

5th Georg Rajka International Symposium on Atopic Dermatitis, May 11–13, 2008, Kyoto, Japan: A Meeting Summary

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The authors attended the above-mentioned symposium in Kyoto. They have written a summary of the meeting and discuss what was debated. (Conflicts of interest: KTP is a consultant for Astellas Pharma and Novartis.)

The 10th meeting on atopic dermatitis was held in Kyoto with Professor Masahiro Takigawa as president. Previous and forthcoming meetings are listed in Table I. The meeting focused on various topics, as highlighted below:

Definition, incidence and epidemiology of atopic dermatitis: is “atopic dermatitis” one or several diseases?

Today, the answer is: one disease. It may be defined as “intrinsic”, i.e. no increase in IgE or type I allergies, or “extrinsic”, i.e. presence of increased IgE and type I allergies. An individual patient (child) can move from “intrinsic” to “extrinsic” atopic dermatitis. Several authors have now come to the conclusion that IgE is secondary to the disease itself – an important point, as the presence or absence of IgE-mediated allergy has little consequence regarding therapeutic approaches. This includes “allergy testing”, which is so commonly requested by parents and patients; however, this issue was not debated further.

A systematic review was presented by Dr Elian Brennickmeijer, analysing 27 published studies on various “definitions” of

atopic dermatitis. The UK criteria were the best validated, but the “definition” of atopic dermatitis still leaves room for improvement. Hywel C. Williams stated that the UK criteria were a distillation from the Hanifin & Rajka criteria.

Atopic dermatitis varies in incidence worldwide. Using World Bank statistics classifying countries into “affluent” and “non-affluent” countries on per capita income, it is evident that affluent countries have a higher prevalence of atopic dermatitis. The reasons for this are unknown. In affluent countries “flexural eczema” is significantly associated with positive skin prick tests. However, this is not the case in non-affluent countries. The reason for this is unknown. The increase in atopic dermatitis has levelled off in affluent countries and may in fact be falling, whereas in Africa it appears to be increasing, from very few with atopic eczema to 5–10%.

Clinical features of atopic dermatitis in adults

Johannes Ring gave an overview of adults with atopic dermatitis, and stated that the prognosis for atopic dermatitis may be rather poor, in the sense that up to 90% of patients will have the disease into adulthood. This is somewhat contradic-

Table I. Previous and forthcoming meetings.

Date	Location	President
1980	Oslo	Georg Rajka
1984	Loen	Georg Rajka
1988	Oslo	Georg Rajka
1991	Bergen	Georg Rajka
1995	Aarhus	Kristian Thestrup-Pedersen
1998	Davos	Johannes Ring and Kristian Thestrup-Pedersen
2001	Portland, OR	Jon Hanifin and Kevin Cooper
2003	Rome	Alberto Gianetti
2005	Archachon	Alain Taieb
2008	Kyoto	Masahiro Takigawa
2010	Munich	Johannes Ring



Fig. 1. Georg and Susanne Rajka were honorary participants at the Symposium.

tory to other studies indicating that two-thirds of patients outgrow their disease.

Very important observations have been made by a Dutch group, showing that the serum cortisol levels and adrenocortico topic hormone (ACTH) levels were significantly depressed in many adult patients with severe atopic dermatitis. It was also shown that “in-patients”, i.e. with severe eczema, had very high levels of TARC /CCL17 (thymus and activation-regulated chemokine), as a measure for severe inflammation. Patients with severe atopic dermatitis who were hospitalized and treated intensively with potent topical corticosteroids normalized their low levels of cortisol during the treatment period. These results indicate that the suppressed hypothalamic-pituitary-adrenal axis in patients with severe atopic dermatitis is induced by inflammation and not by the use of topical and systemic corticosteroids.

Data from the same group indicated that even the use of approximately 2 kg topical corticosteroid per year did not influence a significant loss in bone density as measured in the lumbar spine.

Genetics and atopic dermatitis

The “highlight” of the symposium was the now detailed description of the genes associated with atopic dermatitis. Filaggrin is a protein that is hydrophobic, is expressed in stratum corneum, and thus normally present in healthy skin. In Europe R501X and 2282del4 mutations are seen in patients with ichthyosis vulgaris and in 42% of patients with atopic dermatitis. Approximately ten European studies have all confirmed this observation, none are contradictory. The interesting thing is that in Japan and Singapore the mutations in the filaggrin protein are different from those seen in the European observations.

