Study Of Matrix Metalloproteinase 9 And Histopathology In Sinonasal Diseases Before And After Endoscopic Surgery

by

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LIST OF ABBREVIATIONS

AD	- Atopic Dermatitis
IgE	- Immunoglobulin E
FLG	- Filaggrin
IL	- Interleukin
Th cell	- T helper cell
DC	- Dendritic cell
KLK	- Kallikrein
LEKTI	- Lymphoepithelial Kazal-type 5 Serine Protease Inhibitor
SPINK5	- Serine Protease Inhibitor Kazal-type 5
TSLP	- Thymic stromal lymphopoietin
TEWL	- Transepidermal water loss
HdM	- House dust mite
QOL	- Quality of life
HSV	- Herpes simplex virus
RAST	- Radioallergosorbent assay test
H1	- Histamine-1
TCS	- Topical corticosteroids
TCI	- Topical calcineurin inhibitor
WD	- White dermographism
P. Alba	- Pityriasis Alba

ABSTRACT

Background

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease characterized by intense pruritus. To aid the diagnosis of AD, various criteria are available among which Hanifin and Rajka's criteria is the most commonly used in the hospital set-up by clinicians. Hanifin and Rajka's criteria consist of 4 major and 23 minor criteria. Three criteria from each category are required in making a diagnosis of AD. The frequency of minor criteria may vary population-wise.

Objective

To estimate the frequency of minor diagnostic criteria of Hanifin and Rajka in children with atopic dermatitis.

Methodology

It is a hospital based cross-sectional study. A total of 174 patients with atopic dermatitis aged ≤16 years, irrespective of gender, were enrolled for the study. Detailed history with respect to the present age, age of onset of disease, pruritus, chronicity of the disease, personal and/or family history of atopy, tendency toward cutaneous infections and nonspecific hand/foot dermatitis, recurrent conjunctivitis, itch when sweating, intolerance to wool and lipid solvents, food hypersensitivity, influence of environmental and/or emotional factors on course of disease was recorded from the parents. Clinical and ophthalmological

examination were done and findings were recorded. Blood test to assess serum IgE level was conducted at laboratory.

Results

The most common minor criteria observed in our study were Dennie-Morgan infraorbital fold (71.8%), early age of onset (67.8%), palmar hyperlinearity (67.8%), xerosis (67.2%), p.alba (57.5%) and perifollicular accentuation (47.7%). Out of 143 cases whose serum was tested for IgE level, elevation was seen in 92. History of winter exacerbation was seen in 8% of the cases while summer exacerbation was seen in none. On ophthalmological examination of 111 cases, 'high reading with no obvious keratoconus' was present in 2 cases while 3 cases were labelled as 'keratoconus suspect'. Anterior subcapsular cataract was not noted in any of the study subjects. Criteria such as nipple eczema, recurrent conjunctivitis, food hypersensitivity and white dermographism were not observed in any of the patients.

Conclusion

Clinical features of AD may be variable. Prevalence of AD varies country-wise and within a country, region-wise. The prevalence and severity of AD are influenced by several factors like ethnic/racial factors, environmental factors, dietary habits, etc. Therefore it is relevant for the dermatologists to have a knowledge regarding common clinical features of AD in a given population to diagnose the condition and thereby provide treatment to reduce the morbidity along with appropriate counselling.

Keywords: Atopic dermatitis, Hanifin and Rajka's criteria.

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INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease characterized by intense pruritus. Exacerbations and remissions cause great morbidity in patients affected with this disorder. It may be seen in association with other atopic disorders like, asthma and allergic rhinoconjunctivitis.[1] Clinical features vary at different ages, population and race-wise.[2]

AD has varied clinical presentation, simulating many other dermatitic conditions, such as contact dermatitis and seborrheic dermatitis. Differentiation with these conditions is essential as AD is a chronic disorder and early intervention improves the quality of life in affected patients. Hence, a set of diagnostic criteria is necessary for confirmation of diagnosis of AD.

Several diagnostic criteria exist for use in patients with AD. However, the effectiveness of those criteria in different population is highly variable as found in various studies.[3] This is because the prevalence of clinical features and intensity of symptoms of AD may vary with genetic background, climate, geographical regions, food habits, socioeconomic status, availability of health care facilities and many other factors.[3] Uniform set of diagnostic clinical features can be used for diagnosis in large population studies.[2]

To enable AD diagnosis with certainty, in 1980 Hanifin and Rajka propositioned a criteria commonly known as “Hanifin and Rajka’s diagnostic criteria for AD”.[4] Subsequently, several other criteria have been used for the diagnosis of AD. The most important and commonly used ones are; United Kingdom (U.K) Working Party’s diagnostic criteria (William *et al*., 1994) and ISAAC (International Study of Asthma and Allergies in childhood) questionnaire (1995).[3] Hanifin and Rajka’s criteria is for use in hospital set-up by clinicians

whereas U.K. diagnostic criteria and ISAAC criteria are for use in the community setup.[3] In Hanifin and Rajka's criteria, there are four major criteria and twenty-three minor criteria. Three from each category are necessary for diagnosing AD.[4] The minor criteria may vary population-wise.

A gradual rising trend in prevalence of AD has been observed all over the world due to environmental changes.[5] In phase I ISAAC study, it has been found that the prevalence of symptoms of asthma, rhinoconjunctivitis, and atopic eczema in 56 countries was 0.3-20.5%.[6]

Prevalence of AD varies country-wise and in a given country, region-wise. This may be due to genetic background, varied dietary habits and climate.[5] