no doubt that the production of IgE is controlled by a balance between Th-1 and Th-2 cytokines, but no single cytokine can be said to have significant importance. The redundancy is extreme. Clinical trials with mono-cytokine therapy have also shown moderate clinical effect from using IFN- γ and no change in IgE levels (17). However, further

studies are needed in carefully designed models, including studies of the polyclonal inflammation in the skin of atopic eczema. Such studies should also focus on possible methods of modulating the Th-1/Th-2 balance.

Adhesion molecules

Apart from CLA up-regulation, which binds to selectins, studies have shown that certain integrins are up-regulated¹⁴ and that VCAM-1, especially, is permanently up-regulated in eczematous atopic skin¹⁵.

Staphylococcus aureus

A large study of 100 outpatients with atopic dermatitis confirmed the common presence of *S. aureus* (88%), but no correlation was found between disease activity and the production of superantigens, which could be detected among 48% of the isolated bacteria. Staphylococcal enterotoxin A was only secreted by 15.5% of the bacteria¹⁶. Despite these findings most clinicians use antibacterial therapy. Another study from the same department showed that treatment alone with an antiseptic compound (bath therapy with gentian violet) improved the clinical condition of eczema. The investigators cannot exclude that gentian violet *per se* has an anti-inflammatory effect¹⁷.

A new study resulted in data that showed that a cleavage product of staphylococcal enterotoxin B is highly homologous to the low-affinity IgE-receptor CD23. The significance of this for skin inflammation could relate to its binding to CD21 on B-lymphocytes, thus promoting IgE synthesis¹⁸.

Other infections were also discussed. Russian studies have observed many gastrointestinal parasitic infections, especially with *Blastocystis hominis*, which was found among 30–70% of Russian children with atopic eczema¹⁹.

PATCH TESTING IN ATOPIC DERMATITIS

When Georg Rajka worked at the Department of Dermatology, Karolinska Hospital, Stockholm, in the 1950s, he

¹⁰Higashi N, Gesser B, Lund M, Bang K, Yamamoto K, Thestrup-Pedersen K. Cytokines expression of skin-homing T lymphocytes from patients with atopic dermatitis. 1st Georg Rajka – Symposium, Davos, 1998.

¹¹Wittman M, Kowalsczuk J, Wistokat-Wulfing A, Kapp A, Werfel T. The role of skin-infiltrating T-cells in atopic dermatitis. 1st Georg Rajka – Symposium, Davos, 1998.

¹²Tanaka Y, Jae BS, Hakagawa J, Katayama I. Antigen-induced eotaxin messenger RNA expression and eosinophil infiltration in murine cutaneous late phase response. 1st Georg Rajka – Symposium, Davos, 1998.

¹³Yawalkar N, Ugucini M, Scharfer J, Braunwalder J, Karlen S, Braathen LR. Expression of eotaxin and CCR3 is enhanced in lesional skin from atopic dermatitis. 1st Georg Rajka – Symposium, Davos, 1998.

¹⁴Jung K, Imhof BA, Linse R, Wollina U, Neumann C. Adhesion molecules in atopic eczema: Upregulation of an integrin expression in spontaneous lesional skin as well as in atopen, antigen and irritative induced patch test reactions. 1st Georg Rajka – Symposium, Davos, 1998.

¹⁵Boon W, Song S. The expression of VCAM-1 and ICAM-1 in dermal small blood vessels was compared in two eczematous diseases: atopic dermatitis and allergic contact dermatitis. 1st Georg Rajka – Symposium, Davos, 1998.

¹⁶Hojka M, Mempel M, Ring J, Abeck D. Characterization of *Staphylococcus aureus* colonization in patients with atopic eczema. 1st Georg Rajka – Symposium, Davos, 1998.

¹⁷Brockow K, Grabenhorts P, Abeck D, Ring J. Gentian violet in the treatment of *Staphylococcus aureus* – colonized atopic eczema. 1st Georg Rajka – Symposium, Davos, 1998.

¹⁸Neuber K, Hakansson K, Moll I, Ring J. Characterization of a cleavage product of *Staphylococcal enterotoxin B* (SEB) that is highly homologous to the low-affinity IgE-receptor/CD23. 1st Georg Rajka – Symposium, Davos, 1998.

¹⁹Toropova NP, Safronova NA, Pazdnikova EE. Parasitic fauna in patients with atopic dermatitis – pathogenetic and therapeutic aspects. 1st Georg Rajka – Symposium, Davos, 1998.

conducted a series of studies on delayed reactivity to recall antigens in patients with atopic dermatitis using ordinary patch test technique. He found the reactions to be either absent or reduced compared with those of non-atopic individuals. We know now that with atopy patch test the situation is reversed.

