International Symposium on Atopic Dermatitis

Rome, Italy

August 29–31, 2003

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Heat Killed Mycobacterium Vaccination Suppressed Severe Dermatitis in AD-Model Mouse Converting Th2 into Th1 Cytokine Profile

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Atopic dermatitis (AD) is a chronic inflammatory disease based on T-helper cell (Th2) immune responses. The recent increase of the prevalence of AD has been suggested caused by a cleaner environment and fewer childhood mycobacterium infections. While topical and systemic immunosuppressive medicine improved AD clinically, the reconstitution of the balance between Th2 and Th1 is an ideal therapy for AD. Here we report significant effect of a heat killed BCG vaccine in an AD model mouse Caspase-1Tg (CASP1Tg). CASP1Tg express severe itching dermatitis with elevated plasma histamine, IgE, IL-18, cutaneous mastocytes counts and lesional IL-4, IL-5 and IL-10 mRNA expression. After weekly vaccination with 100 micrograms of heat killed BCG for 10 weeks, the cutaneous manifestations were significantly suppressed. According to improvement of the cutaneous manifestation, levels of plasma histamine, IgE, and IL-18 were suppressed. The lesional IL-4, IL-5 and IL-10 expression were downregulated, but IFN-g mRNA was augmented. No relapse of the cutaneous nor laboratory manifestations of AD was observed over 6 months following-up after discontinuance of this therapy. No particular side effects was observed in this study. Thus, the heat-killed BCG vaccination is a potential therapy for AD, performing an essential role in AD therapy with restoring the balance of Th1/Th2 cells.

IL-18 Transgenic Mice Spontaneously Develop Atopic Dermatitis-Like Skin Lesions

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We have reported skin-specific caspase-1 transgenic mice (CASP1Tg) as a model for atopic dermatitis previously. CASP1, expressed in the epidermis has three functions. It activates the endogenous proIL-1 beta and proIL-18 and secretes as the active forms, and induced apoptosis to the epidermal keratinocytes. To confirm function of IL-18 in vivo, we have established K14 promoter driven mature IL-18 transgenic mice (IL-18Tg). IL-18Tg secreted biologically active IL-18 from the epidermis in a specific pathogen free condition. At 24 weeks-old, IL-18Tg spontaneously developed itching and recalcitrant dermatitis combined with overproduced IgE and Th2 cytokines. The erythematous lesions were with lichenification and fine scales. Histologically, the epidermis showed acanthosis with marked dermal mastocytosis. IL-18Tg takes long time to express the phenotype compared with that of CASP1Tg (8 weeks). To know the difference, we crossed CASP1Tg and IL-1 alpha/beta knockout mouse. IL-1s-/-CASP1Tg developed dermatitis at 24 weeks. IL-18 may be critically involved in an AD-like dermatitis and IL-1s enhance development of the dermatitis.

Cutaneous Route Sensitization with Natural Rubber Latex Elicits in Mice a Strong Th2 Type Systemic Immune Response and Th2 Dominated Lung Inflammation After Airway Latex Challenge

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Atopy and hand dermatitis are important risk factors for the development of natural rubber latex (NRL) allergy. We recently reported that cutaneous route sensitization with NRL induces Th2-dominated dermal inflammation in a murine model. Here we investigated the significance of different sensitization routes in the production of IgE antibodies and in the development of airway hyperresponsiveness in mice. Intracutaneous (IC) and intraperitoneal (IP) but not intranasal (IN) route sensitization with NRL induced a striking increase in the total and specific IgE levels. Both IC and IP sensitization with NRL produced also a significant influx of eosinophils and lymphocytes to the lungs after airway NRL challenge. Infiltration of inflammatory cells was associated with induction of Th2 type cytokine (IL-4, IL-5 and IL-13) and chemokine (CCL3/MIP1-alpha and CCL11/eotaxin-1) mRNA levels in the lungs. Only marginal induction of these cytokines and chemokines was found after IN sensitization with NRL, whereas moderate or strong induction was seen after IP or IC sensitization, respectively. Finally, significant increase in the bronchial reactivity to inhaled methacholine was found after IC and IP sensitization with NRL but not after IN sensitization. These results demonstrate that cutaneous route sensitization induces the production of IgE antibodies and elicits also Th2-dominated airway inflammation and airway hyper-responsiveness after NRL challenge in mice. Cutaneous route sensitization to proteins eluting from NRL gloves may therefore play an important role in the production of NRL-specific IgE antibodies but also in the development of airway hyperresponsiveness to latex.

Up Regulation of Human Manganese Superoxide Dismutase – a Stress-Inducible Enzyme – Can Elicit Autoimmune IgE- and T Cell-Mediated Eczematous Reactions in Atopic Dermatitis

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Although the pathogenesis of atopic dermatitis is still not fully understood, autoreactivity of AD patients to human proteins suggests self antigens as decisive factor driving disease exacerbation. Human manganese superoxide dismutase (hMnSOD) — a stress-inducible enzyme — is known to elicit autoimmune reactions in chronic allergic diseases. Using structurally different, recombinantly produced MnSOD of fungal and human origin, various *in vitro* and *in vivo* investigations in patients with atopic dermatitis, other inflammatory skin diseases and healthy controls were performed. In the current study we found hMnSOD-specific immunoglobulin E (IgE) antibodies determined by ELISA in sera from 29 out of 67 AD patients (36%), but not in sera of other patients or healthy controls - correlating significantly with disease activity ($R = 0.783$, $p < 0.0001$). In sensitised patients, rhMnSOD induced T cell proliferation and showed *in vivo* reactivity, demonstrated by positive skin prick- and atopy patch tests. Expression of MnSOD in lesional skin of AD was stage-dependant and upregulated in atopy patch tests in comparison to the levels detected in non-AD skin diseases or healthy skin, as shown by immunohistochemistry. Primary sensitization to hMnSOD might be induced by cross-reacting fungal MnSOD as all patients showed positive skin reactions to fungal extracts. Moreover, rhMnSOD was able to compete for IgE binding to fungal extracts in RAST inhibition experiments. These data provide strong evidence for an important role of hMnSOD autoreactivity as a disease-exacerbating, stress-dependantly upregulated factor in a relevant subset of AD patients.

Atopic Dermatitis and T Cells

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T lymphocytes are the predominant cell of the cutaneous inflammation creating atopic eczema. They are activated expressing various activation markers. We have demonstrated that an adult with 30% of the skin affected with eczema have double the number of T lymphocytes in the skin than in the peripheral blood. We have also observed a significant reduction of the telomere length of both CD4+ and CD8+ T cells, both in blood and among skin-homing T lymphocytes. Recent studies have revealed that the T cell receptor excision circles (TREC) can be both augmented, but also reduced, in atopic dermatitis. All results point to an increased turn-over in the peripheral T lymphocyte immune system. We have therefore suggested that atopic dermatitis is associated with or maybe caused by a skewed establishment of the peripheral T lymphocyte system – possibly due to an emission of faulty selected T lymphocytes in the thymus. Once the children down-regulate the emission of the faulty selected T lymphocytes, the disease stops.

Dichotomic Nature of Atopic Dermatitis Reflected by Combined Age-Related Analysis of Peripheral T/CLA+ Lymphocytes and Serum IgE Levels

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Background: The different pathogenetic mechanisms leading to the "intrinsic"(low IgE) or to the "extrinsic" (high IgE) form of atopic dermatitis (AD) still have not been elucidated in the absence of clear-cut data. Some authors have hypothesized that circulating or infiltrating T-CLA+ lymphocytes, with a peculiar functional phenotype, may play a role in the pathogenesis of the two forms of disease. Aim of the present work was to evaluate differences in the peripheral T CLA+ levels in atopic patients with normal or elevated serum IgE.

Methods: 99 patients with AD were included in the study. The peripheral T-CLA+ numbers were determined by flow cytometry and analyzed in relation to age or index of disease acitivity (SCORAD) in the 2 groups of patients with normal or elevated IgE levels.

Results: T-CLA+ cell numbers were significantly correlated with age ($P = 0.04$) in patients with elevated IgE and not in those with normal IgE values ($P = 0.53$). Normal IgE levels were associated to younger patients: 80.9%, 52% and 45.4% of patients with normal levels, in the three different age group (<3, 3-15, >15 yrs) respectively.

Conclusion: Our age-related analysis supports the hypothesis that the two different forms of AD, are charatcterized by different IgE levels but also by different age and different pattern of CLA expression in T cells.

T-Cell Receptor Excision Circles (TREC) and Peripheral Turnover of T-Lymphocytes in Patients with Atopic Dermatitis.

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In order to investigate peripheral T-lymphocyte turnover in patients with Atopic Dermatitis (AD), T-cell excision circles (TREC) was measured in different T-cell subpopulations. TREC is an episomal DNA circle produced during T-cell receptor rearrangement and is used as a marker for recent thymic emigrants (RTE). TREC content in CD4+ and CD8+ T-cells was measured in 43 patients and in 41 healthy controls. In five of the patients and one healthy control, TREC content was measured over time. TREC content in CCR10+ T-cells, which are T-cells bound for the skin, was measured in blood from four different AD patients in order to investigate if CCR10+ T-cells differ from CCR10- T-cells.

The results showed significantly lower TREC content in both CD4+ and CD8+ T-cells from male patients with AD compared to TREC content in T-cells from age matched healthy male donors. No difference was seen in TREC content in CD4+ or CD8+ T-cells from female patients and female donors. CCR10+ T-cells had a three to twenty times lower TREC content than CCR10- T-cells. TREC content measured over time indicated that AD patients have a large individual variance in the number of peripheral RTE.These results suggest a massive turnover of peripheral T-lymphocytes in patients with AD compared to healthy donors. The lower TREC content in the skin homing CCR10+ T-cells suggest that these cells are part of an active dividing population. Further studies of TREC content over time and in different subpopulations are ongoing.

Increased CD123$^+$ Dendritic Cells and IL-10 Expression in Lesional Skin of Atopic Dermatitis

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The factors controlling infiltration of inflammatory cells into atopic dermatitis (AD) lesions remain to be fully explored. Recent studies have shown that there are two dendritic cell subpopulations, DC1 and DC2, which induce T_H1 and T_H2 cell differentiation in vitro, respectively. To gain better insight into the presence and distribution patterns of cytokine milieu as well as dendritic cell subpopulations in lesional skin of AD. Our goal was to assess the association of IL-10 and IL-12p70 expressions with DC2 and DC1 subsets respectively and association of IL-10 and IL-12p70 expressions with the inflammation in patients with AD. To determine the percentage of labeled area with different cytokines and dendritic cell subpopulations, immunohistochemical staining and digital imaging technique were used. As compared with non-lesional skin of AD, there was a significant increased expression of CD123$^+$ DCs ($p = 0.012$) and IL-10 ($p = 0.011$) in severely inflamed lesional skin ($n = 10$), whereas CD11c and IL-12p70 were not consistently decreased. Furthermore, CD123$^+$ DCs co-expressing intracytoplasmic IL-10 were also present in the dermis of inflamed skin. Our data presented the predominance of CD123$^+$ DCs and IL-10 in the lesional skin of AD and suggest the association of IL-10 expression with DC2 cells, known to be T_H2-inducing DC subpopulaton. These cytokines milieu and the abundant distribution of DC2 subpopulation may ultimately favor type 2 T lymphocyte-dominated immunity.

IgE- vs Non-IgE-Related Atopic Dermatitis

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Atopic dermatitis (AD) is a multifactorial disease, caused among others by genetic conditions, alterated skin structure, immunologic deviations and environmental factors. A subgroup of AD patients, both children and adults, suffer from a skin disease which clinically resembles the skin lesions and distribution pattern of AD, but is not associated with sensitisation to aero- or food allergens and shows normal total serum IgE levels and shows the absence of other atopic diseases such as allergic asthma and rhinoconjunctivitis. In analogy to the extrinsic and intrinsic types of asthma, the author in 1983 had proposed the term intrinsic type of AD (IAD) as a counterpart to the extrinsic type of AD (EAD). IAD is found in a relevant proportion of all AD patients; its frequency ranges from 10 to 40%. Immunologic differences between the two subtypes in cell and cytokine pattern can be located to peripheral blood but mainly to the affected skin — such as reduced capacity to produce IL-13 by skin T cells. Genetically and environmental caused differences might be responsible for the variation of IgE production. Positive atopy patch tests observed also in IAD patients point to the importance of T-cell-mediated reactions. The new EAACI nomenclature propose now the terms of IgE-associated and non-IgE-associated Atopic Eczema/Dermatitis Syndrome. The discrimination between the two suptypes of AD is not just academic. The classification into an EAD (IgE-associated) and IAD (non-IgE-associated) at each age phase (infancy, childhood, teen age, and adult phase is essential for the allergological management of the patients (allergen avoidance, secondary allergy prevention). For the long-term prognosis it's therefore important to know that the risk of the development of an atopic respiratory disease is much lower in IAD.

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Intrinsic vs. Extrinsic Atopic Dermatitis: A Study on Diagnostic Definition and Prevalence

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Our aim was to study the criteria employed to classify AD patients into the "intrinsic" or "extrinsic" AD group and to evaluate the frequency of these 2 forms among our patient population. 282 patients with AD, 117 male and 165 female, underwent skin prick tests with 2 panels of aeroallergens and food allergens, panel 1 comprising 11 substances and panel 2 including 66 allergens. We observed 171 positive responses to panel 1, whereas the number of subjects reacting to panel 2 increased to 189. Thus a different percentage of our AD patients (61% and 67% respectively) could be considered affected by an extrinsic form of AD, depending on the number of tested allergens. Moreover, atopy patch tests with 20 aeroallergens and food allergens were performed in all patients. Among the subjects with negative prick tests (93 "intrinsic" cases), 68 reacted to atopy patch tests indicating a delayed "extrinsic" influence of allergens on the dermatitis. Therefore, only 25 patients (9%) of our study population could be classified as affected by the intrinsic form on the basis of skin test results. Finally, in 18 subjects among the latter we performed repeated oral food challenges with peanut, cow's milk and egg, and observed a positive response to egg in one patient. Thus one more patient was removed from the intrinsic group and shifted to the extrinsic one. In conclusion, our findings demonstrate that the prevalence of the intrinsic form of AD may be overestimated because of lack of adequate diagnostic work-up.

