REVIEW ARTICLE

Atopic dermatitis revisited

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ABSTRACT

Atopic dermatitis is a common, chronic, relapsing dermatosis affecting infants and children, more common in urban areas. It is caused by a interplay of various factors like- atopy, genetic predisposition, immune dysregulation, environmental factors and food allergies. Atopic dermatitis is believed to be a part of the 'Atopic March'. The most widely accepted criteria for the diagnosis are those proposed by Hanifin and Rajka. The diagnosis can be supported by various laboratory tests like serum IgE levels, specific serum Ig E levels, Skin prick test, etc, but there is no laboratory gold standard for the diagnosis. Conventional treatment options include general measures, wet dressings, topical corticosteroids and antihistamines. Recently, topical calcineurin inhibitors, antibiotics and immunosupressants have been added to the treatment regimens. Treatment improves the quality of life of the patient and prevents complications but the disease tends to be chronic and relapsing.

KEY WORDS: Atopic dermatitis, atopy, atopic march, hygiene hypothesis

ATOPIC DERMATITIS REVISITED

Atopic dermatitis, also known as atopic eczema, is an itchy, chronic or chronically relapsing, inflammatory skin condition, characterized by itchy papules (occasionally vesicles in infants) followed by development of excoriations and lichenification, with a typical flexural distribution. It is often associated with elevated serum IgE levels and a personal or family history of type I allergies, allergic rhinitis, and asthma.[1]

Atopic dermatitis (AD) can be categorized into the extrinsic and intrinsic types. Extrinsic or allergic AD shows high total serum IgE levels and the presence of specific IgE for environmental and food allergens, whereas intrinsic or non-allergic AD exhibits normal total IgE values and the absence of specific IgE. While extrinsic AD is the classical type with high prevalence, the incidence of intrinsic AD is approximately 20% with female predominance.[2]

EPIDEMIOLOGY

Atopic dermatitis is considered to be a disease of the Westernized world. The prevalence of AD is on the rise; in the United States, the lifetime prevalence in children born after 1980 is 15% to 20%,[3,4] a 3- to 4-fold increase compared with the 5% reported in school-aged children in 1950s.[3] In International Study of Asthma and Allergies in Childhood (ISSAC) phase 3, prevelance of atopic

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diseases has been estimated in more than a million children from around 100 countries and the figures suggest that the incidence of AD is rising. In the age group of 6-7 years, current symptom of eczema was detected in 2.7 % of children, severe eczema in 0.3% and lifetime prevalence was 4.4%. In the age group 13-14 years, the corresponding values were 3.6%, 0.4% and 8.9%, respectively.[5] India ,a developing country is believed to be an area with low prevalence (<5%) of AD. A study from Bihar reported an incidence of 0.38%,[6] while the prevalence of AD in Northern and Eastern part is reported to be 0.42% and 0.55% respectively.[7,8]

AETIOPATHOGENESIS

AD is believed to be caused by a complex interplay of several environmental factors, infective factors, behavioral factors, immune dysfunction and skin barrier disruption in genetically predisposed individuals.

Genetics

The increased incidence of allergic dermatitis in children is associated with the prevalence of atopic disease in their parents; approximately 27% of children whose parents are not atopic develop AD versus 38% and 50% respectively of children with one or two affected parents.[9] A parental history of atopic respiratory disease increases the risk significantly more for IgE-associated than non-IgE associated AD. A number of studies confirm the fact that the risk of children developing atopy is significantly higher when the mother is atopic than when the father is.[10] Twin studies have shown a concordance of 85% for AD in monozygotic twins as compared to 20% in dizygotic twins.[11]

Genome screens have identified susceptibility loci on 1q21,[12] 3p24-22,[13] 3q21[14] and 17q25[12] in association with atopic dermatitis. 1q21 locus contains genes that encode Filaggrin (filament aggregating protein) and loss-of-function mutations in this gene is a very strong predisposing factor for atopic dermatitis and asthma accompanying AD.[15]

