Background

Atopic dermatitis is an inflammatory skin condition seen in patients with characteristic eczematous lesions clinically. The prevalence in children is 10-20% and in adults is about 2%. Atopy is a familial predisposition to develop hay fever, asthma and atopic dermatitis in association with high levels of serum IgE in most patients. Atopic dermatitis is likely to result from a combination of factors, including genetic susceptibility, environment, skin barrier defects, infections and immunologic factors. Importance of immune defect is illustrated by observation of atopic dermatitis being transferred during bone marrow transplantation.

The Role of Th2 Cells

The immunoglobulin isotype class switching to production of IgE is induced by IL-4 and IL-13 which are Th2 cytokines, implicating Th2 cells in the pathogenesis of atopy and atopic dermatitis. Increased numbers of activated CLA+ CD4 T cells are found in acute lesions of atopic dermatitis, with elevated levels of Th2 (IL-4, IL-5, IL-13) and decreased Th1 (IFN-γ) cytokines. Decreased CCR6-expressing (Th1-associated chemokine receptor) and increased CCR4-expressing (Th2-associated) T cells are found in lesions of atopic dermatitis. There was one report of increased IL-17 in acute skin lesions of atopic dermatitis compared with chronic lesions or uninvolved skin, but the role for Th-17 cells is not clear.

Other Immunologic Abnormalities in Atopic Dermatitis

There is increased expression of FcεRI on dendritic cells in skin and monocytes in blood. There is increased expression of cAMP-phosphodiesterase, increased PGE2 and increased IL-10 production by monocytes. There are B cells expressed high levels of CD86 (costimulatory molecule) and there are high levels of TSLP (thymic stromal lymphopoietin) in keratinocytes. TSLP activates dendritic cells to prime naive CD4 T cells to produce Th2 cytokines.


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Update in Paediatric Dermatology

(I) Current Concepts in Atopic Dermatitis

Speaker: Christina A Herrick, MD, PhD, FAAD;
Department of Dermatology, Yale University School of Medicine

Background

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The Role of Toll-like Receptor 2 (TLR2)

1. Toll-like receptor 2 (TLR2) is one member of a family of innate immune system receptors referred to as the “toll-like receptors”. They are involved in recognition of conserved molecular patterns on microbes and in alerting the immune system to invading pathogens. Missense mutation in TLR2 gene was found with increased frequency in atopic dermatitis which correlated with greater severity of atopic dermatitis, higher IgE and greater susceptibility to Staphylococcus aureus.

2. Filaggrin is an integral component of the keratin cytoskeleton and is critical for epidermal barrier function. The gene is localised to chromosome 1q21. Two common loss-of-function mutations in the gene encoding filaggrin were recently found to be associated with an increased risk of moderate-severe atopic dermatitis, as well as asthma that was associated with atopic dermatitis.

The Relationship Between Allergen Specific IgE Responses and the Skin Lesions of Atopic Dermatitis

The severity of atopic dermatitis and early onset in infancy correlate with serum IgE levels. Both are risk factors for development of upper airway disease. It is proposed that IgE on the surface of Langerhans cells in the skin can act to focus antigen presentation and facilitate T cell activation; this would explain how exposure to specific allergens might trigger flares of atopic dermatitis.

Recent well-controlled studies argue against a role for dust mites in the flare of atopic dermatitis, while food triggers may play a role in a small percentage of patients with flares of skin disease. It is believed that autoantigens may play a role especially in chronic skin lesions and IgE autoantibodies directed against human skin proteins have been described.

The Role of Staphylococcus Aureus

There is increased colonisation of skin lesions in atopic dermatitis with Staphylococcus aureus (S. aureus) and an antibiotic is useful in treatment. The release of superantigens and α-toxin by S. aureus exacerbates inflammation. α-toxin can also induce release of...
TNF-α, arachidonic acid and platelet-activating factor. In atopic dermatitis, the skin lesion shows increased expression of S. aureus adhesins and these are induced by IL-4.

The Rising Incidence of Aatopic Disease: Does the Hygiene Hypothesis Explain it All?