The Pivotal Role of Eosinophils in Atopic Dermatitis: Neuroimmunological Interactions

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Studies over the past two decades have shown that eosinophils play a major role in atopic dermatitis (AD), characterized by activated eosinophils in the peripheral blood and in the lesional skin. Several lines of investigation indicate that eosinophils are recruited to and activated at tissue sites by Th2 cytokines, such as IL-5 and IL-13. In addition, chemokines (Eotaxin, RANTES) also contribute to eosinophil chemotaxis and activation. Moreover, interaction of eosinophil surface molecules and endothelial cell VCAM-1 and ICAM-1 are important for eosinophil extravasation and activation. Previously, we could demonstrate an inhibition of eosinophil apoptosis in AD, probably mediated by an autocrine release of IL-5, and GM-CSF. Once activated, the eosinophil is capable of releasing an armory of potent cytotoxic granule proteins and chemical mediators contributing to tissue inflammation as shown by the deposition of eosinophils products in the inflamed skin. Moreover, eosinophils may have a key role in neuroimmunological interactions. Increased numbers of peripheral nerve endings are in an active state of excitation in AD lesions, contributing to the intense itch torturing the patients. Indeed, vasoactive intestinal polypeptide (VIP), calcitonin gene-related peptide (CGRP) and substance P positive nerve fibres are prominently increased in lesional skin, mediating eosinophil activation and chemotaxis. Moreover, hypertrophy of nerve fibers represents a characteristic feature of AD skin lesions, due to an increased release of neurotrophins, such as nerve growth factor (NGF). Neurotrophins as well as neuropeptides take their part in the crosstalk between the immune and peripheral nervous system, modifying the functional activity of sensory neurons and immune cells, propagating a neurogenic inflammation. Moreover, NGF itself is known for the inhibition of eosinophil apoptosis and the increase of eosinophil cytotoxic activity. On the other hand eosinophils are capable of NGF production, closing the regulatory loop of nerve activation. Taken together, the neuroimmunological interactions between nerves and eosinophils clearly support the concept of a "neurodermatitis" in the field of AD.

Expression of Chemokine Receptors on Human Epidermal Langerhans Cells and Inflammatory Dendritic Cells in Atopic Dermatitis Lesions

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Background: Inflammatory dendritic epidermal cells (IDEC) are a newly described DC subset accumulating in the epidermal compartment of atopic dermatitis (AD) lesions. Whereas chemokine receptor (CKR) expression of LC has been studied in normal human skin (NS), little is known about LC and IDEC in AD lesions. Therefore, we investigated the expression of CKR on various DC types relevant to AD lesions with a panel of monoclonal antibodies by different techniques.
Methods: Epidermal single cell suspensions were prepared from skin lesions by trypsinization. Freshly isolated and short term cultured cell suspensions were analyzed by quantitative flow cytometry. Other inflammatory skin diseases, NS, freshly isolated monocytes and monocyte-derived DC (MoDC) served as control. In addition, cryosections were immunostained in APAAP technique for all CKR.
Results: In situ expression of CCR-6 was strongest on LC, whereas CCR2, CCR5, CCR6, CCR7 and CXCR1 were detected on IDEC. The in situ expression of CCR7 in inflammatory skin, previously attributed to LC, was restricted to IDEC. Upon maturation, LC and IDEC upregulated CXCR4, whereas CCR5 and CCR6 were downregulated. CCR7 increased in LC and decreased in IDEC upon culture. CKR expression was similar for psoriasis and AD with one exception: CXCR-3 was significantly upregulated on IDEC in AD lesions. IDEC, MoDC and monocytes expressed CCR-5, which is functionally important for cell migration from peripheral blood into the skin. MoDC downregulated their CCR5-expression upon terminal differentiation, as induced by culture in LPS or TNF-α.
Conclusion: IDEC showed a CKR profile highly similar to monocytes, thus suggesting an ontogenic link between both cell types. The expression of CCR5 supports our hypothesis of a *de novo*-immigration of IDEC in AD lesions. The different ultrastructure of LC and IDEC is mirrored by a distinctive immunophenotype of the CKR repertoire and may be relevant for the accumulation of IDEC in AD lesions.

FcεRi^{high} Langerhans Cells and Inflammatory Dendritic Epidermal Cells Ascertain a Different Outcome of T Cell Responses in Atopic Dermatitis

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Atopic dermatitis (AD) is a biphasic inflammatory skin disease characterized by an initial phase predominated by Th-2 cytokines which switches into a second and more chronic Th-1 dominated eczematous phase. Two different FcεRI^{high} dendritic cell (DC) types, Langerhans cells (LC) and inflammatory dendritic epidermal cells (IDEC) have been identified in the epidermis of patients with AD. These DC are believed to efficiently monitor foreign antigens at potential sites of pathogen entry. So far, the small amount of *ex vivo* isolated LC and IDEC available has hampered their detailed functional analysis and consequently our knowledge about these DC. We have developed a novel *in vitro* model which allows for the first time to study the respective FcεRI-mediated mechanisms of LC and IDEC in AD. We examined whether these DC subtypes definitely contribute to the outcome of T cell responses and consequently to the biphasic manner of this disease. We found that as an initial step, FcεRI-activated Langerhans cells (LC) release chemotactic signals such as monocyte-chemoattractant protein-1 (MCP-1) and thereby recruit peripheral blood monocytes which are the precursors of IDEC. More importantly, we have shown that LC induce a Th-2 type T cell response that is characteristic for the acute phase of AD. In a second step, FcεRI-activated IDEC convert the initial Th-2 into a Th-1 response and display a higher stimulatory capacity, implying that they amplify the inflammatory immune reaction in this way. The present study provides clear evidence that LC and IDEC contribute distinctly to the outcome of T cell responses and the biphasic nature of AD. These findings are of outstanding relevance in understanding the complex pathophysiological network of AD.

Stratum Corneum Lipids in Atopic Dry Skin

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The dry skin of individuals with atopic dermatitis displays impaired barrier function as indicated by increased transepidermal water loss and diminished water holding properties. Both of these biophysical anomalies can be related to altered composition of the lipids of the stratum corneum. Normal human stratum corneum contains a series of nine structural types of ceramides, cholesterol and saturated fatty acids as the major lipid classes. In addition, there are two major covalently bound ceramides. A number of previous investigations have documented altered lipid composition in the stratum corneum of individuals with atopic dermatitis. There is general agreement that the total ceramide content of the atopic stratum corneum is decreased, the ratio of cholesterol to ceramides is increased and the relative proportion of one specific acylceramide, CER EOS in the nomenclature system of Motta *et al.* (Biochim Biophys Acta 1182:147–151, 1993). CER EOS normally consists of 30- through 34-carbon ω-hydroxyacids amide-linked to sphingosine bases and bears ester-linked linoleate on the ω-hydroxyl group. This molecule appears to be essential for the organization of the stratum corneum lipids and for barrier function. In addition to CER EOS, two additional acylceramide types have been identified since the most recently published analysis of atopic stratum corneum lipids - CER EOH and CER EOP (J Invest Dermatol 120:581-588, 2003). Our recent and more comprehensive comparison of ceramides from normal and atopic stratum corneum has revealed that the proportion of CER EOP, like CER EOS, is decreased; however, the proportion of CER EOH increased. Several other differences were noted. In addition to the major structural lipids, normal stratum corneum contains significant levels of free sphingoid bases. These molecules have broad antimicrobial activity, and their production may be part of the innate immune system. The bases are thought to be liberated through the action of ceramidases on ceramides. In atopic dermatitis, where the content of ceramide substrate is lower than normal, sphingoid base content is also lower. This may be related to colonization of the atopic skin by bacteria, particularly *Staphylococcus aureus*. Evidence will be presented that when production of sphingoid bases from free ceramides is reduced, a ceramidase partially compensates by hydrolyzing the amide linkage of the covalently bound ceramides.

Keratinocytes Contribute to Inflammatory Circuits in Atopic Dermatitis

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Atopic dermatitis (AD) develops from a complex interplay of environmental, genetic, immunologic and biochemical factors. Relevant to the amplification and persistence of inflammatory and immune responses in AD skin is the contribution of keratinocytes, which can be induced to secrete pro-inflammatory mediators in response to a variety of factors, including the epidermal barrier perturbation characterizing this disease and the potent cytokines released by infiltrating leukocytes. Noteworthy, keratinocytes from AD patients synthesize exaggerated amounts of chemokines and cytokines (e.g. GM-CSF, RANTES, TNF-α), important for enhanced recruitment as well as sustained survival and activation of DCs and T cells. A dysregulated cytokine production by epithelial cells can be primarily involved in the pathophysiology of atopic diseases. The biochemical mechanisms underlying excessive production of certain pro-inflammatory mediators by epithelial cells are probably multiple. Experimental evidence indicates that AD keratinocytes have a constitutive dysregulated activity of specific constituents of AP-1 complex, known to be critically implicated in the control of the expression of numerous inflammatory genes, suggesting the existence of molecular, genetically predetermined mechanisms targeting atopic inflammation to the skin. Studies using gene microchip array technology are currently underway to assess whether AD keratinocytes have an aberrant expression of inflammatory genes. Inasmuch as epithelial cells are an easily accessible target for therapeutic intervention, studies on the mechanisms that regulate expression of inflammatory genes in epithelial cells may ultimately afford new strategies for the control of AD.

TARC Augments TNF-α Induced CTACK Production in Keratinocytes Through the CCR4 Receptor

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TARC (thymus and activation regulated chemokine) and CTACK (cutaneous T cell attracting chemokine) are both pivotal mediators of the inflammatory reaction in atopic dermatitis. TARC attracts CCR4 positive T-cells known to be mainly of Th_2 subtype whereas CTACK attracts skin homing T-cells of both Th_1 and Th_2 subtype that express CCR10. We found that CTACK can be induced in cultured human keratinocytes by TNF-α, but not by TARC alone. However, if the keratinocytes were pre-incubated with TNF-α, TARC was able to augment the CTACK inducing effect of TNF-α. We also found that TNF-α induces CCR4 expression in keratinocytes. CTACK, nevertheless, was not able to induce TARC production in the keratinocytes. We also investigated plasma concentrations of TARC and CTACK in plasma from 48 patients suffering from AD. This revealed that TARC and CTACK concentrations in plasma correlate with each other, however they did not correlate with the SCORAD scores of the patients. Surprisingly p-CTACK correlated inversely with EASI scores of the patients. This could be due to the treatment the patients received, as we also found that dexamethasone inhibits the production of CTACK and TARC in keratinocytes. Our results suggest that the primary Th_2 dominated inflammatory reaction in atopic dermatitis induced by TARC leads to an augmented skin specific inflammatory reaction through CTACK.

Role of Staphylococcal Superantigen in Atopic Dermatitis: Influence on Keratinocytes

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S. aureus may play an important role in atopic dermatitis (AD) by secreting superantigens, such as staphylococcal enterotoxins (SE) A or B and toxic shock syndrome toxin-1 (TSST-1). Dysregulated cytokine production by keratinocytes (KCs) when exposed to staphylococcal superantigens (SuperAgs) can be primarily involved in the pathophysiology of AD. We hypothesized that lesional KCs from AD may react differently to SuperAgs compared to nonlesional skin or normal skin from nonatopics by producing more proinflammatory cytokines such as IL-1α, IL-1β, and TNF-α. We compared HLA-DR expressions in lesional skin versus nonlesional or normal skin by immunohistochemistry (IHC). We performed MTT test with cultured KCs from lesional, nonlesional, and normal skin after adding SEA, SEB and TSST-1. We also compared levels of IL-1α, IL-1β, and TNF-α secreted by cultured KCs by ELISA. IHC showed that expressions of HLA-DR increased significantly in the epidermis of lesional skin versus nonlesional or normal skin. Each concentration of SEA, SEB and TSST-1 showed neither proliferative nor toxic effect on cultured KCs by MTT. The secretions of IL-1α, IL-1β and TNF-α increased significantly in cultured KCs from lesional skin versus nonlesional or normal skin after adding SEA, SEB and TSST-1. Our result suggested that KCs from lesional skin react differently to SuperAgs maybe due to increased expression of HLA-DR and the increased productions of proinflammatory cytokines in response to SuperAgs play a pathogenetic role in AD.

FK506 Up-Regulates Transforming Growth Factor-ß and Down-Regulates Constitutive and Inducible Nitric Oxide Synthase on Cultured Human Keratinocytes: New Insights on How Tacrolimus Ointment Interacts with Atopic Skin

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Tacrolimus ointment (FK506) has been used in recent years for treatment of atopic dermatitis (AD) with favorable results. The direct effects of FK506 on keratinocytes (KC) are investigated in terms of transforming growth factor-beta (TGF-β) and nitric oxide synthase (NOS), both constitutive (NOS-1) and inducible forms (NOS-2), as low TGF-β and high NOS expressions are implicated to participate in the pathogenesis of AD. Our results showed that on FK506 treated KCs, the TGF-β releases are up-regulated, particularly in the presence with tumor necrosis factor-alpha (TNF-α), while the expressions of NOS-1 and NOS-2 are down-regulated. Moreover, the gene expressions of NOS-2 are down-regulated in a dose-dependent manner. These findings suggest that FK506 has direct effects on KC that probably contribute to its therapeutic efficacy on treatment of AD.

