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Atopic dermatitis in infants and children in India

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ABSTRACT

Atopic dermatitis (AD) is a chronic relapsing eczematous skin disease characterized by pruritus and inflammation and accompanied by cutaneous physiological dysfunction, with a majority of the patients having a personal or family history of "atopic diathesis." The term "atopic diathesis" refers to the presence of allergic rhinitis, bronchial asthma or AD. The universal occurrence of AD is no longer debated. However, published material about its natural history, etiopathogenesis, epidemiology, clinical patterns and management leave a lot to be known in the Indian scenario. In the present write-up, we will try to explore the wealth of knowledge about the disease available in our country and try to unfurl the complex interplay of different factors that are implicated for the development of this condition. The diagnosis of AD is based on a constellation of signs and symptoms. There is no laboratory "gold standard" for the diagnosis of AD. In a majority of the cases, the diagnosis is quite easy. Topical corticosteroids form the mainstay of topical treatment and, along with emollient, are able to control the condition in more than 80% of the cases. However, as use of long-term topical corticosteroid has the potential to produce local and systemic adverse effects, topical tacrolimus has come up as a useful molecule for the long-term control of the disease.

Key words: Atopic dermatitis, children, India, infants

INTRODUCTION

Atopic dermatitis (AD) is a chronic relapsing eczematous skin disease characterized by pruritus and inflammation and accompanied by cutaneous physiological dysfunction, with a majority of the patients having a personal or family history of "atopic diathesis." The term "atopic diathesis" refers to the presence of allergic rhinitis, bronchial asthma or AD. The definitive diagnosis of AD requires the presence of all three of the following features: pruritus, typical morphology and distribution, and chronic and chronically relapsing course.

The universal occurrence of AD is no longer debated. However, published material about its natural history, etiopathogenesis, epidemiology, clinical patterns and management leave a lot to be known in the Indian scenario. In the present write-up, we will try to explore the wealth of knowledge about the disease available in our country and try to unfurl the complex interplay of different factors that are implicated for the development of this condition.

ETIOPATHOGENESIS

Role of Heredity

One of the major diagnostic criteria is the personal and/or family history of atopy, with its widely variable incidence. Prospective studies are very limited in the Indian literature.

A study conducted showed personal and/or family history of atopy in 130 children – 83 boys and 47 girls – with AD in the age group of 3 months to 1.5 years, with a mean age of 2.2 ± 1.93 years at onset of AD. The data was compared with those obtained from 130 age- and sex-matched controls. Personal history of atopy was available in 24 (18.5%) patients, 16 (12.3%) with allergic rhinitis (AR), six (4.7%) with bronchial asthma (BA) and two (1.5%) with both AR and BA. The corresponding figure in the control group was seven (5.4%). Both personal and family history of atopy were present in 10 (7.7%) patients and two (1.5%) controls. Family history of atopy was present in 52 (40%) patients, 28 (53.9%) with BA, 10 (19.2%) each with AR

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and AD, three (5.8%) with both BA and AD and one (1.9%) with AR and AD. The corresponding figure in the control group was 16 (12.3%). In 52 patients, 72 of the family members were affected, seven (9.7%) in the first generation, 32 (44.4%) in the second generation and 33 (45.9%) in the third generation. None of the patients had both parents affected.[1]

This study highlights that the figures are rather low for personal and/or family history of atopy in comparison to other series mainly due to the reason that the test group was pediatric population and some of the manifestations of AD develop later in life. The incidence of AR was more than BA, whereas urticaria showed no difference in the study and control groups. An interesting observation was that more family members were affected in the second (44.4%) and third (45.9%) generations than in the first one (9.7%). It is thus quite possible that the low incidence of the personal or family history produces a less-severe form of the disease, which is in contrast to studies from the western world.[1,2]

Role of the environment

AD is more common in the urban than in the rural set up. This is probably because of industrialization and changed life style. Pollution certainly plays a significant role not only in the precipitation of AR or BA but also in AD. The incidence has been found to be higher among the new immigrants to the industrialized countries.