Immune dysregulation

T lymphocytes

The naïve helper T cells or CD4+ T cells can differentiate into either Th1 or Th2 subtype, depending upon the cytokine environment at the time of interaction between Th0 cells and antigen-presenting cells (APCs), as well as costimulatory signals. Th1 lymphocytes produce interleukin 2 (IL-2), interferon gamma (IFN-γ), and tumor necrosis factor (TNF) activate macrophages and promote delayed hypersensitivity reactions.[16,17] Conversely, Th2 lymphocytes produce IL-4, IL-5, IL-6, IL-10, and IL-13, which signal B lymphocytes to produce IgE, activate mast cells and eosinophils, and promote type 1 hypersensitivity reactions.[16-19] In fetal life, Th2 response predominates due to low basal levels of interferon γ. In the post-natal period, as the production of interferon γ is increased, the shift occurs towards Th1 response. However, in infants who develop AD, Th2 response continues to predominate because of low levels of interferon- γ reflecting an intrinsic defect in T-cell function. It is now proposed that patients with AD exhibit a biphasic helper T-cell pattern in which Th2 immune responses appear early in the acute stage, but switch to a more Th1-like profile as chronic lesions emerge.[20] Th2-type cytokines predominate during the acute phase, in part because of a relative increase in IL-4 levels and no change or decreases in IFN-γ levels and stimulate eosinophils, which produce IL-12. In turn, IL-12 activates Th1 and Th0 cells and pro-

motes increased production of IFN- γ, which inhibits TH2 responses and helps to maintain the AD lesion over an extended period.[21]

Immunoglobulins

Majority of patients with AD exhibit hyperproduction of IgE, particularly during the early or acute disease, due to enhanced Th2 response. About 80% of patients with atopic dermatitis have increased amounts of total IgE. If dermatitis is the only clinical manifestation of atopy, the amounts of total IgE may be little above the normal range[22,23] and the patients show no anaphylactic sensitivity to environmental antigens. If there is concomitant asthma or allergic rhinitis the concentrations of IgE may be very much above normal.[22,23] In a study, Shah et al found that an elevated cord blood IgE level modestly correlates with elevated total IgE and is associated with a slightly higher likelihood of allergic sensitization among young adults. However, cord IgE is not a strong predictor of clinical allergic disorders in this age group.[24]

Eosinophils and monocytes/macrophages

Skin infiltration by eosinophils and macrophages, and the consequent production of IL-12, appears to be important in the chronic inflammatory response associated with AD lesions. Eosinophilia in patients of AD is due to increased migratory responsiveness to various chemotaxins, exposure to IL-5, IL-3, and granulocyte-macrophage colony-stimulating factor (GM-CSF) from Th2 lymphocytes which act as chemotactic factors and delayed eosinophil apoptosis due to the production of IL-5.[16] Similarly, IL-10 also may play an important role in the regulation of monocyte survival and macrophage development by inhibiting GM-CSF related antiapoptotic effects early in lesion development.[16]

Skin barrier dysfunction

Intact Stratum corneum serves as a permeability barrier between the body and the external environment, impairment of which is manifested by increased transepidermal water loss and diminished water-binding capacity, thus causing the associated dryness and intense pruritus of AD.[25] The levels of ceramides are reduced in atopics, due to over expression of the enzyme that hydrolyzes the ceramide precursor sphingomyelin. High levels of GM-CSF promote and maintain inflammation through induction of Langhan cell generation, maturation and increased antigen-presenting capacity and is also responsible for hyperproliferation and apoptosis of keratinocytes.[26]

Staph. aureus colonizes both lesional and nonlesional skin in about 90% of atopic dermatitis patients. It can exacerbate or perpetuate skin inflammation by secreting toxins with superantigenic properties leading to the proliferation and activation of T cells & by stimulating keratinocytes to release several immunomodulatory proteins, including cytolytic α protein. These protein products and toxins released further promote inflammation also prevent keratinocytes from producing the antimicrobial peptides β-defensins and cathelicidins sufficient to kill S. aureus.[27]

Environmental factors

Environmental factors have been found to play a key role in the development of AD in genetically predisposed individuals. AD is more prevalent in urban rather than rural areas, attributed to industrialization, pollution, stress and changed lifestyle. In general, AD is known to aggravate during

winters as dry cold weather aggravates the dryness and xerosis of atopic skin. On the other hand, a very humid atmosphere lowers the threshold for itching which is usually very intense.