The Role of Infection in Atopic Dermatitis

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This presentation will examine the role of infection in the pathogenesis of atopic dermatitis acting not only as an exacerbating factor but also having skin disease-sustaining effects resulting from its pro-inflammatory properties. Much of the research has focused on *Staphylococcus aureus,* which appears to mediate its proinflammatory effects at least in part due to the production of potent exotoxins, e.g. superantigens. An understanding of the mechanisms underlying enhanced *S. aureus* colonization and infection in atopic dermatitis and identification of the molecules involved in triggering atopic skin inflammation has important implications in our current approach to the management of atopic dermatitis and the development of new therapies for patients with this common skin condition. Recent studies suggest that the skin of patients with atopic dermatitis have increased binding avidity to *S. aureus* and is deficient in its ability to generate antimicrobial peptides needed to eradicate bacterial and viral infectious agents. The mechanisms for these altered properties in atopic skin appear to be due to a combination of the overexpression of Th2 cytokines and reduced production of certain proinflammatory cytokines and chemokines. These observations are likely to account for their propensity to both bacterial and viral skin infections.

Natural History of Atopic Dermatitis – a Major Research Gap

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All clinicians know that the commonest questions asked by parents during a consultation of a child with atopic dermatitis (AD) are "will he/she grow out of it?" or "will he/she go on to develop asthma?". Yet, the evidence-base for answering such common questions in 2003 is poor[1]. Even though at least 25 studies have evaluated natural history of atopic dermatitis, the quality of studies is generally poor because of inadequate sample size, poor disease definition of the inception cohort, unclear definition of relapse, short follow-up, and large losses to follow-up. The only community-based cohort study estimated that 65% of children who had eczema at 7 years were clear after 9 years. Prognosis of AD cases seen in hospital have reported clearance rates of around 38% for children who were inpatients and 60% for outpatients. The most consistent predictors for more persistent AD identified from 11 studies are: early onset of disease, widespread disease in early life, concomitant asthma/hay fever and a positive family history. Seven studies have evaluated development of subsequent asthma/hay fever and together, they suggest that around 50% of children with AD seen in a hospital setting will develop asthma/hay fever. Three important conclusions can be drawn from this current overview: (1) The prognosis of AD is not as rosy as many dermatology texts like to promulgate; (2) The generalisability of studies dealing with the natural history of AD based on children born in the 1950s to today is questionable, since treatments and access to help has changed so much in the last 50 years; (3) There is a clear need to conduct high quality birth cohort studies that examine the natural history of AD, eg through an observational arm of a birth cohort intervention study.

1. Williams HC, Wüthrich B. The natural history of atopic dermatitis. In: Williams HC (ed.). *Atopic Dermatitis.* Cambridge, Cambridge University Press, 2000, 41–59.

Evaluation of a New Sequential Treatment with an Association of Fusidic Acid and Two Different Steroids

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The role of microbial factors, especially of *Staphylococcus aureus*, in atopic dermatitis (AD) is of great importance. In fact, skin colonization with *S. aureus* is notably increased in AD patients and may trigger and/or exacerbate the inflammatory network of AD. An open study aimed to evaluate the activity of an antibiotic-glucocorticoid treatment in mild to moderate AD. For this purpose patients suffering from localized forms of AD, with signs suggestive of potential microbial superinfections (oozing-crusting, fissuring, excoriations), were selected. Treatment consisted of the application of fusidic acid associated with betamethasone valerate (Fucicort®) twice a day for 10 days, followed by the use of a combination of fusidic acid and hydrocortisone acetate (Fucidin H®) b.i.d. for 10 days. Clinical evaluations were perfomed at baseline, after an appropriate wash-out period from previous active treatment, and after 10 and 20 days of treatment. The severity of skin signs and pruritus was assessed using a 4-point semiquantitative scale. A total of 178 (105 male and 73 female) patients were enrolled in this study; of these, 42 were adults, 87 were 3 to 15 years old, and 49 aged <3 years. At the baseline, AD was severity was mild in 67% of cases and moderate in 33%. Treatment was well tolerated. A relevant and progressive improvement of AD signs and symptoms was noted throught the study treatment: AD severity was notably reduced after the first 10 days and further improved after the subsequent phase. The patients' or parents' opinion on efficacy and acceptability of the treatment was positive in most cases.

Impact of Airborne Pollen, Temperature and Humidity on Severity of Atopic Eczema: Results of the First Population Based Panel Study in Children

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Background: Atopic eczema is a multifactorial disease determined by genetic and environmental factors. A relapsing course with seasonal variations is a well-known clinical feature in many patients. However, no study evaluating short-term variability of disease status caused by climatic factors or exposure to airborne pollen has been conducted so far.

Methods: 43 children with atopic eczema from Augsburg (Germany) participated in a panel study between March and September 1999. These children had been identified in a cross sectional study on all school-beginners in 1996. Results of RAST and prick test were available. Children daily recorded itchiness (1: absent to 5: very intense), extension (% of body surface) and possible trigger factors. Indoor and outdoor temperature and humidity as well as atmospheric concentrations of pollen grains were measured daily too. The association between symptom-scores and temperature, humidity and pollen counts were analyzed using mixed linear models, taking the individual time series structure into account.

Results: The symptoms showed two contrasting temporal patterns. Half of the children had symptoms mainly during spring time, when the study started, and were nearly symptom free in summer. The other children exhibited slightly more symptoms in summer than in spring and were negatively affected by increases of local temperature. These later children additionally showed significantly higher symptom scores at days with high grass pollen load. This association was especially pronounced for children sensitised against grass pollen (n = 8). Itchiness was one point higher (standard error 0.3, $p < 0.001$) for an increase in grass pollen counts of 300 pollen/m^3.

Conclusion: Disease expression of atopic eczema is influenced by climatic factors. Different subgroups of patients may be distinguished according to particular affection patterns. Exposure to airborne pollen causes significant aggravation of eczema symptoms in sensitised patients. Consideration of the individual type of eczema may help to arrange appropriate preventive and therapeutic measures.

How 'Atopic' is Atopic Dermatitis? A Comparison Between Hospital and Community Populations

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Background: The association between atopy and atopic dermatitis remains controversial. This debate has mainly focused on hospital based studies.

Objectives: To compare the prevalence of atopy between hospital and community populations and to estimate the relative risk of atopy in atopic dermatitis, a systematic review of the literature was conducted.

Methods: Papers were identified through systematic searches of Medline, supplemented by an extensive hand search. Only cross-sectional surveys that measured the prevalence of atopy as skin prick test positivity or RAST class were included. The mean prevalence of atopy and atopic dermatitis as well as the relative risk for atopy in atopic dermatitis were calculated.

Results: In hospital studies (n = 14), the mean prevalence of atopy was 63% among patients with atopic dermatitis (range: 44.4–100%) in comparison to a mean of 36.2% in community populations (n = 9, range: 7.4–78.3%). In healthy community controls the mean atopy prevalence was 21% (range: 4.3-76.3%). The odds ratio for atopy in atopic dermatitis in community surveys varied between 1.1 and 5.27. In addition, a number of population based studies comparing different populations suggest that skin prick test positivity can be common in areas where atopic dermatitis is rare. Furthermore, skin prick test positivity can decrease over time in the same population, while the prevalence of atopic dermatitis increases.

Conclusions: The association between atopy and atopic dermatitis is less strong than previously suggested by hospital based studies. Moreover, comparisons across populations and over time indicate only a weak and inconsistent association between atopic dermatitis and atopy.

Atopic Dermatitis and Varicella Skin Manifestations

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Varicella is a common infectious disease with a typical exanthem, usually benign and self-limited. Complications are believed to be rare, most being mainly reported in immunocompromised children and less frequently in immunocompetent children. Cutaneous manifestations are among the most frequent complications. We report in the present study 10 children with atypical and complicated varicella skin manifestations in atopic, immunocompetent children. During the last 3 years 10 children with serious skin complications were admitted to our hospital. Patients' median age was 4.5 years: none was immunocompromised, but all were affected by atopic dermatitis, not necessarily severe. The observed manifestations could be divided into two groups: a. atypical varicella (bullous lesions (2), haemorragic-necrotizing lesions (3)); b. complicated varicella (secondary bacterial infection (3), necrotizing fasciitis (1), bullous erythema multiforme (1)). All of these children underwent treatment with acyclovir and intravenous antibiotics with prompt resolution of the symptoms and without sequelae. Conclusions: Severe and unusual varicella complications normally described in immunocompromised children can be observed also in those with atopic dermatitis, even in the mild form. Skin changes resulting from atopic dermatitis or altered local immunity are likely to lead to unusual manifestations. Careful follow-up and adequate treatment are necessary to avoid sequelae and lethal complications. This observation prompts the study of the immunological characteristics of skin reactivity of atopic and immunocompromised children.

Eczema Herpeticum

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Patients affected by atopic dermatitis (AD) tend to develop common viral infections more frequently than non-atopics. The morphology of these infections does not differ between atopics and non-atopics, and they are treated similarly in both patient groups. In addition, disseminated infections occur in AD, which are predominantly caused by members of the herpesvirinae, molluscipoxvirinae and orthopoxvirinae genus. Whereas the clinical characteristics of the relevant disseminated viral infections and the appropriate diagnostic procedures are largely known, some novel therapeutic options should be considered. Among these infections, Eczema herpeticum (EH) is a clinically distinctive herpes simplex virus infection of eczematous skin, which occurs almost exclusively in AD patients. Two studies have recently been performed to identify the clinical and cellular factors predisposing for EH, which had been largely unknown. First, a retrospective analysis of 100 EH patients and of 105 control patients with AD was performed to identify the clinical features associated with EH: Fever and lymphopenia were associated with EH as such, whereas an elevated ESR was frequently seen in impetiginized control patients, too. The EH cases consisted of both primary and secondary HSV infection. EH patients had a significantly earlier onset of their underlying AD and a significantly higher serum-IgE level than AD control patients. Unexpectedly, more than 75% of the EH patients had not received any corticosteroid treatment in 4 weeks prior to EH onset. In conclusion, the clinical risk factors for EH are those associated with severe AD, and the majority of EH occurs in patients with untreated AD, arguing against a role for topical corticosteroids in EH. Second, we hypothesized a pathogenic role of plasmacytoid dendritic cells (PDC) in EH, which produce large amounts of type-I-IFN upon recognition of viral infection. The presence of PDC and other dendritic cells was investigated in epidermal single cell suspensions of lesional skin from different inflammatory skin diseases and controls. Langerhans cells were found in normal and in inflamed skin samples. In normal skin PDC and inflammatory dendritic epidermal cells (IDEC) were low or absent. Psoriasis and contact dermatitis contained relatively high numbers of both IDEC and PDC. Lupus erythematodes was characterized by high numbers of PDC but low numbers of IDEC, whereas IDEC but only very few PDC could be detected in AD lesions. In conclusion, PDC and IDEC are selectively recruited to different skin lesions, and the lack of PDC in AD lesions may predispose AD patients for EH.

Th1 and Th2 Cytokine Messenger RNA Expression in Lesional Skin of Atopic Dermatitis Patients with and without Very High Serum Ige Levels

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Background: Some atopic dermatitis (AD) patients show elevated serum IgE levels, while others do not.

Purpose: We compared the differences in mRNA expression of Th1 and Th2 cytokines, between AD patients with and without very high IgE levels.

Materials and methods: An RT-PCR method was used to detect Th1 (IL-12p35, IL-12p40, IFNγ, IL-18) and Th2 (IL-4, IL-13) cytokine mRNA. The subjects were 25 AD patients with very high serum IgE levels (>2000 IU/ml), 6 AD patients without (<2000), and 6 healthy controls. We also employed a genome-wide gene chip study to detect 90 types of Th1, Th2 and other affiliated cytokines.

Results: In patients with very high IgE levels, IFNγ mRNA expression was detected in 9 of 25 AD lesions by RT-PCR, while those without IFNγ expression frequently corresponded to those without IL-12 expression. IL-12p35 in AD lesions was significantly down-regulated as compared to normal controls. IL-18 was detected in lesions from all 25 patients and IL-13 in 24 of 25, whereas IL4 in only 3. The expressions of Th1 and Th2 were similar between patients with and without very high IgE levels. In the gene chip study, we failed to detect any Th1 or Th2 genes that showed a greater than two-fold change of expression between two groups.

Conclusions: In lesional skin of AD patients with and without very high IgE levels, a very limited expression of IL-4 mRNA was detected. Further, IL-18, IL-12p40, and IFNγ mRNA expressions were similar to those in normal controls.

Delayed Type Hypersensitivity Reactions to Pollen Derived Factors

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DTH-reactions to epicutaneous application of aeroallergens is well documented in a subgroup of patients with atopic dermatitis. Recently we demonstrated that pollen apart from the allergen also release a variety of bioactive lipid mediators. To delineate the effect of pollen-derived factors on human skin we performed patch tests with native pollen grains and their aqueous extracts. 3 patients with atopic dermatitis, sensitisation to grass and birch pollen and positive APT-reactions were chosen for the study. 3 healthy individuals served as control. Pollen grains (grass and birch) were exposed with petrolatum as carrier. Patch test rest reactions were graded according to the Guidelines of the European Task Force on Atopic Dermatitis.

Biopsies were taken from eczematous lesions after 48 and 72 hours and investigated by immunohistochemistry. Histology of positive pollen patch tests (PPT) showed signs of acute dermatitis with keratinocyte damage and a marked influx of mononuclear cells into dermis and epidermis (90% CD4+, 30% CD25+, 90% CD45RO+).

In negative patch test reaction a scarce influx of mononuclear cells was observed (50% CD4+, 90% CD45RO+). Concerning CD1a no difference could be observed in the epidermis of positive and negative PPT while in positive PPT a higher efflux of CD1a+ cells into the dermis was observed. In this study we demonstrated that pollen derived factors induce eczematous skin reactions in terms of DTH-reaction in susceptible individuals. Further studies will be necessary to reveal the underlying molecular mechanisms and importance of bioactive lipid mediators in the course of this reaction.

Atopy Patch Test with House Dust Mite Allergen - an Ige Mediated Reaction?