The rising incidence of AD in the West has been attributed to the reduced exposure to bacterial and parasitic infections in childhood, which leads to an abnormal development of the immune system, which tends to over react to relatively innocuous antigens – hygiene hypothesis. A study comparing the severity of AD in Indian children in the UK or US and in India revealed a less-severe form of the disease in children born and brought up in India. This study highlighted the influence of acquired factors – temperature, humidity, food habits, clothing and psychological impacts on the clinical expression and severity of the disease.[3,4]

Role of diet

Elimination diet is suggested for patients with AD either for diagnostic reasons to establish the presence of food allergies, for therapy or as a preventive measure in the newborns at risk.

An open-pilot study by us investigated the feasibility of dietary eliminations in the Indian scenario and also assessed the effect it has on Indian children with AD. A group of 100 children were assessed for severity of itching, surface area of involvement and SCORAD index. Children without any systemic disease or those who were not on systemic corticosteroids were included in the study and were advised to strictly adhere to a diet excluding milk and milk products, all kinds of nuts and nut-containing foods, egg and egg-containing foods, sea fish and prawns, brinjal and soyabean for a period of 3 weeks. The food items to be included freely to maintain proper nutrition were dal and dal products, rohu fish, chicken and fruits. Infants who were 6–12 months old were given protein hydrolysate formula instead of milk. All the preintervention parameters were measured again after 3 weeks. The male to female ratio of the study group was 0.92. There was a statistically significant reduction in severity scores after dietary elimination alone.[5]

Role of immunity and IgE

Immunological abnormalities like excessive formation of IgE, with a predisposition to anaphylactic sensitivity, some decrease in susceptibility to delayed hypersensitivity, abnormalities in the expression of surface molecules in antigen-presenting cells and dysregulation of cytokine mediators are often noted. The severity has some positive correlation with the absolute eosinophil count and serum IgE levels in AD patients.

In a study by our group, 102 consecutive patients, both children and adults, with AD were enrolled and 107 age- and sex-matched persons without any personal or family history of atopy were taken as controls. Patients with AD having other systemic diseases were excluded from the study.

Analysis of variance was performed on parameters of severity of AD, eosinophil count and IgE levels with respect to independent variables like sex, family history of atopy (father, mother or both), sex and associated atopic conditions (BA, AR). Each of the parameters were compared against the other using Product Moment Correlation to observe any significant covariance. The mean age at onset of AD was 4.55 (SD 3.63) years and in patients with AD, the mean absolute eosinophil count was 624 (SD 590) and the mean

IgE level was 278.29 (SD 324.85); the corresponding values were 121 (SD 109) and 25.8 (SD 23.36), respectively, for the controls. The absolute eosinophil count and the IgE level were higher in patients with AD than in controls. Similarly, we found that both the absolute eosinophil count and the IgE level showed significant covariance with disease severity. The nonhomogeneous distribution of the absolute eosinophil count and the IgE level were reflected in the large range and higher standard deviation. One-way analysis of variance showed a significant association of the absolute eosinophil count and the IgE level with a family history of AD only when both parents were affected. The eosinophil count and the IgE level also showed a significant association with a history of bronchial asthma in patients with AD but not with allergic rhinitis. The elevated IgE response and eosinophilia observed in patients with AD may reflect increased responses of type 2 T-helper (Th2) cytokines with a concomitant decrease in interferon-gamma (IFN-gamma) production.[6,4]

Another study was designed to assess these allergen-specific antibodies in the diagnosis of AD. This prospective study comprised of 50 patients of AD. Serum IgE levels were estimated and specific IgE antibodies were measured for 20 food allergens and aeroallergens. IgE was elevated in 88% of the patients, and the highest elevation of mean IgE levels was in the 10–20 years age group. Sixty-five percent of the children under the age of 10 years were positive to one or more food allergens. Antibodies against apples and hazelnuts were the more commonly seen specific antibodies in children.[7] Incidence of positivity was much higher in children when compared to earlier studies, and identification of food allergens can be an important factor in the diagnosis of AD.