Our present knowledge of the atopy patch test in adult patients is that a positive reaction is always correlated with specific IgE in serum. Around 40–50% of patients with atopic dermatitis and antigen-specific IgE have positive patch test reactions to environmental allergens⁸. During the first 24-h of the reaction Th-2 cytokines prevail, but at 48 h Th-1 cytokines are most prominent (16). It is thought that allergen specific CLA+ Th-2 cells play a major role⁶ (13).

A German multicentre study used different concentrations of antigen applied to non-abraded skin. It was found that reactions occurred among 10–52% of patients. House dust mite contact sensitivity was the most common. The findings revealed a clear correlation with history, skin prick tests and specific IgE for the allergen. Dose-dependent studies observed that 5,000–7,000 PNU/g gave optimal sensitivity of the tests²⁰. Still, an atopic dermatitis patch test series for routine use awaits an ongoing European multicentre trial.

Another study of 70 patients showed that 20–30% of patients had positive patch test reactions to grass pollen and house dust mite, respectively, but had negative cutaneous delayed type of hypersensitivity to recall antigens²¹.

FOOD AND ATOPIC DERMATITIS

This issue was discussed intensely, with strong polarization. The topic still seems confusing, but a pattern is emerging. The confusion arises mainly because of a lack of stringent definitions.

A prevalence study among adults in the general population of High Wycombe, UK, showed that 20.4% perceived adverse reactions to food items. However, only 1.4% had confirmed food allergies (18).

“Food allergy” is an adverse reaction mediated by an immunological reaction towards a food allergen, i.e. a purified protein, not a mixture of food items. “Food intolerance” is a reaction not caused by immunological mechanisms, e.g. intake of food items with high histamine content (mackerel or tuna), or high amounts of monosodium glutamate (“Chinese restaurant” syndrome). “Food aversion” is a description of symptoms, which cannot be confirmed by double-blind provocation (19).

Food and type I reactions

Food allergy is uncommon among small children. Thus, 3% of all children of approximately 1 year of age have a positive prick test towards milk. By the age of 3 years only 1% express

²⁰Darsow U, Vieluf D, Ring J et al. Specificity and technical aspects of atopy patch testing. 1st Georg Rajka – Symposium, Davos, 1998.

²¹Jung K, Linse R. Aeroallergen Dermatophagoides pteronyssinus as factor of exacerbation for severe atopic dermatitis – positive atopen-patch-test-reactions and concomittant negative delayed type of hypersensitivity of recall-antigens. 1st Georg Rajka – Symposium, Davos, 1998.

a positive prick test, i.e. there is an approximately 80% reduction in type I allergy (20). Almost all children with positive prick tests to food items also have atopic dermatitis, so the frequency among those with atopic eczema is relatively higher. Egg allergy has also been found to decline among those being prick test positive (21). Recently, peanut allergy has also been shown to disappear with time (22). Thus, in those rare cases of atopic dermatitis, where type I allergies are found in infants or children, the allergies tend to disappear with age.

Diets for children with proven food allergy shown by double-blind, placebo-controlled tests can diminish eczema activity or may delay the occurrence of eczema (19). It may be difficult for parents to discover such allergies; thus only 7 of 62 children with allergy to egg were under clinical suspicion for having food allergy²². Diets led to diminishing of clinical symptoms. However, the same author confirmed that food allergies disappear with time.

Fruits, including tomatoes and citrus fruits, can often induce an oral skin irritation in infants with atopic dermatitis. However, this is not “food allergy”, but more an intolerance phenomena, which can be assessed by the Skin Application Food Test (SAFT). This test preferentially measures contact urticaria. Dutch workers have found a correlation between SAFT and prick tests in 64 children, although the use of fresh foods gives a higher frequency of reactions (80% vs. 52%)²³. However, elimination diets do not lead to clearing of the eczema, but to lower disease activity.

Another study of 31 adult patients looked for hypersensitivity to orange juice and observed that 21 had increased disease activity after intake during the ensuing 24 h. However, there was no correlation between the results of skin prick tests, patch tests and specific IgE towards orange and the clinical response²⁴.

A new study showed that, among adults with suspected milk allergy, T-lymphocytes in blood could react towards casein. Patients whose T-lymphocytes reacted most *in vitro* towards casein were those who had the highest clinical benefit from milk avoidance, although the eczema did not disappear²⁵.