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The eczema reaction in the atopy patch test (APT) is proposed to be IgE mediated, but can take place in individuals lacking allergen-specific IgE in serum. We evaluated the importance of allergen-specific s-IgE for the APT reaction. Ten patients with reproducible positive APT to extract of *Dermatophagoides pteronyssinus*, 5 patients with (group A) and 5 patients without (group B) detectable s-IgE to *D. pteronyssinus,* were tested on normal skin of the back for 6, 24, 48 and 72 h. Skin biopsies were and analysed for cell infiltrates, eosinophils (EG2), IgE, FcεRI, CD1a, CD4, CD8 and metalloproteinase 9 (MMP9). The dermal cell infiltrate scores did not differ significantly between the groups at any time point. The number of IgE^+, $CD4^+$, $EG2^+$ and $MMP9^+$ cells increased with time in group A. $Fc\varepsilon RI^+$ cells and $CD8^+$ cells increased with time in both groups. A correlation was found between the levels of *D. pteronyssinus*-specific s-IgE and the score of dermal cell infiltrates at 72 h. The three patients with the highest values of allergen-specific IgE also had the highest expression of $EG2^+$ cells and the highest APT scores. Our study strengthens the hypothesis that the IgE molecule has a key role, at least as an amplifier, in the APT reaction.

Atopy Patch Tests with House Dust Mites in Patients without Atopic Dermatitis

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So far the issue of atopy patch tests (APTs) in subjects not affected by atopic dermatitis (AD) has been poorly investigated and with contrasting results. Our aim was to assess the frequency and intensity of responses to APTs with mite allergens in non-AD subjects, and to compare these data to the ones observed in AD patients. Patch tests were performed employing a mix of Dermatophagoides pteronyssinus/farinae on 75 non-AD subjects, including 33 patients with allergic rhinitis and 42 healthy volunteers, and on 66 AD patients. Positive reactions were observed in 24% of non-AD subjects and in 44% of AD ones. The former showed responses of lower intensity (mean score = 1.3) than AD patients (mean score = 1.9). Thus, positive responses to mite patch tests are observable also in subjects not affected by AD, but their frequency and intensity are significantly ($p < 0.05$) lower with respect to AD patients. Delayed skin reactivity in non-AD subjects may be regarded as equivalent to the finding of specific IgE by skin prick tests or RAST in healthy subjects, indicating an atopic state. For the occurrence of both the induction and the elicitation of the dermatitis other skin factors should probably be concomitant.

Response to Mite Patch Test in Subjects With or Without Atopic Dermatitis

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Background and aims: Only few data are available on the frequency of positive responses to atopy patch tests with Dermatophagoides in children not affected by atopic dermatitis (AD). We currently include a routine patch test with Dermatophagoides in our pediatric standard series. In this study we investigated the prevalence of contact sensitisation to mite allergens in a cohort of 213 consecutive paediatric patients.

Patients and Results: 124 children (<18 years) out of 213 (58.2%) showed a positive allergic response to patch test with Dermatophagoides. Among these patients, 71 (57.3%) children were affected by AD, whereas the remaining 53 (42.7%) patients were subjects without AD. Each patient with positive patch test to Dermatophagoides underwent prick test with an aeroallergen series including Dermatophagoides. Among the 71 children with AD and positive allergic response to Dermatophagoides, 18 showed positive prick test to Dermatophagoides, 17 to other aeroallergens and 36 were negative. Among the 53 non-AD children sensitized to Dermatophagoides, 15 showed positive prick test to Dermatophagoides, 14 to other aeroallergens and 24 were negative. 9 out of these 24 non-AD patients showing positive patch test but negative prick test to Dermatophagoides had no personal or familial history of atopy.

Conclusions: Our preliminary results suggest the usefulness of performing routinary patch testing to Dermatophagoides in the evaluation of contact allergy also in children not affected by atopic dermatitis.

The Utility of Atopy Patch Test for Diagnosis of Adverse Reactions to Food in Children with Atopic Dermatitis

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Background: Atopic dermatitis (AD) is frequently associated with food allergy. Adverse immunologic reactions to food may be a consequence of both IgE- and non-IgE-mediated mechanisms. Non-IgE-mediated allergic responses tent to involve a T-cell mediated delayed hypersensitivity reaction that can be evaluated by the atopy patch test (APT). The aim was to evaluate the diagnostic value of the APT with regard to late-phase reactions observed in double blind, placebo-controlled food challenges (DBPCFCs) with cow's milk, hen's egg, wheat, in children with AD. We hypothesized that a positive APT result would render DBPCFC unnecessary.

Methods: One hundred and thirteen children [69 males, median age 4.2 years (range 4 months-12.7 years)] suffering from AD and suspected food-related clinical symptoms were investigated with APT and DBPCFCs.

Results: Of 229 DBPCFCs, 24 (40%) were assessed as positive for cow's milk, 32 (53%) for hen's egg, 4 (7%) for wheat. Out of 42 patients with APT positive reactions, 20 (53.8%) had positive response to hen's egg, 4 (10.8%) to milk, 4 (10.8%) to wheat, 12 (32.3%) to milk and egg, 2 (5.4%) to milk and wheat. We found that late-phase clinical reactions were associated with a positive APT; the sensitivity to cow's milk was 64%, to hen's egg 86%, to wheat 100%; the specificity was 86% for milk, 73% for egg and 95% for wheat; positive predictive value was 47% for milk, 22% for egg, 40% for wheat; negative predictive values were 93%, 98% and 100% respectively.

Conclusions: Our findings confirm that the APT may be a valuable additional tool in the diagnostic work-up of food allergy in children with AD because of its high specificity and sensibility for late-phase clinical reactions, however DBPCFC must be still considered the diagnostic gold standard test.

No Standard in the Gold Standard for Food Allergy Diagnosis: An Italian Pediatric Survey

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Background: Food allergies are among the earliest manifestations of atopy. Food allergy diagnostic protocols rely on the reference standard of double-blind, placebo-controlled, oral food challenge (DBPCFC); however, there is no standard procedure for the provocation text itself. In order to picture conditions under which oral food challenges are administered in Italy, a nation-wide questionnaire survey of hospital-based allergy centres was administered between January 1st and June 30th, 2003.

Methods: All in-hospital allergy centres received a questionnaire in 23 points detailing organisation and procedures followed during direct provocation tests. Facilities, workloads and medical personnel involved were investigated. Study allergens, preparations of challenge meals, blindness and placebo were also polled.

Results: 375 responded out of 536 healthcare facilities with a paediatric department in activity in 2002. 61% per cent of responders had the facilities to mount direct provocation tests. Among these, frequencies of 85 and 15 per cent respectively for open and variously blinded procedures were recorded. Of centres that offered blinded tests, no uniform procedures are followed. In cow's milk testing, few centers used an amino acid mixture as placebo. Other placebos include lyophilised cow's milk capsules, soy formula, extensive whey hydrolysate or extensive casein hydrolysate.

Conclusion: The picture this nationwide survey reveals is a variety in provocation test criteria, facilities and procedures. This argues in favour of greater standardisation on a transnational, European scale. These data further suggest that resorting to provocation tests in the work-up of food allergy is widely felt and appreciated.

Management of Atopic Dermatitis in France (2001-2002): A Questionnaire Survey

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The management of atopic dermatitis (AD) is not yet standardized, primarily due to the various medical specialists in charge of patient treatment. To evaluate the management of AD in the French population, we conducted a cross sectional study in 2002.

Methodology: A representative sample of 4012 French households were interviewed by phone. The interviewed sample population was representative, as indicated by the quota method after stratification by region and community signs (socio-professional category). First, 190 AD patients were selected through the reading of a precise disease definition, adapted in French from the criteria of the UK working party. Next, data were collected in these 190 patients using self administered questionnaires and phones contacts. Patients were asked about the medical management of their AD, the treatments provided and the severity of their last disease flare (body area involved, intensity of 6 objective signs ranked from 0 to 3). An objective self administered SCORAD was calculated for the last flare of each patient. Finally, data were adjusted (statistical rectification) to be representative of the French population in terms of sex and age.

Results: Among the 190 patients with AD, 105 were children. The group divided into 22 0 to 2 years old, 52 2 to 5 years old, 31 5 to 15 years old and 85 patients of more than 15 years. 90.6% of patients consulted a physician during the last year, with means values of 7 times for children and 5 times for adults. Adults and, to a larger extent, children consulted several physicians for their condition (29% of adults and 44% of children). When only one physician was consulted, general practitioners were cited first (33% in adults, 32% in children), while the remainder divided between pediatricians and dermatologists. None of the patients interviewed had been hospitalized for AD during the last 12 months. 76% of patients used topical corticosteroids (TCS) during the last 6 months. TCS used were classified as low potent in 2.8%, moderately potent in 30.7%, potent in 75.4%, and very potent in 9.9%. The mean duration of TCS use during the last flare was 14 days corresponding to a mean consumption of 21 g and a median of 7 g. Over the last six months, the monthly consumption of TCS was 12.5 g and the median was 7.8 g. Correlation between TCS dose, age of patients and AD severity are represented in Tables 1 and 2.

Table 1. TCS consumption for the last flare in grams correlated with age of patients

	All	15 years	> 15 years	5 years
Mean	21.38	22.85	19.83	24.67
Median	6.84	6.74	6.34	6.74

Table 2. TCS consumption for the last flare in grams correlated with severity of AD*

	Mild	Moderate	Severe
Mean	11.27	21.39	40.90
Median	3.10	7.15	18.61

*severity of AD: evaluated using calculated objective self administered SCORAD (0 to 83) mild: SCORAD <15; moderate: SCORAD = 15-40; severe: SCORAD >40

13% of patients used TCS continuously. Among TCS users, 10% discontinued treatment because of intolerance, while 41% had safety concerns and self limited the amount applied. 76% of patients used emollients during the last six months. The mean duration of emollient use during the last flare was 26 days, corresponding to a mean consumption of 168 g. Over the last six months, the monthly consumption of emollients was 85 g. 75% of patients used emollients during remission periods.

Conclusions: Our data show that the use of TCS during flares associated with continuous use of emollients remains a therapeutic mainstay. This is one of the first studies to report quantitative data concerning topical treatments in AD and their correlation with age and severity score (SCORAD). There is no significant difference between the different age groups concerning TCS dose. However, there is a real correlation with the severity of the disease. This study underscores patient concerns when TCS are used. Specialist visits are available in France for the majority of patients, one possible explanation for the absence of hospitalized patients. Our data show that there is no standard regimen for TCS prescription, and that progressive tapering of TCS use is not common in the majority of patients. Our study clearly indicates a need for practical guidelines for long term disease management.

Leukotriene Receptor Antagonists - a Novel Therapeutical Approach in Atopic Dermatitis?

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Cysteinyl leukotrienes (LTs) play an important role in the pathogenesis of the inflammatory response in atopic diseases such as allergic asthma and allergic rhinitis. Recent experimental findings suggest that cysteinyl LTs may also be important in the pathogenesis of AD. Therefore, beneficial effects of 5-lipoxygenase inhibitors and LT receptor antagonists (LTRA) may be expected if used in the treatment of AD. Indeed, significant improvement of skin manifestations in atopic dermatitis has been published with leukotriene receptor antagonists recently. Newer data and own clinical experiences however support the fact, that LTRA's are not effective in severe AD patients and therefore are not generally recommended for the treatment of AD. In my presentation, I will review the experimental and clinical experience gained in treating atopic dermatitis with montelukast and other leukotriene receptor antagonists (LTRAs) – focusing on the question whether Montelukast and other LTRAs are valuable therapeutic options in the treatment of mild to moderate AD, especially when associated with other atopic diseases such as asthma and allergic rhinitis, and in some subgroups of AD such as atopic dermatitis of the face. In addition, pro's and contra's of a new therapeutic option – namely the combination of topical calcineurin inhibitors and systemic LTRA's will be discussed.

'Wet-Wrap' Treatment with Diluted Corticosteroids and Emollients in Atopic Dermatitis and the Dermatitis Lesion-Free Diaper Area

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'Wet-wrap' dressings with diluted corticosteroids form an intensive treatment in children and adults with erythrodermic and refractory severe atopic dermatitis (AD). The most important side effect is a (temporary) suppression of the hypothalamus-pituitary-adrenal cortex-axis that occurs in less than 5% of the patients. Further diluting of the corticosteroid cream from 25 - 5% diminishes this risk, whilst a good efficacy is maintained. Steroids with an increased benefit – risk ratio such as mometasone furoate and fluticasone propionate cream are preferably used. Long-term treatment at home is feasible when patients (and their parents) are well motivated and are provided with adequate instruction and guidance. A marked improvement of AD skin lesions is noted in all patients. The effect is very quickly achieved. As well in children as in adults, an improvement of 80% is achieved within one week after intensive treatment. Substitution of tubifast bandages by garments ("wet wrap pyjama") will improve the results and handy application. The modern disposable diaper acts also as a wet wrap: the diaper skin is usually free of AD skin lesions. Our studies performed in 1986 (Tio *et al*, 1988) showed that TEWL is higher in the diapered skin. This was recently confirmed by an unpublished study with the most advanced diapers (Odio – personal communication, 2001). In the diagnostic criteria of Sampson this can be used as diagnostic item.

Comparison of Self-Management Plans for Atopic Dermatitis and Asthma

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Self-management plans for the treatment of atopic asthma are recommended by both the United States (NHLBI) and European guidelines (GINA). 25 studies examining these written plans for the treatment of asthma have shown improvement in control symptom free days, fewer emergency room visits and lower costs of medical care. Written self-managements are recommended over medical management plans in the treatment of asthma in the latest NHLBI guidelines (July 2002). Despite the similarities between the diseases, no self-management plans for the treatment of atopic dermatitis have been published. We compared several asthma self-management plans with three independently developed self-management plans for atopic dermatitis. The majority of the asthma self-management plans have 3 steps: every day medications, medications for beginning of symptoms and medications for worsening symptoms. Several asthma management plans are color-coded and others have pictures to help with individual with low reading ability. All three atopic dermatitis plans have initial levels of therapies or maintenance. However, one plan has two steps of step-up therapies and the other plan has 3 levels of step-up treatment. While, the third plan develops separate levels of treatment depending on the severity of underlying disease and includes one level of step-up therapy in the maintenance phase. The plans varied in readability of the language. Neither plans used colors or pictures to help with patients with low levels of reading ability. All plans have maintenance therapies but differ in the number of steps of increasing therapy and level of readability. Studies need to be developed to determine if management plans in atopic dermatitis can increase symptom free days and lower costs similar to asthma.