Correlation between facial lesions and antinuclear antibody (ANA) positivity

A study conducted by us to investigate the correlation between ANA positivity with the severity of AD and presence of facial lesions was initiated in 76 children with AD, of which 46 were males and 30 were females. Their ages ranged from 6 months to 12 years (mean 3.4 years). Age at onset of AD ranged from 2 months to 5.5 years (mean 1.9 years) and its duration ranged from 4 months to 4 years (mean 1.2 years). While facial lesions were present in 56 (73.3%) patients, 49 (64.5%) patients had predominant involvement of the extensors. History of photosensitivity was present in six (7.9%) patients. Serum samples were positive for ANA in a very low titer (1:20) in two of six patients with history of photosensitivity. However, LE cell, rheumatoid factor and C-reactive proteins were negative and serum complement levels were within normal limits. To conclude, positivity of ANA is not a feature of childhood AD, but it could be because of a less-severe AD seen in India.[8]

Role of infection

The carriage state of *Staphylococcus aureus* has been a subject of interest for quite some time. Its role in the pathogenesis and management of AD were evaluated in 50 patients aged 3 months to 12 years. An equal number of age- and sex-matched controls were also studied. The positivity in patients with AD was 50% from eczematous skin, 34% from anterior nares and 26% from normal skin. In controls, the comparative figures were 14% from anterior nares and 10% from normal skin. Treatment with oral erythromycin or cloxacillin (according to sensitivity) resulted in colony counts dropping to 18% from eczematous skin, 14% from anterior nares and 8% from normal skin after 1 week and to zero after 3 weeks, and was associated with significant clinical improvement.[9] The results of this study suggests that *Staph. aureus* aggravates the eczematous process in patients with AD and antibiotics decrease the severity of this condition.

The first author and his colleague mentioned that even in the absence of frank infection, oral cloxacillin 50–100 mg/kg/day or erythromycin 30–50 mg/kg/day for 7–12 days helped to bring down the progression of eczema, control inflammation and even pruritus to a great extent and was correlated bacteriologically by a gradual decrease in *Staph. aureus* load from the skin surface.[9,10]

EPIDEMIOLOGY AND CLINICAL PATTERNS

The diagnosis of AD is based on a constellation of signs and symptoms.[11] There is no laboratory "gold standard" for the diagnosis of AD. In a majority of the cases, the diagnosis is quite easy. However, it may prove difficult in certain situations, e.g. in early stage of the disease, during remission and when the morphology of the skin lesions have been modified by treatment. Establishing a firm diagnostic criteria for all forms of AD is difficult due to the clinical and pathophysiological heterogeneity.

Atopic individuals can also suffer from other dermatitis or dermatoses, and because every dermatitis in an atopic individual need not be atopic, Hanifin and Rajka for the first time proposed a systematic approach toward the standardization of the diagnosis of AD by incorporating three major/basic and 23 minor features. They suggested that a diagnosis of AD can be established if three of the major and three of the minor criteria are present.[11]

Major/basic features

1. Pruritus
2. Typcial morphology and distribution: flexural lichenification or linearity in adults, facial and extensor involvement in infants and children
3. Chronic or chronically relapsing dermatitis
4. Personal or family history of atopy (asthma, AR, atopic dermatitis)

Minor or less-characteristic features

1. Xerosis
2. Ichthyosis/palmar hyperlinearity/keratosis pilaris
3. Immediate (type 1) skin test reactivity
4. Elevated serum IgE
5. Early age at onset
6. Tendency toward cutaneous infections (esp. *Staph. aureus* and Herpes simplex)/impaired cell-mediated immunity
7. Tendency toward nonspecific hand or foot dermatitis
8. Nipple eczema
9. Cheilitis
10. Recurrent conjuntivitis
11. Dennie–Morgan infraorbital folds
12. Keratoconus
13. Anterior subcapsular cataracts
14. Orbital darkening
15. Facial pallor/facial erythema
16. Pityriasis alba
17. Anterior neck folds
18. Itch when sweating
19. Intolerance to wool or lipid solvents
20. Perifollicular accentuation
21. Food intolerance
22. Course influenced by environmental/emotional factors
23. White dermographism/delayed blanch

A clinicoepidemiological study on a North Indian pediatric population was carried out by us in 672 children, of which 210 were infants (up to 1 year) and 462 were children. Mean age at onset and mean duration of the disease were 4.2 months and 3.3 months, respectively, in the "infantile AD" group and, in the "childhood AD" group, the corresponding figures were 4.1 years and 1.9 years. Patients from urban areas significantly outnumbered those from rural backgrounds. In the infantile AD group, the disease was aggravated in winter in 67.14%, in summer in 23.36% and in spring in 9.51% of the patients. In the childhood AD group, aggravations were 58% in winter, 32.92% in summer, 7.43% in spring and 1.74% in the rainy season. In the infantile AD, personal and family history of atopy were seen in 0.91% and 36.19% of the patients, respectively. In the childhood AD group, 15.35% had a personal history of atopy, 36.44% had a family history of atopy and 7.36% had both a personal and family history of atopy. A history of drug allergy was reported in 3.16% of the children. In the infantile AD group, 79% had facial involvement, 42% had flexors affected and 5.70% had both flexors and extensors affected. The types of eczema seen were acute in 52.72%, subacute in 23.35%, chronic in 23.35% and follicular in 0.46%. In the childhood AD group, 74.50% had facial involvement, 35.53% had flexural involvement, 56.32% had extensor involvement and 8.24% had both flexors and extensors involved. Acute eczema was seen in 28.79%, subacute in 23.38%, chronic in 47.40% and follicular in 0.43% of the children.[12]

Another hospital-based North Indian study later on documented an incidence of 29.9% of total patients. The population comprised of 125 patients, including 26 infants and 99 children, showing a mean duration of disease of 3 months in infants and 6 years in children. The male to female ratio was 2.25:1, with a mean onset of 4.5 months. The urban population had more prevalence of infantile and childhood AD at 76.9% and 68.7%, respectively, than the rural one. The infants had more of facial involvement and acute eczema whereas the children had nonspecific distribution and chronic eczema, with overall mild to moderate AD more prevalent. Winter exacerbation was noted in the majority of the population (62%).[13]

A similar study followed from the East, with slightly different observations. One hundred children were evaluated for epidemiological and clinical patterns. The prevalence rate noted was only 0.55%, a figure

much smaller than in the West. The mean age was 4.94 years, age of onset was 4.58 years, with a boy to girl ratio of 1.3:1, and the majority had acute type of eczema (42%). Most of the patients (54%) had mild AD, 54% had personal history of atopy, 65% had family history of atopy, majority (40%) had summer exacerbation, with predominant site being the flexors (39%). In sharp contrast to a previous study, only 20% had facial involvement.[14] These contrasts point toward a regional variation in the features of AD as North India experiences severe and more prolonged winters.

Significance of minor clinical features

History and clinical features still form the cornerstone for diagnosing AD as there is no laboratory gold standard. A pilot study was conducted by us to evaluate 19 of the 23 minor criteria in 50 patients compared to 50 controls. The observations showed that cheilitis, nipple eczema, perifollicular accentuation, white dermographism, recurrent conjunctivitis and anterior neck folds were seen in patients and controls alike, conforming to the findings of Kang and Tiang. Diffuse scalp scaling and infra auricular fissuring emerged as more significant minor indicators for diagnosis in this group, which may be explained by high colony counts of Pityrosporum producing subacute dermatitis. This study also noted an early age of onset and put forward the logic of atopic facies.[15,16]

Another study showed age-related analysis in 100 children with AD and an equal number of controls showing minor features as nonspecific, e.g. ichthyosis, nipple eczema, cheilitis, pityriasis alba, anterior neck folds, food intolerance; the ages of 3 months to 12 years were divided into four groups taking up to 5 years as early onset limit – 85% had early onset. Minor features of importance were xerosis, early onset, infections, Dennie Morgan fold and facial erythema. Itch with sweat, wool intolerance, white dermographism and delayed blanch were also of significance. Diffuse scaling of the scalp was significant, but infra auricular fissuring and Hertoghe's sign (thinning of the outer eyebrows) was not. Seasonal variation was noted in 44% of the patients, with winter exacerbation in 29% and summer exacerbation in 15%.[17] Emphasis was laid again on the modification of the minor clinical features in AD.

SEVERITY GRADING

A cross-sectional study using the SCORAD Index to measure the severity was performed in children born of Indian parents living in the UK or US and born of Indian parents living in India. Each group had 33 children matched in age, sex and history of atopy extended over a 3-year period. The mean severity scores were 8.64 among the cases and 6.34 in the controls, which was a statistically significant difference.[3] This suggests a more severe AD in the study group.

A study by the first author and his colleague of 80 children with AD in North India over a 1.5-year period comprising of 48 boys and 32 girls was graded using the system of Rajka and Langeland; 33 had mild, 44 had moderate and three had severe forms of AD, with mean severity scores of 3.5, 5.7 and 8.3, respectively. Boys had more severe disease and early and late onset patients showed severe AD.[18] Moderate AD had a positive personal history of atopy and a prolonged course. Overall, this study showed milder disease in the North Indian children.

PATCH AND PRICK TESTS

AD is aggravated or triggered by various allergens. Atopic patch test (APT) can be used in patients with allergen-triggered AD. Patch testing has been undertaken to produce an eczematous reaction by applying prick test allergens under occlusion on intact skin. Seventy-five subjects with AD were included in a study and patch tests using prick test allergens were applied to the back.[19] Patch testing was carried out using prick test allergens in aluminum patch test chambers. The antigens were loaded in aluminum patch test chambers with filter paper using the dropper provided by the manufacturer. A drop from the dropper was approximately 1/16 ml. The test site was the upper back. The antigens used were dust mites, *Dermatophagoides farinae* and *D. pteronyssinus*,[4] pollens of *Cynodon dactylon* and *Parthenium hysterophorus*, foods like rice, wheat, milk and egg and dog and cat epithelia. The reading was taken after 48 and 72 h and interpretation and grading of APT reaction was performed according to the guidelines by the European task force on AD consensus.[5] The patch test solutions were aqueous allergens supplied by Creative Drug Industries (Allergology division, Navi Mumbai, India) containing 50% glycerine as stabilizing factor and preserved with 0.4% phenol, with their strengths expressed in protein nitrogen units (PNU) and for food series expressed in weight by

volume. Dust mites, i.e. *D. farinae* and *D. pteronyssinus* had 1500 PNU while all others (*Cynodon dactylon, Parthenium hysterophorus*, dog and cat dander) had 5000 PNU. All food antigens were 1% weight by volume (w/v). Forty-seven percent showed positive reactions, with Parthenium accounting for 42% of all positive reactions. Epicutaneous application of prick test antigen on intact skin can produce a reaction, and Parthenium was the most common. Patient counseling based on patch test helped in improving the quality of life.[19]

A study with prick test was carried out in 15 patients with AD and 10 patients with chronic urticaria (CU). Of the various aeroallergens tested, house dust mite (HDM), pollens, *Aspergillus fumigatus* and insects were found to be most commonly positive. The common food allergens showing prick test positivity were egg white, fish, milk, brinjal, dal, groundnut and banana. Use of nasal filters showed 10–20% improvement in AD and 5–10% improvement in urticaria. Withdrawal of the responsible food article showed 20–30% improvement.[20]

ASSOCIATED DERMATOSES

A variety of dermatoses are associated and lead to severity of AD through exacerbations and stress. Infections, bacterial, fungal and viral, are frequent and often become recurrent and chronic. Others like alopecia areata, drug reactions and pigmentary disorders are also encountered often.

