The 6th Georg Rajka Symposium, 22–24 July 2010, Munich, Germany

Kristian Thestrup-Pedersen[1], Mette Deleuran[2] and Christian Vestergaard[2]
[1]*The Skin Clinic, Nykobing F,* [2]*Department of Dermatology, Aarhus University, Denmark*

The authors of this meeting report attended a congress packed with news and information. Below you can find a summary of what were, in their opinion, some of the most interesting lectures delivered at this meeting.

The meeting was a joint meeting between New Trends in Allergy VII and the Georg Rajka Symposium, which was started in 1979 and thus celebrated its 31st anniversary. Georg Rajka himself was present, along with over 300 other active participants. Thus, "allergy" as a topic was to the fore during this intense 3-day meeting. Below is a summary of some of the topics covered.

Climate, environment and allergy

Several presenters discussed the influence of climate change on "allergy". *Heidi Behrendt* mentioned that although solar irradiation has decreased, the average global temperature has increased by 0.8 °C since 1860 and she considered this to have been caused by human activity (www.eurad.uni-koln.de). Climate change leads to differences in vegetation. *Ambrosia artemisiifolia*, a plant from North America, was not found in Bavaria before 2005. It can release billions of pollen grains, which can carry pollution. This change in vegetation may lead to changes in insect populations. An increase in temperature will increase the incidence of infectious diseases, many transmitted via animals to humans (www.ipcc.ch). The use of antihistamines has increased markedly in areas of Bavaria where the Ambrosia plant is present.

Reference was made to Bach JF, who in 2002 commented in New England Journal of Medicine on the rise of autoimmune and allergic disorders, together with a significant fall in infectious diseases, especially bacterial diseases. Carsten Flohr found, among 1,566 school children in Vietnam (age range 6 to 17 years), a 70% incidence of hookworm infestation and a 5% incidence of ascaris, and observed that "worms" lead to less atopy (IgE-mediated reactions) (Flohr C et al, Clin Exp Allergy, 2010).

Epidemiology and atopic eczema

Erica von Mutius repeated that there is an up to 20-fold variation in the prevalence of atopic eczema around the globe. Atopic sensitisation is associated with eczema in rich countries, but not in poor ones. The ISAAC study has created an enormous database and the following have been found to influence the incidence of atopic eczema: gross national budget, use of paracetamol by the mother (Beasley et al. Lancet, 2009), use of antibiotics (Foliaki et al, Journal of Allergy and Clinical Immunology, 2009), and number of trucks (diesel exhaust).

Genetics and atopic eczema

The discovery of mutations in filaggrin and their strong association with atopic eczema have been confirmed by many groups. These mutations are not a risk factor for the development of asthma, which is associated with an increase in total IgE. Carriers of filaggrin mutations have increased rates of hyperlinearity of the palms, keratosis pilaris and more scaly skin. Still, approximately half of patients with atopic eczema do not carry filaggrin mutations – at least not mutations that have so far been identified.

M. Moffat presented data from a very large study on the "atopy" gene. Initial studies on 938 patients only showed linkage to 17q12-q21, but a phase 2 study involving 10,365 cases and 16,110 controls led to the discovery of associations with the following loci: 2q12, 6p21 (which is associated with IgE production and is the area where the HLA-DR genes are located), 9p21, 15q and 17q12-q21 – the locus with the strongest linkage. Although Stephen Holgate has claimed that the ADM33 gene is strongly associated with asthma, such an association was not observed in the very large study of Dr. Moffat and colleagues, underlining the limitations of genetic studies. Thus, filaggrin mutations currently provide the strongest known associations with atopic eczema.

In the Flaky tail mouse, which has a single-base mutation in the filaggrin gene (Fallon & Sasaki, Nat Genetics, 2009), dry skin develops, especially on the tail. This model was used by Dr. Kabashima and colleagues to induce "eczema" through repeated application of a contact sensitising allergen. In this model, he observed increased IL-10 and IL-17 levels and increased numbers of Treg cells that reduce inflammation, as shown when anti-hCD52 antibody is injected. The model is, in our opinion, a contact eczema model, not quite equivalent to atopic eczema. The symposium also ran

a session on animal models of atopic eczema, but we did not attend it.

Skin barrier and atopic eczema

The observation that there is reduced or no filaggrin in the epidermis of atopic eczema patients has placed a strong focus on barrier function and its importance. A simple hypothesis is that atopic eczema is fundamentally an ectodermal (epidermal) disturbance leading to a skewing of many immune reactions and ultimately "eczema".

Alain Hovnanian from Paris gave an excellent talk on the enzymatic "loops" in the epidermis in Netherton's syndrome, in which he described the SPINK5 gene mutation that leads to a loss of LEKTI inhibition. He showed that there were high levels of the cytokine TSLP in keratinocytes in Netherton's syndrome. Readers interested in this topic should take a look at Briot et al, Journal of Experimental Medicine, 2009. Separately, Torbjörn Egelrud and his colleagues have contributed to our understanding of the complex interplay of signalling pathways in the establishment of a normal skin barrier.

Jens Schröder lectured on the "3 chemical barriers" of the epidermis and its innate immunity. Some of the peptides produced are released, while others are not, instead adhering to the epidermal cells (e.g. RNAse-7). Psoriasin, which got its name for its high expression in psoriasis, is also present in atopic eczema-affected skin (Gläser et al, J Invest Dermatol, 2009). Dr. Schröder mentioned that filaggrin mutations do not influence antimicrobial peptide levels – a statement which seems to go against Ong et al's observations of decreased beta-defensin and cathalicin levels in atopic eczema (NEJM, 2002). Th2 cytokines do, however, inhibit the expression of anti-microbial peptides, which would seem to support Ong et al's finding.