The Anti-Inflammatory Actions of H_1-Antihistamines

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Histamine is responsible for the vasodilation, increased vascular permeability and mucosal hypersecretion tipical of IgE-mediated allergic diseases such as rhinitis, conjunctivitis and acute urticaria. Numerous observations however have amplified the contribution of histamine to a variety of inflammatory and immune responses. Histamine other then being stored by mast cells (MC) and basophils can be produced (although not stored) by leukocytes and keratinocytes. In these cells, histidine-decarboxylase is rapidly induced upon activation with cytokines (IL-1, TNF-α), bacterial products or UV radiation. The four histamine receptors (H_1-H_4) are expressed by many cell types that participate to the development of immune responses, including dendritic cells (DCs), monocytes, T cells and epithelial cells. Histamine inhibits TNF-α and IL-12, whereas increases IL-10 release from mature DCs and monocytes via activation of H_2 and H_3 receptors. As a consequence, DCs exposed to histamine more easily induce Th2 compared to Th1 cell differentiation. Histamine also directly affects the functions of T cells, MC and eosinophils, as well as endothelial and epithelial cells Anti-H_1 antihistamines are widely used anti-allergic and anti-pruritus agents. However, it is likely that these drugs exert anti-inflammatory actions via both receptor-dependent (inverse agonism) and receptor-independent mechanisms. Anti-H_1 drugs block histamine release from MC and basophils, and stabilize their cell membrane rendering them less sensitive to degranulating agents. Moreover, certain anti-H_1 (desloratadine) suppress IL-4 and IL-13 production by MC and basophils. Anti-H_1 inhibit accumulation and activation of inflammatory cells in the skin and respiratory mucosae by inhibiting the expression of chemokines and adhesion molecules. In murine models, anti-H_1 and anti-H_2 agents accelerate epidermal barrier repair. Some of these activities may be secondary to the capacity of anti-H_1 to reduce NF-κB activation. In conclusion, anti-H_1 histamines have the potential to exert effective anti-inflammatory actions not only in MC- or IgE-dependent diseases, but also in other disorders.

Combined Therapy in Atopic Dermatitis

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Topical corticosteroids have been the mainstay of treatment for atopic dermatitis. They induce several changes in skin metabolism leading to reduction of inflammation and itching and can be used both in acute and chronic phases of the disease. Their mechanism of action is broad and complex, affecting several pathways of inflammation and gene expression. Due to their potential side effects and depending upon the clinical severity of the disease, their use should be limited to the acute phases and then replaced by other treatments. Low to mild potency steroids should be preferred. Pulse steroid therapy in association with emollients or barrier restructuring creams has been shown to be effective, safe and useful in keeping disease- free chronic patients. In particular, physiologic mixtures containing free fatty acids, cholesterol and ceramides can penetrate a disrupted stratum corneum, reach the nucleated epidermal cell layers and be incorporated into nascent lamellar bilayers of the stratum corneum interstices. Clinical trials of ceramide-dominant barrier repair moisturizer has been shown to reduce the severity scoring of atopic dermatitis, normalizing TEWL and improving stratum corneum integrity. Combination therapy of mild corticosteroids with physiologic lipid mixtures can be a useful, low cost and safe approach to the long term management of atopic dermatitis.

Selectivity as a Means of Extending the Therapeutic Window Provides Improved Safety and Efficacy

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Increased understanding of the pathophysiological mechanisms of inflammatory skin diseases, such as atopic dermatitis, has led to the development of treatment regimens that act early in the inflammation cascade and provide improved disease management and safety in both the short and long term. Pimecrolimus cream 1% (Elidel®) is a new, non-steroid, cell-selective inflammatory-cytokine inhibitor with an excellent safety profile that differs from both corticosteroids and tacrolimus. Pimecrolimus is lipophilic, resulting in a high affinity to the skin, and selectively inhibits the synthesis and release of inflammatory cytokines from T cells and activated mast cells. Unlike corticosteroids, pimecrolimus has no effect on other immune-competent cells; has no atrophogenic potential when applied to human skin; and is safe for application on sensitive areas, such as the face and neck. Pimecrolimus penetrates well into the skin, but permeates through the skin less than tacrolimus and corticosteroids; consequently, it has a lower risk of systemic side-effects. When used at the first signs and symptoms of atopic dermatitis in double-blind, controlled trials, pimecrolimus produces rapid relief from pruritus, erythema and infiltration, and prevents progression to flare in all ages and all disease severities. The excellent safety and efficacy of pimecrolimus, when considered together, extend the therapeutic window for the management of atopic dermatitis.

Disease Management as a Way to Achieve Disease Modification

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Atopic dermatitis (AD) is a chronic, persistent disease with a recurring pattern of flares. Early prevention of flares has the potential to modify disease progression and the development of other atopic diseases. Double-blind, controlled studies show that pimecrolimus cream 1% (Elidel®), when applied at the first signs or symptoms of AD, prevents progression to flare and thereby provides long-term disease control. When used in all age groups, up to 61% of patients in the pimecrolimus group remained flare-free, compared with 34% of patients treated conventionally ($p < 0.001$). Flare prevention also results in a considerable reduction in steroid use; the majority of patients did not require steroids for the duration of the studies (up to 1 year). Other studies have reported a high degree of cosmetic acceptability with pimecrolimus cream 1% in daily practice, which is important for patient compliance. Assessment of disease signs indicates that flare reduction is due to a reduced level of disease activity following treatment with pimecrolimus cream 1%. AD is often the first manifestation of the 'atopic triad'; up to 80% of children with AD will develop asthma or allergic rhinitis later in life. Recent evidence indicates a common pathophysiological link between these diseases. A trial of early and consistent use of pimecrolimus cream 1% is planned to test this hypothesis.

From ETAC to EPAAC

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The prevalence of asthma, atopic dermatitis and allergic rhinitis has increased considerably over the past decades, and there is a common progression from atopic dermatitis to allergic asthma (allergic march).[1] Approximately 50% of children with atopic dermatitis in early infancy and who have both parents with atopic disease will develop asthma at the age of 5 years.[2] Cetirizine, a second generation anti-histamine, has shown also some anti-inflammatory, since it inhibits allergen-induced ICAM-1 expression in nasal and conjunctival epithelium during allergic inflammation[3] and reduces eosinophil chemotaxis.[4] The ETAC study (Early Treatment of Atopic Child) was a 5 year prospective, randomized, double-blind, parallel group and placebo controlled trial involving 817 young children in 12 European Countries and Canada.[5] The aim of this study was to investigate if treatment with cetirizine may prevent or delay the onset of asthma in children (1-2 years of age) with atopic dermatitis and a family hystory of atopy. The study was conducted in two phases, involving 18 mounth treatment period and 42 mounth follow-up period. After the first 18 mounth study period, clinically relevant effect of cetirizine in reducing development of asthma was not shown in all patients, but only in children who were sensitized to grass pollen and/or house dust mite at baseline. This effect remained significant for children sensitized to grass pollen after 18 mounth follow-up period, while less effect was shown in children sensitized to mite allergens.[6] The EPAAC study (Early Prevection of Asthma in Atopic Child) was recently initiated. The purpose of EPAAC study is to provide the body of evidence that would confirm the findings generated by the subgroup analysis carried out in ETAC, and to demonstrate that asthma can be prevented in young children with atopic dermatitis sensitized to specific aeroallergens. For this study levocetirizine, which is the active enantiomer of cetirizine, will be used. 500 children (250 for group) are planned to be randomized in 80 Centers in Europe, Australia and South Africa. The trial includes 18 mounth treatment period and 6 month follow-up period after discontinuation of the trial medication. The study is currently in progress.

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The Size of Thymus and Atopic Dermatitis. A Cross-Sectional Study

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Atopic dermatitis (AD) is a common skin disorder of unknown aetiology with peak incidence in early childhood. The disease includes immune deviations such as T-cell accumulation and activation. Thymus is a key organ for selection, accumulation and activation of the cellular immune response in early life. We therefore wanted to study if there was any association between the size of thymus and current atopic dermatitis. A cross-sectional study was performed. Thirty-seven in and out-clinic patients with current AD were enrolled from the dep. of dermatology in Aarhus and compared to 29 healthy controls. An interview and medical examination was performed by one doctor (ABO). For children with AD SCORAD and the use of steroids were registered. Within 3 days after examination an ultrasound scan was performed. The thymus index was obtained using a trans sternal approach. Sonography was performed by one doctor (GA) with a Siemens scanner using a 7.5 MHz sector transducer. The size was significantly increased in children with active atopic dermatitis compared with healthy controls ($p < 0.05$). The main analysis showed that the thymus index declined significantly with age ($p < 0.05$) to a comparable degree in both children with atopic dermatitis and healthy controls. The individual measurements showed a large range in the size of thymus in both groups of children. There was no difference among the two groups concerning: breastfeeding, family size, time of introduction of first dietary supplement and daily care of the child. This study demonstrates increased size of thymus among children with active atopic dermatitis compared to healthy controls. In an earlier study we found no association between the size of thymus at birth and atopic disease at the age of 5 (1). The increased size of thymus may be associated with increased activity and emission of T lymphocytes.

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Nitric Oxide in Atopic Dermatitis: a HPLC Method for the Simultaneous Measurement of Arginine Metabolites

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Nitric oxide (NO), a signaling molecule derived from L-arginine by NO synthase, is shown to have potent immunomodulative properties. Several studies suggest its involvement in atopic dermatitis (AD). Recently, it has been demonstrated that arginase and arginine decarboxylase, which also use arginine as a substrate may regulate NO synthase activity and *vice versa* by competing to the L-arginine. The presence of both arginase and NO synthase in the skin have been shown previously. We aimed to measure the activities of NO synthase, arginase and arginine decarboxylase in normal and AD skin as well as in peripheral blood mononuclear cells. We have developed an HPLC method with radiochemical detection for simultaneous measurement of arginine, citrulline, ornithine and agmatine after adding the radiolabeled arginine to the tissue or cell preparation. The compounds are separated in normal phase column under isocratic conditions in less than 30 minutes with good sensitivity. Preliminary data will be presented and discussed in context of current concepts of the pathogenesis of AD.

Correlation of Clinical Features and Skin Barrier Function in Adolescent and Adult Patients with Atopic Dermatitis

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Xerotic skin change in atopic skin is considered to be related with the diminished water-permeability barrier. However, whether abnormal skin barrier function is a main cause of atopic dermatitis (AD) or a secondary change of the disease is still controversial. Noninvasive bioengineering methods including transepidermal water loss (TEWL) and water capacitances have been commonly used to evaluate skin barrier function. Our objective was to evaluate the corrrelation of clinical features of each evaluation site and skin barrier function by the severity of AD. We checked TEWL, capacitance and pH on 5 evaluation sites-postauricle, forearm, abdomen, thigh and popliteal fossa. The subjects were 25 patients, adolescent and adult, with AD and 25 age-matched normal controls. We also scored the clinical severity from 0 (no clinical manifestations) to 3 (severe) for erythema, induration/population, lichenification and xerosis on each evaluation site of the patients with AD. Based on the data, we found that the clinical severity score is correlated with TEWL and capacitance in more than half of the evaluation sites. Erythema and induration/population usually showed statistically significant correlation with TEWL. Lichenification and xerosis usually showed significant correlation with capacitance. However, severity scoring of clinical features mostly did not show significant correlation with skin pH. The patients had higher TEWL and lower capacitance than those in the normal controls.

Synthesis and Evaluation of the Novel Ceramide Analogue Based on L-Serine For the Skin Barrier Repair

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Stratum corneum ceramides are fundamental for maintaining the skin barrier function. The ceramide content is decreased in several skin diseases including atopic dermatitis and ceramide supplementation is one of the therapeutic approaches. However, the syntheses of ceramides are difficult and expensive. We designed novel ceramide analogue 14S24 and we report convenient two-step synthesis. The difference between 14S24 and ceramide 2 is only the presence of ester bond instead of hydroxyl in position 3 and *trans*-double bond in position 4 of sphingosine. Skin permeation experiments were performed using porcine full thickness skin and theophylline as the model permeant. The experimental skin barrier disruption was induced by lipid extraction. The permeability of the disrupted skin was significantly higher than that of the normal skin. This elevated permeability was reduced by 2 hours topical application of the 0.1% 14S24 almost to the values of untreated skin. Ceramide analogue 14S24 is easier and cheaper to synthesize than physiological ceramides and it is effective in skin barrier repair in vitro. This ceramide analogue could be beneficial in skin diseases with impaired barrier function. This work was supported by the Charles University (grant 256/2001/B-CH/FaF) and the Ministry of Education of the Czech Republic (grant MSM 111600001).

Lack of Evidence of Relationship Between Helicobacter Pylori Infection and Atopic Dermatitis in Children

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There is increasing evidence for systemic effects of gastric Helicobacter pylori (HP) infection which may result in extragastrointestinal disorders. Based on a number of reports a possible relationship of HP infection to a variety of different dermatoses has been suggested, including urticaria, rosacea, alopecia areata, Sjogren's syndrome, Schonlein-Henoch purpura and atopic dermatitis, but the data are still conflicting. In particular a positive association between HP antibodies and atopic dermatitis (AD) as the sole manifestation of food allergy has been reported. This study was designed to determine whether a significant association between AD and HP infection could be found in pediatric patients. Thirty-three patients (age range, 7-12 years) affected by moderate to severe AD as defined according to the criteria of Hanifin and Rajka and 29 age- and- sex matched healthy controls were tested for HP infection with the urea breath test using urea labeled with carbon 13 (^{13}C). Among the patients with AD only one had a positive C-urea breath test result while 32 had a negative result. Among the 29 healthy controls 5 had a positive C-urea breath test result and 24 had a negative result. Our data show that in our patients the prevalence of HP infection in children with AD is low and it is comparable with that observed in the healthy controls. In conclusion there is a lack of evidence of a relationship between HP infection and AD in children.