A study of 550 patients of AD for a period of 2 years showed 97 patients having such dermatoses. Fungal infections that are superficial mycoses, mostly recurrent and chronic, were present in 23/97 cases of AD and, instead of the usual 4 weeks required, needed longer periods of therapy. Bacterial infections were present in 33/97, response to treatment was good, but relapses were frequent. Viral infections were present in 15/97 and response to treatment was moderate, but recurrences were common. Pigmentary disturbances such as hypo and hyperpigmentation were present, 6/97 had postinflammatory depigmentation, 4/97 had widespread hyperpigmentation and 8/97 had cutaneous amyloidosis. Drug reactions were present in 6/97 in the form of exaggeration of AD in three, fixed drug eruptions in two and urticaria in one.[21]

Alopecia areata was present in 5/97 cases, including one presenting as ophiasis. Many other dermatoses were present, i.e. seborrhoea capitis in 5/97, prurigo nodularis in 3/97, keloids in 2/97 and pityriasis versicolor, idiopathic urticaria, persistent dermographism, etc. Another 100 patients evaluated with alopecia areata showed evidence of atopy in 50, including patients alone (23), patients and first-degree relatives (11) and first-degree relatives alone (16). Intracutaneous tests were positive in 23 of 50 patients tested randomly.[21,22] There was an inclination toward increasing frequency of severe alopecia as evidence of atopy increased.

AD AND GROWTH

A total of 100 children with AD and 100 age- and sex-matched controls (without any personal or family history of atopy) were evaluated by us for growth status and compared (with patients having AD along with other systemic diseases were excluded from the study).[23] Clinical examination was performed to calculate the surface area of involvement of the disease (Wallace's rule of nine) and the severity of the disease (SCORAD index). To document growth status of the child, a "cross sectional method" was adapted, where the child was evaluated only once at a given age. Only weight and height were recorded and those were matched with the weight and height percentile of the "National centre of health statistics" (NCHS), USA. Weight was recorded using a spring weighing machine. In children below 2 years of age, length was recorded using an infantometer, while in children above 2 years, the standing height was recorded using a stadiometer. When the weight and height of the patients and the controls were matched with that of the NCHS for their respective age and sex, 42% of the patients had weight below the 3rd percentile and 34% had height below the 3rd percentile for age and sex, while none of the controls had weight or height below the 3rd percentile mark. This indicates occurrence of growth retardation, as depicted by height and weight in our present study in cases of children with AD.[23]

In an earlier Indian study by Saraswat *et al.*,[24] growth impairment was found in preschool children (up to 5 years of age) with pure AD, the magnitude of growth impairment being more in boys than in girls.[24] However, no clearcut correlation was found between

the severity measured by SCORAD index or disease extent in terms of body surface area involved with respect to either height or weight of the children.

Another longitudinal study was carried out to look for the effect of AD on growth.[25] The growth patterns of 62 children aged 3–5 years and suffering from AD were studied in terms of body weight, height and head circumference. Sixty-eight normal healthy children matched for age, sex and socioeconomic status were taken as controls. The growth velocities were lower in patients than in controls. The mean values for height and head circumference were found to be significantly lower in girls than in the girls of the control group whereas in boys, these values for the patients remained comparable or higher than in the boys of the control group at some of the ages. Girls had comparatively more severe disease than boys. Growth retardation was observed among children with a more severe form of the disease. Height of the affected children was mostly compromised.[25]