Disruption of the skin barrier was shown to involve upregulation of TSLP in keratinocytes (Angelova-Fischer I, et al).

Cytokines and atopic eczema

This area is so complex that one may ask: "which came first – the chicken or the egg?" Many cytokines are upregulated, notably members of the Th2 cytokine family, which can alter the function of dendritic cells, as well as skin barrier function, as shown by *Mette Deleuran* and colleagues. They observed that IL-25 is present in dermal dendritic cells and that it can reduce filaggrin mRNA expression. In addition, Th2 cytokines can down-regulate caspase 14, which is important in the induction of filaggrin expression (Vestergaard Christian, et al.).

Which cytokine is the best marker for clinical activity in atopic eczema? A total of 23 markers have been examined and TARC is the cytokine that best reflects disease activity in atopic eczema. There were many presentations on cytokines as they are present and likely influence atopic inflammation, although they could be secondary to primary unknown effects.

Allergies and atopic eczema

The division of atopic eczema cases into extrinsic (associated with IgE-mediated allergy) and intrinsic (no allergy) was discussed. The percentage of intrinsic versus extrinsic varies from 40 to 70% approximately, although it should be stressed that patients may "move" from the intrinsic group to the extrinsic one. *Hanne Joenhke* and colleagues from Odense, Denmark, reported that among more than 500 neonates subjected to repeated testing for IgE, around 80% had at one time given a "positive test" result (prick test, RAST, histamine-release test), but only just over 40 children developed atopic eczema during the first 18 months of life (the time period in which the study took place). Thus, is sensitization a trigger for atopic eczema? There is some evidence to suggest that, in some children with eczema, their type I allergies are a consequence of skin inflammation.

Jon Hanifin reviewed the food allergy question. He considered that up to 30 to 50% of adults with severe atopic eczema have food allergies relevant to their eczema activity. In the SAM study of 1½- to 3-year-old children RAST-tested for milk, egg, peanut, soy, wheat and seafood allergy, 9 of 40 participants who completed the study gave a positive RAST, in most cases to egg, peanut and milk but not the remaining allergens.

Nerves and souls in atopic eczema

The lectures on this topic concentrated on itch. A study has shown that 91% of adults with atopic eczema itch daily, but that the rest go for more than a month without itching – quite a puzzling observation. Brain-derived neuronal factor is increased in atopic eczema. *Uwe Gieler* presented data showing that approximately 17% of adults with atopic eczema have depressive moods, which have been notably linked to increased clinical disease activity. Around 5% of adult patients have considered suicide – indicating the severe impact the disease can have on them.

BCG vaccination and atopic eczema

H. Mizutani from Japan demonstrated that vaccination of mice with a major antigen from tuberculosis-causing bacteria, Ag85B, reduced oxazolone-induced contact eczema. They had

performed excellent studies, including the transfer of Ag85B using a paramyxovirus vector, as well as simple nasal application, and demonstrated reductions in ear swelling and IgE responses. However, he concluded that, although it is effective in mice, BCG vaccination does not seem to work in humans with atopic eczema.

Bone mineral density (BMD) and atopic eczema

Inge Haeck and colleagues in Utrecht have performed some highly relevant studies on BMD in atopic eczema patients. Children with atopic eczema do not have reduced BMD unless they have been administered cyclosporine, used to treat very severe cases. Among 125 adults with atopic eczema, 30 had low BMD (Haeck et al, Br J Dermatol, 2009). The use of topical steroids is not associated with changes in BMD. It is uncertain if adult atopic eczema patients should be advised to take calcium and vitamin D supplements if a significant reduction in BMD has not been observed.

Therapy and atopic eczema

Hywel C Williams from Nottingham draw attention to databases that are a "one-stop shop" for access to data from randomized controlled trials involving atopic eczema. Approximately 250 well-conducted trials are listed. The websites are www.library.nhs.uk/skin/ and www.greatdatabase.org.uk and represent a significant contribution from the Nottingham group.

Thomas Werfel from Hanover and colleagues had conducted a study on desensitisation involving weekly house dust mite allergen injections for 12 weeks in a cohort of adults with atopic eczema and type I allergy to this allergen. There was a 10–18% improvement in SCORAD, but the study was hampered by a drop-out rate of almost 50%.

Dagmar Simon from Bern gave an excellent overview of "biologicals and atopic eczema". Many have been tested, but mostly in small open studies. Although some studies showed improvements, overall there is today no convincing evidence that biologicals produce positive effects in atopic eczema, in sharp contrast to what we know about psoriasis.

Finally, as *Staphylococcus* spp. bacteria are known to be present on the skin of patients with active eczema, Dr. Craig et al. from Nottingham recommend a 0.005% sodium hypochlorite bath (Arch Derm, 2010) for treating infected skin.

Conclusion

There were many more presentations, including posters. One of these posters, presented by *Naouki Higashi*, showed that one-third of adults with atopic eczema have increased levels of ANA antibodies, but also that anti-DFS (dense fine speckled) 70 antibody levels are increased in approximately one fifth of patients, indicating that autoimmune responses are also involved. Whether they are secondary to the immune disturbances in these patients is, at present, unknown.

The only way to get all the information is to participate in the 7th ISAD meeting, planned for January 2012 at the Regional Dermatology Training Centre (RDTC), Moshe, Tanzania. Organizational work is starting and you should see this event not only as a chance to visit the RDTC, but also to visit to Africa, and specifically Tanzania. The hospital itself offers views of Mt. Kilimanjaro and there will be possibilities for Safari treks. Mark the date in your calendar now!

The authors did not receive financial support for participation in the meeting and have no conflicts of interest.