Association of Food Allergy with Interleukin 4 Receptor Alpha Chain Polymorphism Gln551Arg of Atopic Dermatitis in Korea

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Atopic dermatitis (AD) is an allergic inflammatory skin disease, which results from the interaction between genetic and environmental factors. Several candidate genes for atopic dermatitis including human interleukin 4 receptor alpha (hIL-4Rα) chain has been proposed. A variant of hIL-4Rα with arginine at amino acid 551, instead of glutamine, has been reported to be correlated with hyper IgE syndrome and severe atopic eczema. Hereby, hIL-4Rα Gln551Arg polymorphism was investigated in 33 AD patients (mean 7.9 years of age, 1/12 - 35) and 8 healthy volunteers (mean 27.5 years of age, 24 – 33) as normal controls. Double-blind placebo-controlled food challenge (DBPCFC) were performed for several foods. Among 53 AD patients, 26 (49.1%) were heterozygous for the Arg551 allele (Gln/Arg), one (1.8%) was homozygous as Arg/Arg, and 26 (49.1%) were homozygous as Gln/Gln, but this allele did not occur in all normal controls. Between Gln/Gln atopic dermatitis and Gln/Arg AD, there were no laboratory differences in blood total IgE levels, eosinophil fractions to WBC, and total eosinophil counts. Interestingly, 56.3% (9/16) of AD with Gln/Arg heterozygous genotype showed allergy to egg comparing with 33.3 % (4/12) with Gln/Gln homozygous genotype. In contrast, 57.1% (8/14) of AD with Gln/Gln homozygous genotype showed allergy to milk comparing with 23/1% (3/13) with Gln/Arg and 66.7% (6/9) with Gln/Gln showed allergy to soyabean comparing with 23.1% (3/13) with Gln/Arg. Prevalence of allergy to wheat was similar in both Gln/Gln homozygous genotype and Gln/Arg heterozygous genotype. In our study, none of normal healthy controls showed a hIL-4Rα chain variant. The frequency of hIL-4Rα Gln551Arg polymorphism was much higher in Korea than those of previous reports. hIL-4Rα Gln551Arg polymorphism seemed to be related with the causative foods in atopic dermatitis. hIL-rRα Gln551Arg polymorphism might be possible as an important indicator for the classification of atopic dermatitis as subtypes and further study will be needed.

A Comparison Study of the Staphylococcal Exotoxins and Staphylococcal Enterotoxin A-Specific IgE Antibody Between Childhood and Adulthood Atopic Dermatitis

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The skin of patients with atopic dermatitis (AD) exhibits a striking susceptibility to colonization with *Staphylococcus aureus* (*S. aureus*). Superantigens produced by *S. aureus* and their specific IgE antibodies are thought to be important precipitating factors of AD, but there are few reports evaluating these 2 factors at the same time, particularly in adulthood AD patients. This study was done to investigate the differences in the culture degree of *S. aureus* from the lesion, non-lesion, and control group of childhood and adulthood AD patients, to research the correlation between the exotoxin production, total IgE, anti-SEA IgE and the disease severity by SCORAD index, to ascertain the differences between childhood AD patients and adulthood AD patients. *S. aureus* colonizations were found in 11 (36.7%) of the lesional skin, in 5 (16.7%) of the non-lesional skin of 30 childhood AD patients, and in 26 (86.7%), in 20 (66.7%) of 30 adulthood AD patients, respectively. The colonization rates of *S. aureus*, 36.7% of lesional skin and 16.7% of non-lesional skin in childhood patients were much lower than those in adulthood patients, 86.7% of lesional skin and 66.7% of non-lesional skin. Staphylococcal exotoxins were detected in 5 (45.5%) of the 11 colonizations from lesional skin, in 2 (40%) of the 5 colonizations from non-lesional skin of children, and in 10 (38.5%) of the 26 colonizations, in 9 (45%) of the 20 colonizations of adults, respectively. SEA was most frequently detected in both groups. *S. aureus* colonization was correlated with the severity of AD in childhood, but not in adulthood. However, there were no statistical significances between severity of AD and others such as exotoxin production, and the level of total IgE and anti-SEA IgE in both groups. In conclusion, the colonization of *S. aureus* was more common in adulthood AD patients than childhood AD patients. Anti-SEA IgE level was much higher in adulthood AD patients than in childhood AD patients. It is tempting to speculate that the colonization of *S. aureus* and exotoxin production might be related to the disease duration rather than clinical severity of AD.

Atopic Dermatitis and Food Allergy: Diagnostic Role of SPTs and DBPCFC in 62 Children

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Background: Food allergy (FA) plays an important role in the pathogenesis of atopic dermatitis (AD), indeed it affects about one-third of the children with AD in the first few years of life. Immediate-type clinical reactions to food can be identified by clinical history, skin prick tests (SPTs), measurement of specific IgE and oral food challenges.

The aims of the study were to evaluate: a) the role of FA in children with AD and b) the relationship between early-phase and/or late-phase reactions in double-blind, placebo-controlled food challenges (DBPCFC) and SPTs positivity.

Methods: 62 consecutive children [38 males; median age 2.2 (range 6 mo – 13 yrs)] with severe AD were included in the study. All patients performed SPTs (prick test and prick by prick with fresh food) and then were maintained on an exclusion diet for 4 weeks. Children who presented a reduction of the SCORAD of at least 1/3 were defined as responders and underwent the DBPCFC with the food identified by SPT or with that suspected by the clinical history.

Results: 42 patients (67.8%) completed the trial. In the 34 responders, SPTs were positive to cow's milk, hen's egg, potato, wheat, carrot and veal. Of the 63 oral challenges, 21 (33.3%) were positive and 42 (66.7%) negative. Amongst 6 (28.6%) positive and in 8 (19%) negative challenges both SPT and DBPCFC were positive; amongst 15 (71.4%) positive and in 28 (66.7%) negative challenges, both prick by prick with fresh food and DBPCFC were positive. These different diagnostic tests allow us to identify the most commonly offending foods in AD: cow's milk (42.9%), hen's egg (19 %), wheat (19%), potato (9.5%), carrot (4.8%) and veal (4.8%). The 62% of children with positive challenges showed early clinical reactions (urticaria, worsening of eczema with erythema and itch, wheezing), the 28% showed late reactions (exacerbation of eczema and itch) and 10% combined early and late clinical reactions.

Conclusions: The study suggests that SPTs, although helpful in the diagnostic work-up for FA, cannot substitute the DBPCFC that remains the gold standard for its diagnosis in children with AD because its negativity helps to prevent unnecessary restrictive diets.

Role of Foods in Irregular Aggravation of Atopic Dermatitis in Japan

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Background: Although it is well known that patients with atopic dermatitis often show irregular aggravation of skin lesions, it remains to be determined what factors could cause the irregular worsening of the disease. In the present study, we investigated whether foods play a role in the irregular exacerbation of skin lesions in adult patients with the disease in Japan.

Method: The study population consisted of 195 adult patients with atopic dermatitis who showed irregular aggravation of skin lesions. They were asked to keep a diary of foods and skin conditions for 2 months. We then chose food items which were eaten, not every day, but on the day or the preceding day of the irregular exacerbation. Elimination and open challenge tests with suspect foods were performed. Challenge-positive foods were determined by evaluating comparable before-after challenge photographs. When possible, specific IgE antibodies to the offending foods were measured by the radioallergosorbent test (RAST). We then observed the skin condition for 3 months during which patients were prohibited from eating the offending foods.

Results: Challenge-positive foods were confirmed in 86 (44%) of the 195 patients examined. Predominant offending foods were chocolate, cheese, coffee, yogurt and some Japanese foods such as glutinous rice cake, soy sauce and fermented soy beans. Positive RAST reactions to the offending foods were rare. Exclusion of the offending foods brought about a progressive improvement of the disease.

Conclusion: Foods play an important role in irregular aggravation of skin lesions in adult patients with atopic dermatitis.

The Use of Atopy Patch Tests With Aeroallergens in Diagnosis of Atopic Dermatitis in Children

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Atopic dermatitis is a multifactorial, chronically relapsing skin disease. It has been demonstrated that food allergens are most important environmental antigens early in life. In older children the aeroallergens plays an important role. In this study the outcomes of atopy patch tests with aeroallergens in three groups of children were compared; group I- children with atopic dermatitis and negative skin prick tests, group II – children with atopic dermatitis and positive skin prick tests, group III - with atopic dermatitis, positive skin prick tests and allergic diseases of the respiratory tract. Tests were done in 39 children and 20 (51%) of them had positive outcome. The control group consist of 12 children with allergic diseases of the respiratory tract and positive skin prick tests without atopic dermatitis. In this group only 2 children had positive outcome of atopy patch tests. The outcomes and atopy patch tests in whole group of children with atopic dermatitis were compared. 18.6% of children with atopic dermatitis had positive outcome of skin prick tests, and 14.1% of them had positive outcome of atopy patch tests. It seems that atopy patch tests are as useful as skin prick tests in diagnosis of atopic dermatitis.

Patch Testing with Egg Represents a Useful Integration to Diagnosis of Egg Allergy in Adolescents and Adults with Atopic Dermatitis

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Food atopy patch tests are considered a useful tool for the diagnosis of food allergy in patients with atopic dermatitis. Hypersensitivity to eggs has been investigated by means of atopy patch tests only in infants and children, so far. Our aim was to investigate atopy patch test and skin prick test responses to egg in adolescents and adults with atopic dermatitis, and to evaluate the relevance of these results by performing repeated open challenges with egg. Atopy patch tests and skin prick tests with egg were performed in 58 atopic dermatitis patients, aged from 16 to 47 years, employing egg yolk and white separately. All subjects underwent repeated open challenges with egg. 17.2% of our patients reacted to the challenge. Positive responses to atopy patch tests were recorded in 18.9% of the patients, whereas in 12.1% positive skin prick tests were observed. Atopy patch test sensitivity and positive predictive value proved significantly higher than skin prick test's. Our data suggest that atopy patch tests with eggs may represent a useful tool in the diagnostic work-up of food allergy in atopic dermatitis patients.

Patch Testing in Children with Atopic Dermatitis

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Background and aims: Recent studies have demonstrated that contact sensitization in children is not uncommon, being more frequent than previously thought. However, conflicting data have been reported on the difference in patch test reactivity between children with or without atopic dermatitis (AD).

Methods: We have studied the patterns of response to patch testing in 238 children ($\leq$16 years) with atopic dermatitis (130 females, mean age 9.05 ± 4.2) and with suspected allergic contact dermatitis (ACD) and compared the results with a control group of 119 children with mucosal atopic diseases and with suspected ACD (67 females, mean age 10.9 ± 3.9) and a group of 348 children with ACD but without any personal history of atopic diseases (236 females, mean age 10.2 ± 4.4).

Results: The prevalence of positive patch test to at least one hapten was similar in the group of children with atopic dermatitis and in both control groups (50.8% vs 47.1% and 50.8% in patients with AD and ACD, mucosal atopy and ACD and only ACD, respectively) and only few allergens showed a statistically significant difference in the sensitization rate among children with AD compared with children without AD when evaluated with age-adjusted logistic regression. The most frequent contact allergens in children with atopic dermatitis were nickel (12.6%), potassium dichromate (8.1%), lanolin (6.3%), perfumes (5.8%), disperse blue (4.2%), neomycin (3.4%), and kathon CG (3.4%).

Conclusions: These findings suggest a similar reactivity to delayed hypersensitivity allergens among children with suspected ACD with or without AD and support the use of routine patch testing in children with AD.

Is Immunophenotyping Useful in Diagnosis of Atopic Dermatitis Diagnosis?

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Introduction: There are many in vitro and in vivo diagnostic tools to perform immunological dysfunction in the pathogenesis of atopic dermatitis (AD). Immunophenotyping of inflammatory cell surface markers in the biopsies of AD lesions was made.

Methods: To perform the presence of inflammatory cell surface markers in the biopsies of skin lesions we performed immunohistochemical analysis in 15 AD patients and 5 healthy subjects. Standard avidin-biotin immunoperoxidase staining of paraphin-embadded, 4 µm skin sections with semiquantitative counting of cells labeled with anti-CD3, anti CD8, anti CD20, anti-HLA DR (HLA human leukocyte antigen), and anti -immunoglobulin E (anti-IgE) primary antibodies, was done.

Results: The results of our study showed that CD4+ prevail over CD8+ in the infiltrate of AD skin lesions. In comparison with normal skin, a higher expression of HLA DR on dermal lymphocytes and epidermal LCs and IgE+ cells were found. The infiltrating cells expressing CD3, CD4 and HLA-DR cell-surface markers in the dermis and epidermis, CD8 in the dermis and IgE+ cells in the epidermis.

Conclusion: Immunohistochemistry has recently become a recognized and necessary part of pathodiagnosis in dermatopathology. The comparison of the AD patient group and the control group of healthy subjects showed that the two groups differed in the number of infiltrating cells expressing CD3, CD4 and HLA-DR cell surface markers in the dermis and epidermis, CD8 in the dermis and IgE+ cells in the epidermis.