AD AND EYE

A recent study has investigated ocular abnormalities in 100 Indian patients from 1 to 14 years of age and reported 43% with ocular changes in the form of lid and conjunctival changes.[26] The conjunctival changes were mostly cobblestone appearance of the papillae, with papillary reaction and papillary hypertrophy, and the lid showed isolated blepharitis and loss of the eyelashes and eczema of the eyelids along with blepharitis. These changes had a male preponderance, and family history of atopy was a significant indicator of for ocular changes.[26]

DIFFERENTIAL DIAGNOSIS OF AD

In an individual patient, one must consider a number of other conditions that may simulate AD. In an infant, seborrheic dermatitis is the most common differential diagnosis. At times, it may be difficult to differentiate between these two because of some overlapping features shared by them. Pruritus, age at onset and a family history of atopy cannot reliably discriminate between these two entities. Lesions over the forearms and shins and specific serum IgE to egg white and milk favors a diagnosis of AD. In case of infantile seborrheic dermatitis, the lesions are found in the axillae and/or the napkin area.

Scabies in babies often undergoes eczematization, particularly over the face, quite closely simulating AD. A history of acute itching among the family contacts, presence of burrows and inflammed papules and nodules over the genital and axillary areas support a diagnosis of scabies with eczematization.

There are a number of genetic and metabolic disorders where an eruption resembles AD (with or without other atopic disorders) or which are associated with a raised IgE level. Many such conditions are immunocompromised states. Thus, in other words, the following conditions are to be suspected when a patient is having eczema-like AD but is not responding to conventional treatment.

1. Agammaglobulinemia
2. Anhidrotic ectodermal dysplasia
3. Ataxia-telangiectasia
4. Coeliac disease
5. Cystic fibrosis (heterozygote)
6. Histidine depletion (experimental)
7. Hurler's syndrome
8. Hyper IgE syndrome
9. Hypereosinophilic syndrome
10. Jung's disease
11. Nephrotic syndrome
12. Netherton's syndrome
13. Phenylketonuria
14. Wiskott-Aldrich syndrome

Most of these conditions are rare, which are diagnosed not very infrequently in day-to-day practice.

PRACTICAL MANAGEMENT

Therapy with hydrating topical agents and avoidance of specific provocation factors is a first line modality of management. Antiinflammatory treatment consisting of topical glucocorticosteroids and topical calcineurin antagonists are used for exacerbation management. Topical corticosteroids remain the mainstay of therapy, but topical calcineurin inhibitors, tacrolimus and pimecrolimus are preferred in certain locations. Systemic antiinflammatory agents like corticosteroids and immunomodulators like cyclosporine are treatment options for severe refractory cases.[27] Microbial colonization and superinfection may induce disease exacerbation and can justify additional antimicrobial/antiseptic treatment. Systemic antihistamines (H1) can relieve pruritus and adjuvant therapy includes

UV irradiation, preferably of UVA1 wavelength or UVB 311 nm. However, there is no single effective treatment for AD.

Treatment in severe cases need regular monitoring. Topical corticosteroid forms the mainstay of topical treatment and, along with emollient, is able to control the condition in more than 80% of the cases. However, as use of long-term topical corticosteroid has the potential to produce local and systemic adverse effects, topical tacrolimus has come up as a useful molecule for the long-term control of the disease.

Tacrolimus ointment, an immunomodulator, has been found to be effective and safe in the treatment of AD.[28] A pilot study was initiated to evaluate the efficacy of tacrolimus 0.1% ointment in the treatment of atopic hand eczema (AHE).[28] The study was an open-label noncomparative study using tacrolimus 0.1% ointment in 10 patients with AHE. Inclusion criteria included patients with hand eczema, known history of atopy, AD, hay fever or asthma. Patients had to stop topical application of steroids and systemic use of steroids or antihistamines for 4 weeks. Patients applied tacrolimus 0.1% ointment twice daily for 4 weeks. Evaluation was performed before treatment, after 4 weeks of treatment and after a follow-up period of 4 weeks. During follow-up, the patients used emollients. Treatment efficacy was established at each visit based on the following parameters: itch (and/or burning sensation), dryness, erythema, lichenification, erosions and fissure. Of the 10 patients who entered the study, four patients had marked or complete improvement at the end of treatment, four cases had partial improvement while in one patient the treatment failed. One patient left the study due to side-effects.[28] Efficacy, safety and tolerability of tacrolimus ointment has been established in Indian patients with moderate to severe atopic dermatitis in an open multicentre study.[29]