The incidence of all atopic diseases doubled over the past 2-3 decades and the rate of rise suggested environmental influence. "Hygiene Hypothesis" postulated that increased atopic disease is a result of decreased exposure to infections in early life; based on a study(or studies) showing increased number of siblings is protective for development of allergies. Further studies have supported the observation that early attendance at daycare (another surrogate marker for infectious exposure) is also protective for development of atopy. The original theory put forth was that exposure to infections stimulated Th1 immune responses, thereby suppresses Th2 responses which are responsible for atopic dermatitis; i.e., without the Th1 inducing infections, Th2 responses were left unopposed.

More recently, it has been proposed that a failure to develop "regulatory T cells" may account for increases in both allergic and autoimmune diseases. Regulatory T cells develop as part of the natural response to infections, helping to contain the pathogen-directed inflammatory response. These cells are then capable of suppressing both unwanted Th1 and Th2 type immune responses.

Interestingly, patients with IPEX syndrome (immune dysregulation, polyendocrinopathy, enteropathy and X-linked inheritance) have a mutation in FOXP3. This gene has been shown to be critical for development of CD25+ T regulatory cells. These patients display both autoimmune disease and eczema.

(II) Kawasaki Disease

Emergency Paediatric Dermatology
Speaker: Norman Levine, MD, FAAD; Tucson, Arizona

Paediatric Diagnostic Update
Speaker: Robert Sidbury, MD; Dermatology Program, Department of Paediatrics, Division of Immunology, Children's Hospital Boston, Harvard Medical School

Kawasaki disease is one of the leading causes of paediatric acquired heart disease. It is also a potential risk for adult ischaemic heart disease and sudden death in young adults. It occurs most commonly in Asians and Japanese. The cause is unknown but multiple theories were suggested including adenovirus infection, novel human coronavirus infection and environmental pollens.

The pathogenesis involves inflammation of the arteries with proteinases and cytokines release. There is a possible role of IgA secreting plasma cells related to respiratory viral infection. Coronary artery lesions developed and resulted in aneurysmal dilatation and later stenosis. There is premature atherosclerosis.

The classical clinical diagnostic criteria are fever for more than five days. In addition there are cervical lymphadenopathy (only 15% in US), non-exudative conjunctivitis (87%), crusty lip and strawberry tongue (90%), truncal exanthem (85%), and palmoplantar erythema and desquamation (90%). The diagnosis is unusual in patients with age more than 10 years. However it can also be seen in adults with similar clinical features. Adult patients have more hepatitis (65% vs. 10%) and arthralgia (61% vs. 25%) than children, but there are less coronary aneurysms (5% vs. 20%) and thrombocytosis (55% vs. 100%) in adults than children. If the clinical features are incomplete, there are some dermato logic findings useful for diagnosis, such as bilateral groin desquamation in acute phase (days 1-4) and fingertip desquamation in subacute phase (days 8-12). There may be micropustular eruption, reactivation of BCG and flare of psoriasis.

Laboratory findings include elevated ESR, CRP and leucocytes. There may be echocardiographic findings of coronary aneurysm.

The principal management is IVlg and aspirin. IVlg is given in dose of 1-2g/kg body weight in single infusion. Repeat of therapy is necessary if there is evidence of persistent inflammation. High dose aspirin (50-100mg/kg body weight) must be given within 10 days of fever onset for best effect.

Recent studies have mixed results regarding the use of systemic corticosteroid as adjunct to IVlg therapy in Kawasaki disease. The addition of steroid to IVlg compared with IVlg alone improves outcome in one study with decreased number of aneurysms, shorter duration of fever, faster normalisation of laboratory results and fewer initial treatment failures. In another study, however, there is no difference in outcomes between the patients with or without corticosteroid as adjunctive therapy.

About 10-15% patients with Kawasaki disease fail initial therapy of IVlg infusion alone and 3-4% fail second dose of IVlg. These non-responders have refractory Kawasaki disease and they usually have similar baseline characteristics with the responders. These patients have higher risks of coronary artery aneurysm and later complications. Second line treatment for refractory disease such as cyclophosphamide, plasma exchange, cyclosporine and infliximab have been reported but not yet supported by randomised trials.

References