Long Term Follow-Up in 205 Children with Atopic Dermatitis. Preliminary Data

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We studied 205 children (104 boys and 101 girls) with atopic dermatitis (AD), whose diagnosis was made on the basis of Hanifin and Rajka's criteria. The children were 3–36 months of age at the time of the first examination; the evaluation of the severity of the disease was made using the Rajka and Lageland clinical score considering the intensity, extent, and course of lesions. Patients with a total score of 3–4 were considered to have mild AD, 5–7 moderate AD, 8–9 severe AD. After a mean period of 17.5 years an interview by a questionnaire was performed. AD completely disappeared in 124 cases (60.5%) while it remained in 81 cases (39.5%) with differing scores of severity. The severity of the disease at the time of first observation was not associated with the different outcome follow up regarding AD: in the 67 children with mild disease, AD persisted in 23 cases (34%), in the 99 children with moderate form it persisted in 43 cases (43%); in the 39 children with severe form, in 15 cases(38%). Family history of atopy and high IgE level at the first observations were not related to the disappearance of AD. Rhinoconjunctivitis (RC) appeared in 116 cases (56%), asthma (A) in 67 cases (32%) and oral allergic syndrome (OAS) in 59 cases (29%). The appearance of A was statistically significant ($p < 0.001$) and higher in the group with severe AD at first observation (56% of cases) than in moderate (24%) or mild (31%); RC and OAS were observed with similar percentages in the 3 groups of severity. OAS was significantly ($P < 0.01$) associated with persistent AD (32 cases:40%) than in the group where disappeared (27 cases:22%), while the persistence of AD was associated with a slight but not significant increase in RC (65% vs 51%) and A (37% vs 30%).

Multidiscplinary Approach to Atopic Dermitis in Children: a Single Center Experience at Bambino Gesù Children's Hospital

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Atopic dermatitis is a cutaneous manifestation of atopy, that is well known to predispose to the onset of allergic manifestations by many organs. This disease is very difficult to treat due to several problems: chronic-recurrency, severe itching, unaesthetic appearance, psychological problems. For these reasons the Dermatology Unit of our Hospital started, since September 2001, a multidisciplinary approach to atopic dermatitis involving specialists in Allergology, Broncopneumology, Dermatology, Gastroenterology, Infectious Diseases, Otorhinolaryngology and Psychology. Our young patients also undergo, if required, haematological examinations, prick tests, patch test and topical treatment under the guidance of our nurses who, shaming a play for the children, teach the parents how to treat their children. Later, parents have to demonstrate to be able to make treatments on their own. Sixty consecutive children were included in the evaluation of the multidisciplinary approach. Patients' mean age was 27.71 months, 64% of them had associated allergic diseases of organs other than the skin (asthma, rhinitis, gastrointestinal symptoms and otorrhea). 26% of the patients suffered from psychological insomnia and hyper-excitability. At the end of the treatment 84% of the patients presented clinical improvement, 7% was unchanged, and 9% had clinical worsening. The high incidence of extra-cutaneous manifestations and the psychological problems underlie the importance of co-ordinated approach to the treatment of atopic dermatitis. In conclusion, our experience suggests that the child affected by atopic dermatitis has to be treated with a professional multi-specialised approach with the collaboration of several specialists and nurses. Moreover, parents should be guided and supported in order to better face a chronic disease, that could create discomfort to the child and the entire family.

Specific Allergy Vaccination in Atopic Dermatitis

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Allergen-specific immunotherapy (ASIT) is based on the administration of gradually increasing doses of allergen extracts to allergic patient. ASIT has been widely used to treat allergic rhinitis and allergic asthma. At the same time there is not enough evidence of therapeutic efficacy of ASIT in atopic dermatitis (AD). The aim of the study was to evaluate the efficacy of ASIT in AD patients.

Materials and methods: 165 AD patients were included it this study. All of them had symptoms of AD and respiratory allergy: allergic rhinitis and/or allergic asthma. All the patients received ASIT with HDM and pollen allergen extracts after clinical improvement of AD symptoms had been achieved by means of topical steroids and H1 blockers. During ASIT itching and skin irritation were observed in 63% of patients, but none of them dropped out during the study. Clinical efficacy and safety were evaluated.

Results: ASIT appeared to be efficacious in 83% of AD patients in spite of slight skin exacerbation which did not need any special treatment. We observed the improvement of skin and respiratory symptoms, reduction of needed medications.

Breast-feeding and Atopic Dermatitis in Infants

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Background: Infancy is a specially vulnerable period in which infants are in increased risk of becoming sensitised to food and other allergens. Atopic dermatitis (AD) occurs with high incidence in period of infancy. 60% of affected individuals manifest AD during the first year of life. Human milk (HM) provides passive and likely long-lasting active immunity. Thus the protective immune factors in HM and delayed interduction of cows milk and solid food are possible preventive effect in appearance of AD. The aim of the study is to confirm the important role of exclusive breast-feeding (BF) in prevention of AD at infants.

Methods: Total of 468 infants born during the period of 01.01.96 to 31.12.01 year were including in the study. First group of 300 (62.4%) infants were long term exclusively six mounts BF infants with solid food avoidance in this period. Second group of 168 (37.6%) infants were short time 1–2 mounts or not at all BF infants complementary feeding with cows milk formula (CMF).

Results: In the first group of 300 exclusively BF infants only 11 (7 male and 4 female) infants developed AD (3.4%). In the second group of 158 infants feeding with traditional CMF 31 (19 male and 12 female) infants develpoped AD (18.2%) in the first year of life.

Conclusions: The study present the favorable results of exclusively BF and it is recommended as a preventive measure for the development of AD in period of infancy. Due to fact that AD is the first manifestation of atopic diseases in childhood this primary prevention of AD may have long term positive consequence for decreasing risk of this diseases.

Clinical Study on the Significance and the Frequency of Atopic Dermatitis in Nummular Eczema

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Nummular eczema has been reported to be one of the minor clinical manifestation of atopic dermatitis. The frequency of nummular eczema in atopic dermatitis patients has been reported to be about 16.9% compared to 1.0% in normal population of Korean. But there was no previous literature evaluated the frequency of atopic dermatitis in nummular eczema patients in Korea. The aim of this study was to evaluate the frequency of atopic dermatitis in nummular eczema patients and to help the treatment and the prevention of nummular eczema patients. A total of 49 patients who had visited Department of Dermatology, Our Lady of Mercy Hospital, from January 1995 to December 2002, were diagnosed as nummular eczema with clinical and histopathological findings. The retrospective analysis of medical records, photographs, and biosy specimen was performed. The results are summarized as follows: (a) The number of patients with atopic dermatitis was 18 (36.7%) and non-atopic dermatitis was 31 (63.7%); (b) The mean age of patients with atopic dermatitis was 18.8 years and non-atopic dermatitis was 41.7 years; (c) The mean onset age with atopic dermatitis was 16.7 years and non-atopic dermatitis was 39.7 years; (d) Other minor clinical features of atopic dermatitis in nummular eczema patients were anterior neck folds, xerosis, superficial folliculitis, keratosis pilaris, recurrent herpes simplex, white dermographism, cheilitis, Dennie-Morgan infraorbital fold, orbital darkening, and pityriasis alba in the order of frequency; (e) The mean IgE level with atopic dermatitis was 856.9 ng/ml and non-atopic dermatitis was 150.1 ng/ml; and, (f) The mean eosinophil count with atopic dermatitis was 271.1/mm^3 and non-atopic dermatitis was 130.5/mm^3. This data shows that nummular eczema was frequently associated with atopic dermatitis. The onset age of nummular eczema was younger in patients with atopic dermatitis than in non-atopic dermatitis. We suggest that while caring the nummular eczema patients, dermatologist should consider that atopic dermatitis may be frequently combined with nummular eczema. Additional supportive managements such as avoidance environmental factor, food allergy, irritant allergy, infection factor, and so on, might be helpful in the treatment of nummular eczema patients.

Nummular Eczema in Childhood: a Retrospective Study of 245 Cases

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Nummular eczema is characterized by a typical morphological appearance. Usually an acute eruption of a well-demarcated coin-shaped lesion, 1–5 cm in diameter, is observed. Lesions more than 10 cm in diameter are seldom seen. It was described for the first time by Devergia in 1857 and its lesions are the result of the confluence and peripheral extension of minute vescicles and papules. In the acute phase the lesions consist of erythematous patches associated with severe itching which results in loss of sleep and restlessness. These patches are more often located on the extensor surfaces of the limbs and on the face, but also the trunk can be involved. In a five year period between 1997 and 2002, 2830 out patients affected by eczema were referred to the pediatric department of our dermatology clinic. 245 of these (8.6% of the patients with eczema), presented the clinical appearance of nummular eczema. In 18 patients only one lesion was present, while in the other 227 patients lesions were multiple. The patients consisted of 153 males (65%) and 92 females (35%). In our patients the onset of clinical manifestations was between 40 days of life and 12 years, 200 of whom showed a higher prevalence in the first 2 years of life. In 57 of our cases an adequate follow-up was not possible. In the other 188 patients, 136 children (72.3%) were affected by atopic dermatitis, 7 had a contact dermatitis and in 45 cases etiology could not be established.

Keratoconus and Atopic Dermatitis: a Puzzling Problem

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Keratoconus (K) is a disease characterized by thinning and ectasia of the central cornea. The association with atopy has been reported on several occasions. In a study of 182 cases of K a history of atopy was found in 35% compared with 12% in the controls. The serum IgE was significantly raised in K and markedly so in atopic patients [1]. In 162 K patients, the prevalence of asthma was from 0.4% to 1% in the control group to 17.9% in the K group and the incidence of hay fever in K patients was found to be 35.7% [2]. However in a study on 2723 patients, atopy was not statistically related to outcome of K [3] and in 240 cases of atopic dermatitis K was detected only in 1.3%, of cases [4] or considered non specific [5]. In addition, a recent study suggests that the most significant cause of K is eye rubbing, while atopy may contribute probably via eye rubbing associated with the itch [6]. Different hypothesis state that there is abnormal processing of the free radicals and superoxides within the K corneas [7]. Indeed in K, corneal levels of extracellular superoxide dismutase were half those in the controls [8] and K corneas showed evidence of oxidative damage from cytotoxic byproducts generated by lipid peroxidation and the nitric oxide pathway [9] suggesting that K corneas do not process reactive oxygen species normally, which may play a major role. This fact could explain success of antioxidant treatment (selenomethionine and vitamin E) in those patients [10].

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Marginal Vesiculopustular Band of the Sole Occured in Remission Phase of Severe Atopic Dermatitis

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Atopic dermatitis (AD) is characterized by the typical morphology and distribution. In adults, the eruption involves the classic antecubital and popliteal fossae, the front sides of the neck, the forehead, and the area around eyes. Flares of atopic dermatitis are commonly triggered by exposure to antigens, acute infection and emotional upsets, and result in the wide spread type of involvement. The intensive therapies with topical corticosteroid and systemic anti-allergic drugs control the skin lesions around a week later. In contrast to the improved skin lesions, newly developed vesiculopustular lesions distributed along the margin of the sole, especially median side. A biopsy specimen revealed an intraepidermal large spongiotic vesicle with neutrophil and eosinophil infiltration. These lesions were commonly observed in the AD cases with systemic flare up (5 of 5 cases with systemic exacerbation), but not in the less involved milder cases. The pathogenesis of these lesions are obscure now. Around 30% of the atopic individuals have ichthyosis. The margin of the sole is a transit zone from the hypohidrotic to hyperhidrotic skin. Dyshidrosis may be involved the pathogenesis of these lesions.

Lichen Amyloidosis Associated with Atopic Dermatitis

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A 40-year-old man, father of an 8-year-old girl affected by atopic dermatitis (AD) since the age of 6 months, referred to us for papular pruriginous lesions. The father had suffered from AD since early childhood and from allergic asthma since the age of 8 years. Clinical examination revealed tiny, dome-shaped papules on the lichenified skin of the pretibial regions and the antecubital fossae of both legs. Crops of similar papules were found on the back, shoulders and buttocks. Two biopsies of papules were performed and histology showed hyperkeratosis and acanthosis of the epidermis and deposits of amyloid in the papillary dermis. A diagnosis of lichen amyloidosis (LA) was made. Family history revealed that the man's father had suffered from systemic amyloidosis with cardiac involvement secondary to multiple myeloma without cutaneous involvement since the age of 63. One year after he had died of cardiac shock. No other members of the family were affected by systemic or cutaneous amyloidosis. Association between LA and concomitant atopic respiratory diseases has been previously reported in the literature and recently a case of LA associated with AD has been described. An association between persistent scratching and genetic factors has been proposed in the etiology of cutaneous amyloidosis. The presence of a member affected by systemic amyloidosis and of another with LA and atopy is a very particular association never reported in the literature, to the best of our knowledge.

Nocturnal Itch and Sleep Disturbance of Atopic Dermatitis

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Itching is the major symptom of atopic dermatitis (AD) and the resultant scratching apparently worsens the skin lesion. It is known that itch worsens and the patients scratch severely during the night. We have been measuring nocturnal scratching of AD patients using an infrared video camera (Br J Dermatol 141:82–6, 1999) and a wrist activity monitor (Br J Dermatol 144:305–9, 2001). Scratching time (total duration of time spent in scratching) correlated well with the severity of the disease, and decreased in response to the treatment of AD. The video recordings gave the physicians true images of how severely patients scratch during the night. Itch interferes with sleep in patients with severe AD. To investigate further the details of sleep disturbances in AD, we recorded polysomnography (PSG) in 6 adult patients of varying severity. In one patient with mild AD, almost normal sleep both in quality and quantity was observed, while in the patients with moderate and severe AD sleep was disturbed according to the severity. Sleep efficiency was reduced to 50 to 70% of normal in these groups. Scratching was less frequent in deep stages of sleep. The PSG study showed that sleep was disturbed in proportion to the clinical severity of AD. Scratching took place mostly in the early hours of the night. The triggering factor of itch during this period should be sought for better sleep and better control of AD.

Atopic Dermatisis: How Does it Affect the Family?