A placebo-controlled study with topical tacrolimus (0.1%) in 15 children aged 3–15 years of 6 months to 5 years duration with moderate to severe AD was documented. The ointment was applied on three patches 3 cm x 3 cm twice daily for 2 weeks. The controls were treated with sunflower oil for the eczema. Significant reduction in severity scores ($P < 0.05$) was noted in all the 15 children, and three of them reported mild burning and pruritus.[30] The suggestion was to use the formulation more for the face and the flexures in children with moderate to severe AD.

Studies in children with AD have demonstrated an increased carrier state of *Staph. aureus* in both involved and uninvolved skin. AD is reported to be exacerbated when the density of *Staph. aureus* is >106 CFU/cm^2. The Staphylococcal superantigens produced by *Staph. aureus* may actually perpetuate the eczema and produce steroid insensitivity. Topical and/or systemic antibiotics reduce the quantity of *Staph. aureus* colonizing the skin and nasal mucosa, and thus improve the eczema.[10] Topical mupirocin is highly effective against all strains of *Staph. aureus* and is effective in clearing it from the skin and nasal mucosa.

One can therefore presume that a combination of a moderately potent topical corticosteroid like fluticasone and an antibiotic like mupirocin should tackle AD more effectively than fluticasone alone. In this context, Khobragade reports that 2 weeks of treatment with a combination of fluticasone and mupirocin led to a significant improvement in AD in 90% of the patients in an open-label uncontrolled study.[31]

In patients with widely distributed eczematous lesions, a course of an oral anti-Staphylococcal antibiotic is preferable to a topical steroid–antibiotic combination. Several studies, including one by our group, have found that such a course improves the eczema even in patients without evident infection. Once the lesions become localized, application of a topical steroid alone to the residual lesions should suffice. In the first author's experience, a topical steroid–antibiotic combination is most appropriate for treating eczematous lesions close to the anterior nares, flexures, perianal areas and finger or toe web spaces.

Sharma reported contact allergy to neomycin, gentamicin and chinoform in patients with AD.[32] The risk of sensitization is the main reason why most dermatologists do not prefer neomycin as a topical antibiotic in patients with AD. In India, neomycin-containing topical antibacterials are commonly prescribed for cuts, abrasions, minor burns, furuncles, etc. The incidence of cross-sensitivity between neomycin and gentamicin is as high as 40%. Topical betamethasone in combination with gentamicin has

been successfully used to treat AD for the past two decades. However, it is quite possible that gentamicin might induce sensitization in many patients with AD and that patients who cease to respond to a topical steroid–gentamicin combination are actually developing sensitivity to gentamicin rather than tachyphylaxis to steroids (that is what we usually suspect). The sensitization potential of mupirocin does not appear to be a major issue presently.[32]

NATURAL HISTORY AND PROGNOSIS

Studies on the natural history on AD have produced variable results. In one study, the disease was seen to undergo spontaneous resolution by 10 years of age in 90% of the children. However, other studies have shown that in only 60% of the affected children the disease cleared by 16 years of age.[33,34] Overall, our experience in India has been that the disease, when started in infancy, follows a stepwise reduction in severity over the next 10–12 years and, by 12–15 years, it heals completely. However, the true clearance rate is actually far from these figures and concepts. Many children or individuals probably relapse at some stage in adulthood either in the form of irritant hand eczema or pompholyx or dyshidrotic eczema of the hands. We do not have adequate data to validate these issues. Factors that may indicate a poor prognosis include severe childhood disease, early onset and concomitant family history of asthma/hay fever.

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