The only clinical feature linked to mutations in the filaggrin protein is hyperlinearity of the palms. Otherwise the clinical phenotype of atopic dermatitis is the same. Why mutations in the filaggrin protein are so heavily linked to atopic dermatitis is unknown.

Animal models

The Nc/Nga mouse model with the development of “itchy skin”, increased IgE and increase in TARC is still in use, but several different investigators cannot confirm that all mice develop an atopic dermatitis-like condition. This is due to the fact that the mice only develop eczema when kept under conventional conditions, and not when kept under “clean” conditions. In fact, several groups have used haptens as con-

tact sensitizers to initiate “inflammation” in the mice. Beagle dogs have also been analysed, but as of today there is no good animal model for atopic dermatitis.

Skin barrier pathology in atopic dermatitis

The barrier is diminished in atopic dermatitis, as measured both by increased transepidermal water loss and by reduced thickness of stratum corneum, especially following therapy with topical corticosteroids. How the lack of normal filaggrin contributes to this malfunction is not known, but the fact that filaggrin is hydrophobic, i.e. binds more water molecules, is probably part of the explanation. Emollients are the standard therapy of atopic dermatitis and several well-conducted studies have shown that emollient alone may keep up to one-third of the children free of “inflammation” (i.e. eczema) when used properly.

Immunology and atopic dermatitis

Cytokines, such as TARC/CCL17, CTACK/CCL27 and TSLP, are increased in atopic dermatitis. Regulatory T cells, defined as CD4+CD25+Foxp3+, are decreased. Interestingly, treatment with cyclosporine initially leads to an increase in regulatory T cells, which is followed by a decrease after 3 and 6 weeks of treatment. In an animal model Henino et al. demonstrated that presence of CD8+ epidermal T cells leads to inflammation in atopic dermatitis. This was confirmed by a Dutch group, also finding an increase in CD8+ cells. It is interesting to note that when patients with atopic dermatitis are “stressed”, the only observed immunological parameter is a temporary increase of CD8+ T cells in peripheral blood. Recently, our group have shown that variations in TREC (T cell receptor excision circles) occur especially within the CD8+ T-cell population (Just et al.).

Food allergy and atopic dermatitis

This area is – and has always been – a highly debated issue. One may postulate that there are “believers” and “non-believers”, especially as to how common “food allergy” is among children with atopic dermatitis. Several groups are convinced through skin prick tests and especially food patch tests that this is a very common phenomenon. However, many food items contain proteolytic enzymes and “irritants”, and testing children with sensitive skin thus leads to “positive reactions” that may not necessarily have anything to do with antigen specificity.

An important study from Finland included 201 children who, following patch testing, were put on strict diets for a 10-year period. Their severity of atopic dermatitis was significantly reduced, but not alleviated. It is then fair to ask why introduce

such strict measures into the life of small children, when they really want an ice-cream or chocolate, if their eczema is not prevented by such measures? Ethical issues are at play. There was no control group involved in the study.

Some presenters advocate patch testing in children – others (the Berlin group) have stopped. The area is confusing and needs further clarification at the next atopic dermatitis meeting.

Superinfections and atopic dermatitis

The presence of *Staphylococcus aureus* on skin and in the nose of patients with atopic dermatitis was confirmed. The potential role of “superantigen” was demonstrated, but otherwise nothing much new was evident.

A study showed that 53% of containers with cream or ointment used by patients with atopic dermatitis were contaminated with bacteria and 25% with *S. aureus*. Emollients should be kept in the refrigerator to avoid bacterial growth.

The role of “disinfecting” the skin with hypochlorite 0.005% bath twice weekly was demonstrated as a useful remedy.

Itching

Itching is one of the key symptoms of atopic dermatitis. Mediators involved are many, from histamine, bradykinine, substance P, calcineurin gene-related peptide, serotonin, and others. Itch and pain perception differ in their use of different nerve fibres. Yet, a significant understanding of “itch” is still lacking.