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Atopic Dermatitis (AD), for its characteristics - early onset, chronic and recurrent course, rising prevalence- remarkably influences the life quality of Italian families within many contexts, among which the economic one. The group sample of this study is made of 100 subjects, males and females, hospitalized with an AD diagnosis, subdivided by age differentiation in two groups of 50 subjects (1–6; 7–12 yrs old); and their related families. Objectives of our study were (a) to evaluate the AD impact, as a chronic disease, on the patient's family; (b) to observe in patients and in their families common behaviors and/or characteristics; and (c) to identify the economic expense of the disease and its "weight" on the family budget. The methods used were a Parents Questionnaire, to detect the family's most significant behaviors and psychological characteristics; an Expenses Questionnaire, to identify the economic expense of the disease, subdivided in monthly amount, annual amount and singular purchase; and the SCORAD index, for a standardized evaluation of the AD severity. We display the related outcome data, underlining how dysphoric feelings observed in parents interfere with the medical prescription compliance and how the disease expenses do not appear to be directly correlated with the gravity of the dermopathy, but with other elements, particularly with those dysphoric feelings.

A Study to Determine the Short-Term Efficacy of Wet Wrap Dressings as a Treatment for Moderately Severe Atopic Eczema in Children

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Background: The wet wrap dressing technique was developed and has been progressively modified at Great Ormond Street Childrens Hospital NHS Trust, London. It is an effective means of controlling more severe or generalised atopic eczema which has failed to be controlled with a simpler regime and can be a valuable adjuvant therapy.

Objective: To establish superior short-term efficacy & safety of wet wrap dressings applied over a mild topical corticosteroid in moderate-severe childhood atopic eczema compared either to the same topical corticosteroid alone or to identical wet wrap dressings applied over emollient alone.

Methods: Children whose eczema could be objectively characterised as moderately severe or severe were recruited from the outpatient department and ward admissions. All patients had failed to respond adequately to standard topical therapy with emollients, weak topical corticosteroid and oral anti-histamines. Patients treated with oral or inhaled corticosteroid or systemic antibiotic in the preceding week were required to complete a one-week run in period before entry into the trial. They were randomised to receive treatment with wet-wrap dressings & emollient, wet wrap dressings with topical corticosteroid or topical corticosteroid alone. Response to reatment was assessed using 2 validated scoring systems (SASSAD, GOS score), haematological, biochemical and immunological assays. Asessments were conducted one week apart by a single blinded investigator.

Results: 37 patients (14m, 23f; mean age 7.2 yrs, range 3–15 yrs) were randomised to one of 3 treatment limbs. Individuals treated with wet wraps & corticosteroid enjoyed a substantially better & clinically valuable therapeutic response when compared to either of the other 2 groups. There was no evidence of haematological, renal or hepatic toxicity in any of the 3 groups.

Conclusion: Treatment for 1 week with wet wrap dressings and topical corticosteroid gave significant improvements in eczema scores, when compared to treatment with either topical corticosteroid alone or wet wrap dressings & emollient. Children found wet wrap dressings acceptable whilst their parents considered them a worthwhile treatment. The advent of wet wrap dressings as a treatment for atopic eczema in children has provided a substantial improvement in the provision of short-term relief of symptoms. It is the authors opinion that this treatment is frequently underused.

Efficacy of 0.03% Tacrolimus Ointment in Patients With Atopic Dermatitis of the Head and Neck

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Atopic dermatitis (AD) is an inflammatory skin disease with chronically relapsing course. Tacrolimus (FK506) is a novel immunomodulatory agent exerting its effects by acting on the signal transduction pathways inside T cells and inhibiting gene transcription. Unlike topical corticosteroids, tacrolimus ointment doses not cause skin atropy. We studied the open clinical efficacy of tacrolimus for patients with AD of the head and neck. Twelve patients with atopic dermatitis of the face and neck applied with tacrolimus ointment 2 times a day. Treatment efficacy was evaluated using the average subjective satisfaction scores for each symptom and the global clinical response. In addition, the SCORAD (Scoring AD) index of the head and neck was adopted to evaluate the severity of AD as objectively as possible. Most of patients (10 of 12 patients) had remarkably improved when applying with tacrolimus objectively or subjectively. Significant effects were observed after 1 week of application with tacrolimus. The side effects such as burning (50%) or itching sensation (50%) were developed, but well tolerated to continue the study. Conclusively, the topical application of tacrolimus is an effective regimen for the treatment of atopic dermatitis of the head and neck.

Insight into Genetics of Atopic Dermatitis: Future Approaches and Directions

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Atopic dermatitis (AD) is a chronic infiammatory skin disease typified by itchy inflamed skin, associated with cutaneous erythema and severe pruritus and characterized by an onset mainly in early childhood. In developed countries the prevalence of AD is approximately 15%, with a strong increase during the last century. AD is a multifactorial disease triggered by both genetic and environmental risk factors and twin studies indicate that the genetic contribution is substantial. Many genomewide linkage studies mapped a number of susceptibility regions on chromosomes 1q21 (ATOD2), 3q21 (ATOD1), 5q31-q33 (ATOD6), 13q12-q14 (ATOD5), 17q25 (ATOD4), 20p (ATOD3). Three of these loci (1q21, 17q25 and 20p) are closely coincident with psoriasis susceptibility loci, although AD is quite distinct from psoriasis and rarely the two diseases occur together in the same patient. Probably AD is influenced by genes that regulate the dermal responses to environmental factors independently from atopic mechanisms. Preliminary genetic studies have identified genes or clusters of genes that are expressed in the outermost layer of the skin to be just as important as genes that may modify the atopic process. In addition recent studies showed five overlapping chromosomal regions (1q21, 2q33, 5q31.1–q33.1, and 6p21, 11q13) that co-localize with disease loci for the following diseases: diabetes, asthma, atopic dermatitis, osteoporosis, and inflammatory bowel disease (IBD). It is most likely that the same predisposing genes are involved in different complex diseases. Finally, association studies approach based on maps of single nucleotide polymorphisms can be lead to the identification of the genes involved in pathogenesis of AD. Identification of genes or cluster of genes immediately leads to knowledge of relevant proteins and any understanding of the molecular and physiological basis of disease.

The Global Initiative for Asthma (GINA) Guidelines: An Update

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Asthma is a major cause of chronic morbidity and mortality throughout the world. The Global Initiative for Asthma (GINA) was created to increase worldwide awareness of asthma and to make recommendations for prevention and management in order to encourage a concerted worldwide effort. The presentation provides an overview of the 2002 GINA recommendations and some of the scientific evidence on which they are founded. These guidelines redefine asthma, placing greater emphasis on the key role of the underlying inflammatory response in asthma. This definition calls for new approaches to clinical diagnosis, prevention, and management of the disorder, which are presented here. Also described are newer clinical findings that will impact future iterations of GINA recommendations.

Allergic Rhinitis Comorbities: Conjunctivitis

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Allergic rhinitis is an inflammatory disorder of the nose induced by an IgE-mediated reaction following allergen exposure of the mucous membranes lining the nose. Allergic rhinitis is still increasing in prevalence affecting 25–35% of the population. It is characterised by rhinorrhoea, itching, sneezing and nasal obstruction. 33–56% of patients with allergic rhinitis experience symptoms of allergic conjunctivitis. Allergic rhinitis results from IgE-mediated allergy, associated with cellular inflammation of the nasal mucosa (eosinophilic inflammation, enhanced expression of endothelial and epithelial adhesion molecules, cytokines and chemokines). A continuous low-dose allergen exposure involves a mucosal minimal persistent inflammation (MPI). The clinical history and in vivo or in vitro tests for detection of specific IgE confirm the diagnosis of allergic rhinitis. Treatment of allergic rhinitis comprises avoidance of the allergens, oral/nasal antihistamines, decongestants, chromones, and intranasal/oral corticosteroids. It is advised to follow 'a stepwise approach'. Allergic conjunctivitis is the most common ocular allergic disorder, affecting 5–22% of the population. Ocular allergy involves typical symptoms (itching, watery, stringy or ropy discharge and redness, periorbital oedema) and recurrent/intermittent/persistent episodes. Symptoms can show variation due to fluctuation in allergen load. Treatment of allergic conjunctivitis includes oral/eyedrop antihistamines, topical cromones and topical corticosteroids. A combined antihistamine and ocular mast cell stabiliser is more effective at relieving symptoms compared with either antihistamines or chromones alone. Oral treatment with antihistamines modifies both nasal and ocular symptoms and provides effective control throughout a 24 h period with very high tolerability. Specific immunotherapy, when indicated, plays a role by changing the natural history of rhino-conjunctival associated disease. Topical corticosteroids are appropriate for short-term use in severe conditions only. All this matter has been recently summarized in the ARIA-WAO-WHO document. New medications against other inflammatory mediators may be the next significant advance in this model of treatment. Partially supported by A.R.M.I.A.

Double-Blind Placebo Controlled (DBPCFC) Cake Challenges for Hidden Egg in Older Children with Atopic Eczema

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Food allergy can be a significant problem in young children (<2years) with atopic eczema (AE). (1) Although allergy to peanuts and fish tend to be lifelong, tolerance to other allergens such as milk and eggs usually develops within the first five years of life. Only a minority of the older children has persistent problems to these allergens. In the younger child, the specific IgE level to eggs can be a useful guide to the predictor of sensitivity. (2) In addition, some of the egg allergic children can tolerate hidden eggs, for example in cakes & sweets, although react to eggs 'as is'. This study aimed to: 1) challenge (DBPCFC) older egg allergic children with AE to 'hidden' egg 2) examine whether the specific IgE level is a useful predictor of outcome. Twenty five children (14 girls: 11 boys) aged 6–13 years (mean 8.99±2.25) were included in the study. All were allergic to eggs having had a previous positive DBPCFC to eggs. The total specific IgE ranged from 0–>5000 ku/l (mean 706.3±637.6) with a specific IgE to egg from 0–41.7 ku/l (mean 6.04±8.77). All attended the Day Unit for the challenge, where resuscitation facilities are available. Two cakes (one egg free) were tested: children were given incremental amounts of one in the morning and the other one in the afternoon. 18/25 (72%) of the challenges were negative allowing unnecessary dietary restrictions to be lifted. Of the seven positive challenges: 3 were purely cutaneous (urticaria & facial erythema). One was gastro-intestinal with abdominal pain & nausea. Two were more significant, with only tiny amounts of cake leading to respiratory problems in one child (which settled spontaneously) and to pallor and a choking sensation in the second, that settled with oral chlorpheniramine. In contrast to younger children, neither the total nor specific IgE levels were helpful in determining outcome. The mean total IgE was 592 ku/l (±575) v 718 (±820) with a specific IgE to egg of 6.0 ku/l (±9.6) v 5.0 (±7.1) in the tolerant group & sensitive group respectively. Dietary restrictions become more irksome as children grow older and it is important that unnecessary dietary restrictions are lifted. However, some children remain sensitive to eggs and it is useful to establish safely whether this applies to all egg products or whether 'hidden egg' can be tolerated.

1) Lever R., 2001 The role of food in atopic eczema J Am Acad Dermatol 45 S57-60 Morton J, Waugh P, Lever R Double-blind food challenges in children with atopic eczema Poster Presentation Scottish NHS Conference 2000

Antinuclear Antibodies in Patients with Atopic Dermatitis

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Background: So far several autoantibodies have detected in the patients with atopic dermatitis (AD). Twenty to thirty percentages of AD patients showed positive antinuclear antibodies (ANA). However, the role of autoantibody in the pathogenesis of AD has not yet been fully elucidated. Recently we have treated with AD complicated with systemic lupus erythematosus (SLE).

Objective: The aim was to re-elucidate the prevalence of ANA in patients with AD and the difference between ANA(+) and ANA(−) patients with AD.

Methods: Disease severity, photosensitivity, ANA, blood eosinophil count, total IgE levels, specific IgE antibodies to enviromental antigens were checked in 64 patients with AD. The relationship between ANA(+) and ANA (−) patients with AD were statistically evaluated.

Results & Conclusion: Eighteen of 64 (28.1%) AD showed positive ANA at titers ranging from 20X to 640X. Eight of 37 (21.6%) and 10 of 27 (37%) AD with ANA(+) were male and female respectively. Positive ANA had relevance to photosensitivity and severe facial lesions in patients with AD.

Atopic Dermatitis Complicated with Systemic Lupus Erythematosus

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The relationship between allergic and autoimmune disease remains to be uncovered. So far there are a few case reports of atopic dermatitis (AD) complicated with systemic lupus erythematosus (SLE). Case1: A 25-years-old male, who had suffered AD since 5 years of age, was admitted to our hospital complaining of butterfly erythema. Laboratory test gave the following results: leukopenia, antinuclear antibody (ANA)(n<20X), 640X< (Sp); anti-ssDNA (n<25), 36.9 AU/ml; anti-RNP (n<10), 500< U/ml; anti-SSA (n<10), 27.4 U/ml; CH50 (n=32–44), 10.7 IU/ml; C3 (n=80–150), 51 mg/dl; C4 (n=15–40), 7 mg/dl, IgE (n<250) 9400 IU/ml and proteinuria (0.3 g/day). Membranous nephropathy stage III was diagnosed. Case2: A 27-years-old male, who had suffered mild AD since childhood, was admitted complaining of facial edema. Laboratory test gave the following results: leukopenia, hypoalbuminemia, liver distrubance, renal disorder, ANA 320X< (Ho+Sp+Nu); anti-ssDNA, 37.5 AU/ml; anti-dsDNA (n<12), 137.2 IU/ml; anti-SSA, 86.2 U/ml; CH50, <6.3 IU/ml; C3, 28 mg/dl; C4, 3 mg/dl; IgE, 140 IU/ml and proteinuria (4.1 g/day). Lupus nephritis IV b was diagnosed. Histopathological findings of skin showed slight liquefaction degeneration of the basal layer, and lupus band test was positive in both cases. Discussion: In our department, three patients who had suffered from AD (15%) in 20 of SLE patients. It is well known that enhanced Th2 cytokine profile is observed in AD and SLE. It seems that some part of common immune dysfunction underlie in etiology of AD and SLE.