Several studies have confirmed the role of inhaled allergens or aeroallergens in exacerbating not only respiratory allergies but also atopic eczema. Aeroallergens like house dust mite, pollen, molds and animal dander have been implicated and supported by the observation that alleviation of AD occurs with dust-free environment and immunotherapy.[28,29]

The relationship between decreased exposure to microbial antigens associated with a western lifestyle and the increasing severity and prevalence of atopic diseases has become to be known as the ***'hygiene hypothesis'*** .It had its origin in a small report published by Strachan in 1989.[30] He observed that the incidence of eczema & hay fever was inversely related to the number of children in the household and proposed that a lower incidence of infection in early childhood, transmitted by unhygienic contact with older siblings or acquired prenatally could be a cause of the rise in allergic diseases.[30] It could be explained on the basis that innate immune cells, such as macrophages and dendritic cells, express pattern recognition receptors (PRRs) that recognize pathogen-associated molecular patterns (PAMPs) associated with microorganisms. Activation of these receptors induces a Th-1 type response. Lack of microbial antigen-induced immune deviation from the Th-2 to Th-1 type profile could explain the development of enhanced Th-2 cell responses to allergens. Further, the range of microbes postulated as responsible widened to include not only pathogens capable of causing infection, but also non-pathogenic types or strains (commensals and environmental strains), and components of microbes such as bacterial endotoxins.

The most consistent evidence for an inverse relationship between exposure to a specific pathogen and atopy is shown by Hepatitis A virus (HAV), an infection associated with large family size and low socio-economic status. Matricardi et al [31] and Bodner et al[32] also found seropositivity for HAV in the general population was associated with 40% and 37% reductions in atopy, respectively. Another putative pathway for a protective effect of microbial exposure against atopy involves the bacterial flora of the gut. Bjorksten et al[33] found that the intestinal flora of allergic children differed from those with no allergies: aerobic bacteria, coliforms and Staphylococcus aureus were more common in the flora of allergic children. The non-allergic children had a greater prevalence of Lactobacilli and Bifidobacteria spp. in their gut flora. In a study by Eigenmann it was found that a combination of probiotics and prebiotics given from pregnancy until early infancy has a higher potential for protecting the infant from developing early manifestations of eczema than short administration of one specific organism.[34]

Infections

The increased incidence of a carriage state of Staph aureus in patients of AD has been a focus of interest. Exacerbation of AD is reported to be induced when the density of Staph aureus is greater than 106 Colony forming units/cm2. David and Cambridge suggested that as clinical signs of infection are not always apparent, it is advisable to try an oral antibiotic treatment in any child with AD not responding to standard treatment.[35]

Interestingly, human papillomavirus - induced warts, fungal infections, viruses (such as HSV1

and 2, vaccinia, coxsackie A and the pox virus of molluscum contagiosum) are also frequent pathogens causing, in some cases serious consequences.[36]

CLINICAL FEATURES

AD occurs slightly more frequently in females than males by a ratio of about 1.5:1.[37] The majority of cases, at least 60%, arise within the first year of life; the remainder appear in two peaks: age 2 to 12 years and from puberty into adulthood.[38] The cutaneous manifestations of atopy often represent the beginning of the atopic march. On the basis of several longitudinal studies, approximately half of AD patients will develop asthma, particularly with severe AD, and two thirds will develop allergic rhinitis further in life. Intense pruritus and cutaneous reactivity are the cardinal features of AD. Pruritus may be intermittent throughout the day but is usually worse in the early evening and night. Acute skin lesions are characterized by intensly pruritic, erythematous papules associated with excoriation, vesicles over erythematous skin and serous exudates. In chronic AD the features are thickened plaques of skin & lichenification. The dry atopic skin is another consistent feature.

The clinical manifestations of AD are divided into 3 phases according to the age distribution:

1. **Infantile phase-** (from birth to two years of age) It is characterized by intensely erythematous papules and vesicles, typically beginning on the cheeks and spreading to involve the forehead, scalp and trunk. Often, the napkin area is relatively spared. By the age of 8-10 months, as the child begins to crawl, the extensor aspect of extremities get involved.