Food and type IV reactions

Several studies were presented in which investigators looked for type IV allergies using patch tests. All studies confirm that fresh food items give the highest frequency of reactions, whereas purified allergens do not induce responses. It is therefore important to discuss whether the reactions are a sign of true “allergy” or whether they represent “intolerance” or

²²Lever RM. Personal communication. 1st Georg Rajka – Symposium, Davos, 1998.

²³Oranje AP, Elst EF, Mulder PGH, Munte K, Devillers ACA, de Waard-van der Spek FB. Comparison of diagnostic tests in children with atopic dermatitis and food allergy. 1st Georg Rajka – Symposium, Davos, 1998.

²⁴Hautmann C, Brockow K, Rakoski J, Borelli S, Ring J. Hypersensitivity to oranges in adult patients with atopic eczema. 1st Georg Rajka – Symposium, Davos, 1998.

²⁵Werfel T, Reeckers R, Wittmann M, Kapp A. The role of food antigens as trigger factors of atopic dermatitis. 1st Georg Rajka – Symposium, Davos, 1998.

“irritation”. In this context it is noteworthy that French workers have observed how almost all children with atopic dermatitis show positive reactions when tested at 1 year of age, whereas only 20% react positively at 5 years of age²⁶. The frequent reactions in small children have been extensively studied by Finnish workers, who found that more than half of children react with “positive patch test”, when fresh food items are applied to the skin²⁷. However, proper testing of healthy children is lacking and careful long-term observations of the effect of diets are still lacking. Also, it is fair to ask about the relevance of the non-physiological application of fresh food items under occlusion to the skin. The observations above could indicate that the atopic skin barrier is significantly reduced in small children with a low threshold for irritancy, but that it changes rapidly during growth.

The therapeutic approach of diet in atopic dermatitis

Finally, it was pointed out that there are 2 main approaches towards investigations for food allergy and the role of diets in atopic dermatitis: the American approach is to select patients through double-blind, placebo-controlled investigations, which will select a very small group of patients. Those patients improve on diets. The UK approach is to introduce “few food diets” and then document the effects. First of all the UK experience shows that any introduction of a “diet” will lead to a placebo effect. Two controlled studies have not been able to document any long-term effect (1 year) from a “few food diet” (23, 24). Also, it should be remembered that food allergy can go away, although it may re-appear.

In patients with “anaphylactoid reactions” immune mechanisms may not be the only ones involved. Thus, German investigators have observed that anaphylaxis patients have a reduced angiotensin II level (25).

Our summary of Food and Atopic Dermatitis is that patients with proven, specific allergies (IgE mediated) may benefit from diets. Children, however, are more difficult to advise and controlled studies have not been able to document a long-term effect. The many positive patch test reactions with fresh foods need much more stringent analysis regarding “allergy” vs. “intolerance”. This is necessary in order not to introduce cumbersome and costly diets, which may not be of value for the patients (23, 24).

PSYCHO-NEURO-IMMUNOLOGICAL ASPECTS OF ATOPIC DERMATITIS

This topic was discussed with reference to the fact that approximately 70% of dermatologists (and many patients) are convinced that stress worsens atopic eczema. New studies have shown that an acute stress in atopic dermatitis patients leads to a reduction in the level of ACTH, i.e. the dysfunction is at a pituitary gland level. Adrenaline levels are much higher

²⁶Roul S, Leaute-Labreze C, Ducombs G, Taieb A. Abnormal epidermal barrier function and chronology of aeroallergen sensitization in children with atopic dermatitis. 1st Georg Rajka – Symposium, Davos, 1998.

²⁷Turjanmaa K, Holm K, Majamaa H. Value of protein patch tests with foods in diagnosis of atopic eczema. 1st Georg Rajka – Symposium, Davos, 1998.

in atopic dermatitis patients. After acute stress there is a slight increase in total serum IgE level within 2 days, but IFN- γ is mostly increased in non-atopic patients and IL-4 shows a slight, although not significant, decrease (26). Chronic stress has not been studied because of its complexity. So far, psycho-neuro-immunology is likely to be involved in atopic dermatitis, but we still lack ways of measuring such changes.

OTHER OBSERVATIONS

A Japanese study observed a low-molecular weight compound in house dust mites, acaridial, which in concentrations between 0.3% and 0.5% could induce strong positive reactions in up to 60% of both patients with atopic dermatitis and in controls, whereas a dilution to 0.1% showed almost no reactivity. Some of the reactions were standing for weeks to months in the atopic dermatitis patients, but only up to 3 weeks in controls. Further studies are needed²⁸.