Fig. 2. From left to right: Professor Kazuya Yamamoto, Grethe Thestrup, Kristian Thestrup-Pedersen and Dr Toshiko Yamamoto during a Japanese tea ceremony at one of the many temples in Kyoto.

Psychosomatics and atopic dermatitis

Uwe Gieler gave an overview of this important aspect of atopic dermatitis. Stress is a significant part of atopic dermatitis, but the physiological consequences of “stress” seems only manifest in a temporary increase in CD8+ T cells in the blood. The use of anti-depressant drugs has not been investigated in well-conducted studies. This would of course only be relevant for adults with severe atopic dermatitis.

Therapy and atopic dermatitis

Three elements are important: the use of emollients, topical corticosteroids and calcineurin inhibitors. The new “biologicals” have been used in a total of 250 patients, but none are convincingly effective, especially given the costs of such therapy. Emollients are able to keep “eczema” under control in up to one-third of the patients (those with mild disease) and topical steroids are likewise effective. However, there is documentation for a major compliance issue as only one-third use their medication as prescribed. It is an essential issue for any doctor dealing with parents and patients suffering from atopic dermatitis.

Is there an “ideal” emollient? No. Each doctor has to discuss this issue with the parents. However, an American study using “Atopiclear” demonstrated a significant effect of avoidance of “flares” of atopic dermatitis. It is surprising that so few studies that have been performed on this important issue.



Fig. 3. Mette Deleuran and Christian Vestergaard at a traditional Japanese sushi restaurant in Tokyo.

Topical corticosteroids are effective. Intermittent therapy is able to control eczema for longer periods of time. However, the “side-effects” of steroids are the thinning of the stratum corneum and thus a weakening of the skin barrier, leading to greater sensitivity to irritants and allergens.

Carle Paul gave an overview of the topical calcineurin inhibitors (TCI). The FDA (Food and Drug Administration) black box warning in 2006 led to a very significant drop in the usage of TCIs, drugs that can be used for long-term control of atopic dermatitis. We all know that atopic dermatitis is a “chronic disease” and that we need to have remedies for it. Intermittent topical steroids are one option, the use of TCIs another.

Systemic immune suppression is known to be associated with an increased risk of non-melanoma skin cancers and lymphoma. The question is – as suggested by the FDA and EMEA (European Medicines Agency) – whether such risks are associated with the use of TCIs. Two studies document that this is not the case. There seem to be no “danger signals” based on observations from patients participating in the controlled studies or from the reported observations.

Two studies were performed on the use of topical therapy with anti-STAT6 and anti-NF-kappa B. Theoretically, this is an interesting approach, but as the molecules are around 20,000 kDa molecular weight – they can never penetrate the skin, and the documented results could as well be the effect of the emollient.

The Dutch studies on low to insignificant levels of ACTH among adults with severe atopic dermatitis may mean that a subgroup can benefit from systemic prednisone; something that has not been studied in a controlled way.

Information and atopic dermatitis

Several authors raised this important topic. Atopic dermatitis is not a disease for which you simply prescribe a cream. It is absolutely necessary to establish good communication between the parents (especially the mother) and the patient



Fig. 4. The serene rock garden of the Ryoanji Temple in Kyoto.

and his or her doctor. This takes time, and as “time is money”, this is too-often neglected.

Today there are several websites providing information to patients. However, personal contact with a “good doctor who cares” is still the optimal therapy for atopic dermatitis.

6th Georg Rajka International Symposium

The 6th Georg Rajka International Symposium will be held in early July, 2010, in Munich under the patronage of Johannes Ring. Dates will be confirmed and a website set up. For those of you who participated in Kyoto, we are sure you enjoyed the efforts of Masahiro Takigawa and Hideo Hashizume, who organized the event.

For those of you who were not there: come to Munich and participate. The most important thing is to “discuss” atopic dermatitis. We have thousands of pieces of knowledge about atopic dermatitis, but we are still lacking a clear understanding of this disease. At present our concept is that atopic dermatitis is a genetically determined “ectodermal” disorder, which disturbs the evolution of the T lymphocyte immune system – and in most patients (although this is debatable) subsides as they mature.