2. **Childhood phase-** (from 2 years to puberty) The sites most characteristically involved are the elbow and knee flexures, sides of the neck, wrists and ankles. The sides of the neck may show a striking reticulate pigmentation, sometimes referred to as 'atopic dirty neck'.[39] On the other hand, some patients may show 'inverse' pattern, i.e, involvement of extensors & the distribution is said to be commoner in Asian or black children. Periorbital and perioral areas are involved, in contrast to infantile phase in which there is relative sparing of these areas. The erythematous and oedematous papules tend to be replaced by lichenification.

3. **Adult phase-** (from puberty onwards) The distribution of the lesions is again 'flexural' with involvement of face, neck, upper arms, back and dorsal aspect of hands and feet. The skin lesions show changes of chronic dermatitis, ie lichenification. Patients often complain of photosensitivity.

Other manifestations of atopic dermatitis include:

a. **Atopic hand eczema-** Hand eczema has been noted to occur in 70% of children with AD[40] and upto 57% of patients with juvenile palmar-plantar dermatosis.[41] A patchy, somewhat vesicular and lichenified eczema is common in children, while adults show a more diffuse, chronic lichenified eczema of the hands. The nails are often involved, resulting in coarse pitting and ridging.

b. **Nipple dermatitis-** Nipple dermatitis is noted in 12%–23% of patients with AD.[42] It is commoner in postpubertal girls. The very sensi-

tive areolar skin koebnerizes with the slightest rubbing or friction of clothing. It is frequently symmetrical, scaly, oozing, and papulovesicular, and it may extend onto the adjacent breast skin.

c. **Infra-auricular fissuring-** The infra-auricular fissuring has been deemed pathognomonic for AD and is considered as a bed side marker of disease severity.[43]

d. **Pityriasis alba-** It has been reported to occur in 20%-44% of atopic children, with or without other evidence of AD. Sites of predilection include the face, neck, and upper trunk.[44] These hypopigmented lesions become more apparent after UV exposure.

e. **Infantile seborrhoeic dermatitis-** It normally starts earlier than atopic dermatitis, and it may be possible to distinguish between the two conditions clinically. However, there are a number of children who present with what appears to be seborrhoeic dermatitis and then progress to typical atopic dermatitis.

f. **Allergic contact dermatitis-** Patients can develop sensitivity to a variety of contact allergens such as topical medicaments, including topical corticosteroids. There is also a risk of protein contact sensitivity, such as that associated with latex in rubber gloves.

g. **Lip-lick cheilitis-** Perioral eczema is quite common in children with AD. It is usually attributed to repeated lip licking, thumb sucking, dribbling or chapping.

h. **Food allergy-** A subset of patients with AD may have food induced aggravation. The commonest symptom in patients with food allergy is gastrointestinal symptoms (abdominal cramps or diarrhea), followed by respiratory symptoms (wheeze or bronchospasm). Skin symptoms occur third in frequency. Specific serum IgE levels may help in the identification of allergens.

i. **Allergic shiners-** Bluish-grey discoloration of periorbital skin ,occurs in 60% of atopic patients and in 38% of non-atopic individuals.[45]

j. **Dennie-morgan lines-** Symmetrical, prominent folds, extending from the medial aspect of the lower lid.

k. **Head-light sign-** Sparing of the nose in case of atopic eczema.

l. **Allergy salute-** Transverse nasal crease across the middle of dorsum of nose, due to repeated upward rubbing of nose.

m. **Hertoghe's sign-** Thinning or loss of lateral one-third of the eyebrows. This sign is significantly more frequent in patients with respiratory disease and AD.

n. **Alopecia areata-** Atopy has been reported to occur with an increased frequency in patients with alopecia areata. Atopic dermatitis is two to three times more common in patients with alopecia areata.[46]

DIAGNOSTIC CRITERIA FOR AD

Hanifin and Rajka introduced the first set of di-

agnostic criteria for AD. Later the U.K. Working Party's Diagnostic Criteria for AD were proposed using discriminatory features from the Hanifin and Rajka criteria in a questionnaire form. With regard to all the included validation studies, the U.K. diagnostic criteria have been validated the most, both in hospital- and in population-based settings. Unlike the Schulz - Larzen, Diepgen, Kang and Tian and ISAAC criteria, which have been validated only once or twice, other existing criteria such as the Lillehammer, Japanese Dermatology Association, Millennium and DARC have not yet been validated. Following are the U.K. refinement of Hanifin and Rajka's diagnostic criteria for AD:[47]