Avoidance of house dust mite in 1 Japanese patient lead to a complete clearing of the skin²⁸ and a Belgian study documented a case report of severe atopic dermatitis in which *Pityrosporon orbiculare* was the eliciting factor with an ensuing complete clearance of eczema²⁹. Thus, some patients with atopic dermatitis may have allergen-driven skin inflammation.

Naevi are significantly less common among patients with atopic dermatitis³⁰. This raises the issue as to whether atopic dermatitis patients may have fewer melanomas, which again could have importance for the risks associated with high-dosage UV therapy. Clearly, studies are needed.

A total of 2,106 patients have been evaluated during various climatic conditions. It was documented that snow and fog are associated with diminished itching, as are high temperatures, increased vapour pressure and an increased number of sunshine-hours. In contrast, thunder was significantly associated with a worsening of itching³¹.

Russian studies of 263 patients with atopic dermatitis followed for 15–25 years observed vitiligo among 13% and alopecia areata among 8%³².

TOPICAL THERAPY

An investigation of emollients showed that the difference in clinical efficacy between various types of emollient is difficult to demonstrate despite the fact that many propriety emollients are 7–10 times more expensive than generic brands. Use of

²⁸Nakayama H, Kumei A, Kuwahara Y. Acaridial, a newly discovered strong contact sensitizer in house dust mites. 1st Georg Rajka – Symposium, Davos, 1998.

²⁹Morren M, Nemery B, Noland N. Fungi as a significant trigger in a patient with atopic dermatitis: a case report. 1st Georg Rajka – Symposium, Davos, 1998.

³⁰Broberg A. Atopic dermatitis and melanocytic naevi. 1st Georg Rajka – Symposium, Davos, 1998.

³¹Vocks L, Ring J, Borelli S. Climatic influence on itch intensity in atopic eczema. 1st Georg Rajka – Symposium, Davos, 1998.

³²Toropova NP. Combination of atopic dermatitis with alopecia areata and vitiligo: regular or accidental? 1st Georg Rajka – Symposium, Davos, 1998.

emollients improves atopic dermatitis, but a clinical discrepancy factor of 2 could not be demonstrated in a controlled study³³.

Steroids are the most significant remedy for relief of inflammation and itching. Several studies have proven their efficacy, which relates to their potency³⁴. Addition of antibiotics was not helpful according to 1 study, but has been shown to be effective during the first week of therapy in another study (27).

Wet wraps are an excellent technique for treating children with severe atopic dermatitis. This method is somewhat time-consuming, but worth the effort³⁵. Eczema schools can be helpful for parents in order to achieve necessary practical guidance for therapy. A recent study on the combined use of psychological and dermatological treatment strategies has demonstrated a significant 1-year improvement in young adults with atopic eczema (28). Such treatment options will need careful cost-benefit considerations.

SYSTEMIC THERAPY

High dosage UV-A1 can be given daily (up to 130 J/cm²) for a total of 10 treatments. Then, no further therapy should be given. This leads to significant clinical improvement^{36,37}. However, the long-term hazards must be considered. Photopheresis has been used in very few patients with recalcitrant atopic dermatitis with a significant outcome.

Cyclosporin A (CsA) has a documented effect. A Finnish study compared an 8-week treatment period of cyclosporine with UVA-B light therapy. A significant higher number of patients withdrew from the planned 1-year study in the UV group (21 patients vs. 4 patients in the CsA group). The CsA dosage was 4 mg/kg, which was reduced to 2.5 mg/kg according to the clinical response. Patients on CsA had a relapse after stopping the drug. An average of 4 treatment schedules was needed during the 1-year study period³⁸.

Azathioprine is used by many, but double-blind, placebo-controlled trials are lacking. Also, 0.3% of patients may have reduced thiopurine methyltransferase activity and therefore have higher significant side-effects. A recent study of 775 patients treated over approximately 9 years for a gastrointestinal disease did not have increased number of lymphomas (29). Nineteen of 34 adult patients had good to moderate improvement, including the ability to omit systemic steroids³⁹.

³³Dalton SJ, Patel L, David TJ. Controlled studies of emollient ointments and creams in the treatment of atopic dermatitis in childhood. 1st Georg Rajka – Symposium, Davos, 1998.