An itchy skin condition (or parental report of scratching or rubbing in a child)

Plus three or more of the following minor criteria:

1 Onset below age 2 years (not used if child is under 4 years)

2 History of skin crease involvement (including cheeks in children under 10 years)

3 History of a generally dry skin

4 Personal history of other atopic disease (or history of any atopic disease in a first degree relative in children under 4 years)

5 Visible flexural dermatitis (or dermatitis of cheeks/forehead and outer limbs in children under 4 years)

COMPLICATIONS

1. **Growth delay-** Prepubertal children with atopic dermatitis show features consistent with constitutional growth delay and the stunting can also be attributed to the corticosteroid therapy used in the treatment of AD.[48]

2. **Bacterial infections-** Repeated cutaneous infections with staphylococci or streptococci is common and are responsible for the flares in AD.

3. **Kaposi's varicelliform eruption-** In patients with AD, infection with herpes simplex virus can lead to an acute, generalized eruption of papulo-vesicular lesions, rupturing to form superficial erosions and crusting along with constitutional symptoms like high grade fever.[49]

4. **Ocular abnormalities-** The ocular manifestations can range from conjuctival irritation to keratoconus and cataract. Cataract occurs in up to 10% of the more severe adult and adolescent cases of AD patients. AD is a risk factor to develop both posterior and anterior subcapsular cataracts. There is a slightly increased probability of posterior subcapsular cataracts, however, anterior subcapsular cataracts are more specific to AD.[50]

5. **Psychosocial aspects-** When severe, AD can be extremely disabling, causing major psychological problems and in the case of a young child, be overwhelming to the entire family. In children, the most troublesome symptoms are itching, distress at bath time and sleep disturbances. This can lead to behavioural difficulties in severely affected children.

DIAGNOSIS

The diagnosis of AD is usually based on typical skin lesions along with personal or family history of atopy. SCORAD is a clinical tool used to assess the extent and severity of eczema (**SCOR-**

ing Atopic **D**ermatitis). It takes into account the body surface area involved, signs like- erythema, edema/population, oozing/crusting, scratch marks, skin thickening (lichenification) and dryness and subjective symptoms like itch and sleeplessness.[51]

Total Serum IgE levels are elevated in over 80% of patients with AD, though 20-40% of patients with AD may have normal IgE levels. There is a positive correlation between the extent and severity of disease and respiratory atopic disease.[52]

Specific IgE levels can be detected with help of RAST (radioallergosorbent test). The skin prick test (SPT), typically used by allergy specialists, is another means of detecting allergen- specific IgE (sIgE) antibodies. Both serum sIgE tests and SPT are sensitive and have similar diagnostic properties. Advantages of the SPT include immediate results visible to the patient/family and low cost compared with serum sIgE tests.[53] Also, some authors have found Atopic patch test to be more sensitive and specific method than SPT/sIgE in diagnosing delayed food allergy in children with AD.[54] However, there is no 'laboratory gold standard' for the diagnosis of AD.

MANAGEMENT

Atopic dermatitis is a chronic disease which must be managed rather than cured. A wide range of both topical and systemic agents are available for the treatment of AD. As with other diseases, 'treatment fatigue' can occur and adherence to treatment regimens can diminish over time, resulting in treatment failure. There is no standardized treatment protocol for AD, but in general, the treatment can be categorized into two broad groups: general measures & specific therapy.

General measures

Measures should be taken to identify and possibly avoid various risk factors associated with flare-ups of the disease. Most of the patients are advised to avoid contact with woollens & wear cotton clothes. Extreme caution should be taken while bathing- avoid bathing with very hot water, avoid soaps and detergents which can act as irritants and also deplete lipids and oils from the surface of skin and have a drying effect. Use of a moisturing soap or soap-free cleansers should be encouraged. Emollients are the mainstay of maintenance therapy for atopic dermatitis. Liberal amounts of a lubricant or emollient cream should be applied to the skin immediately after bathing and two or three times in a day. Regular cleaning of the bedroom in particular, with hoovering and damp dusting, may be helpful. Animal dander can aggravate atopic dermatitis.