³⁴David TJ, Ainley-Walker P, Patel L. Side to side comparison of topical treatment in atopic dermatitis. 1st Georg Rajka – Symposium, Davos, 1998.

³⁵Wolkerstorfer A, de Waard-van der Spek FB, Oranje AP. Wet wrap dressing as therapy for atopic dermatitis. 1st Georg Rajka – Symposium, Davos, 1998.

³⁶Abeck D, Boeck K, Mempel M, Schmidt T, Ring J. Acute and long-term efficacy of UVA1-medium dose therapy in atopic eczema. 1st Georg Rajka – Symposium, Davos, 1998.

³⁷Krutmann J. New developments in the photo(chemo)therapy of patients with atopic dermatitis. 1st Georg Rajka – Symposium, Davos, 1998.

³⁸Granlund H, Erkkö P, Reitamo S. Comparison of cyclosporin A and UV-B phototherapy in the treatment of atopic eczema. 1st Georg Rajka – Symposium, Davos, 1998.

DEVELOPMENT OF NEW TREATMENT MODALITIES

FK-506, which has a proven efficacy in atopic dermatitis (30), has been found not to introduce skin atrophy⁴⁰. Another study showed that ascromycin is also capable of introducing significant clinical improvement in atopic dermatitis⁴¹. The possible role of these in future treatment modalities will be awaited with great expectations.

GENETICS

The most important parameter for development of atopic dermatitis is genetic inheritance. This issue was not discussed during the meeting. Research within the last decade has looked for an association with the gene(s) determining IgE, and such an association has been found for asthma, but not for atopic dermatitis (31). Three recent observations need confirmation; the first is an association between atopic dermatitis and the beta subunit of the high affinity IgE receptor (32). The second observation is increased chymase expression in atopic dermatitis skin, i.e. an increased activity of mast cells is associated with the skin disease (33, 34). A third observation is that there may be a polymorphism of the IL-4 receptor, leading to a gain-function of the receptor (35, 36). This may explain why the immune system is skewed towards a Th-2 reactivity. However, further studies are needed.

If atopic dermatitis is found to be linked to genetically determined changes in the immune system, then atopic dermatitis seems *a priori* to be an immune system disease. However, the genetic linkage could also be associated with ectodermal tissue (i.e. the skin), because patients with atopic dermatitis have epidermal changes other than “eczema”, such as an altered skin barrier and lipid content. If the primary genetically determined defect was associated with lipid metabolism in the ectodermal tissue, this could influence T lymphocyte maturation; which would be important early in life (11, 12).

CONCLUSION

Atopic dermatitis is still a puzzle. However, increasing knowledge about the disease makes it likely that before long findings will lead to a breakthrough in our understanding of the development of the disease. If so, this will open avenues for new treatment strategies or even for prophylactic measures aimed at disease prevention or expression. However, it needs to be remembered that even the discovery of a genetic trait for atopic dermatitis will not diminish the complexity of the disease or facilitate doctors in advising patients.

The tables show factors which can “augment” or “reduce” the Atopic Skin Inflammation.

³⁹Zachariae H. Azathioprine in atopic dermatitis – is it worth while? 1st Georg Rajka – Symposium, Davos, 1998.

⁴⁰Reitamo S. Tacrolimus improves atopic eczema without causing skin atrophy. 1st Georg Rajka – Symposium, Davos, 1998.

⁴¹Van Leent EJM, Graber M, Ebelin ME, Burtin P, Thurston M, Wagenaar A, Spuls PH, Bos JD. Topical treatment with SCZ ASM 981 in atopic dermatitis combines efficacy with low systemic exposure. 1st Georg Rajka – Symposium, Davos, 1998.

Factors which create, augment or are associated with atopic skin inflammation:

- Genetic factors of yet unknown character
- Mast cells with changed chymase activity
- Skin-homing, immature T lymphocytes
- Gain-of-function of IL-4 receptors on T lymphocytes
- Allergen-specific immune inflammation (type I and type IV allergies)
- Any stimulation of the immune system leading to T lymphocyte activation (e.g. infections)
- Impaired skin barrier with increased susceptibility to skin irritation
- Super-antigens from bacteriae
- Climate conditions
- Biochemical changes (pituitary gland function; catecholamine metabolism)
- Stressor factors
- Use of contraceptive pills; social class

Factors which will diminish the atopic skin inflammation:

- Increased age
- Previous viral infections (hepatitis A, morbilli)
- Sun exposure including UV therapy
- Skin barrier improvement
- Anti-inflammatory therapy

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