Sensitization to foods, triggers isolated skin symptoms in about 30% of children. In an Indian study comprising 100 children with AD, specific dietary elimination for 3 weeks was recommended which included food stuffs like milk and milk products, nuts and nut-containing foods, eggs and egg-containing foods, seafish and prawns, brinjal and soyabean. SCORAD index was measured before and after the desired time period of three weeks. There was a statistically significant reduction in severity scores after dietary elimination alone thus confirming the role of diet in AD.[55]

During pregnancy, there are no global recommendations regarding dietary interventions and aeroallergen avoidance for the mother; there is no conclusive evidence that manipulation prevents AD either in the infant or child. Probiotic treatment during pregnancy and nursing may delay the onset of AD in infants and children.[56]

Specific therapy includes topical therapy and systemic therapy

1. Topical therapy:

a. **Topical corticosteroids-** Topical corticosteroids are widely being used in AD because of their anti-inflammatory, antiproliferative, vasoconstrictive and immunosuppressive action. More potent steroids are generally used in moderate to severe cases and low potency steroids are usually reserved for mild dermatitis, face, flexures and when large areas are to be treated for long time. Ointments are generally preferred due to their occlusive effect and enhanced drug penetration and potency. However, the therapy has it limitations- striae, bruises, telengiectasias, acneiform eruptions, tachyphylaxis, etc. Systemic absorption may lead to stunting of growth in children and HPA- axis suppression. Methylprednisolone aceponate is a potent fourth generation corticosteroid which has demonstrated efficacy and safety in acute and maintenance programmes in infants and children.[57]

b. **Calcineurin inhibitors-** The topical calcineurin inhibitors tacrolimus and pimecrolimus were approved by the US FDA in 2000 and 2001, respectively, as second-line topical therapy for AD. Tacrolimus was found to be as effective as class III-V topical corticosteroids for AD of the trunk and extremities, and more effective than low-potency class VI or VII corticosteroids for AD of the face or neck. Pimecrolimus is less effective than both tacrolimus and low potency topical corticosteroids for moderate to severe AD. The short-term safety studies found that, compared with topical corticosteroid-treated adults, patients treated with topical calcineurin inhibitors had an increased frequency of application-site reactions, an equivalent infection risk, and a decreased risk of skin atrophy. The long-term safety of topical calcineurin inhibitors remains under investigation.[58]

2. Systemic therapy:

a. **Antihistamines:** Conventional class 1 (first generation) H1- antihistamines are the mainstay of the treatment because of their additional sedative effect. In infants, these preparations may occasionally cause paradoxical excitation. They are best used in short courses, for example 10-14 days, as tachyphylaxis can occur with prolonged use.[59] Many patients with AD also have accompanying urticaria, dermatographism, and allergic rhinoconjunctivitis, and therefore they may be benefited by the use of antihistamines for these concurrent medical problems.

b. **Systemic corticosteroids:** They can be used to tide over acute flares of AD. Prednisolone is usually given in a dose of 1 mg/kg body weight per day and rapidly tapered off. Steroid sparing agents are better used in disease requiring long therapy.

c. **Immunosuppressants-** Cyclosporine (3-5mg /kg body weight per day), azathioprine (1-2.5 mg/kg body weight per day) & mycophenolate mofetil (1-3 g in two divided doses) are a promising therapy for severe cases of atopic dermatitis unresponsive to other therapies.

d. **Antibiotics-** Anti-staphylococcal antibiotics are very helpful in the treatment of patients who are heavily colonized or infected with

Staph. aureus. For patients with recurrent flares, intranasal and perianal application of mupirocin ointment or a course of rifampicin 450 mg/day may help.

Others modalities like- Phototherapy (both UVA & UVB), high dose intravenous immunoglobulins, essential fatty acids, leukotriene inhibitors, methotrexate, desensitization injections, theophylline and papaverine, thymopentin, tumor necrosis factor inhibitors, oral pimecrolimus, allergen-antibody complexes of house-dust mites have been found to be effective but not validated.

CONCLUSION

A significant volume of ongoing research is focused on improving the knowledge on pathogenesis, newer treatment modalities, validation & standardization of the available options & ensuring their long term efficacy and safety. Enhanced understanding of features of AD such as provocative factors and predictors of disease will ideally lead to more effective preventive and therapeutic measures, ultimately improving the prognosis of AD.

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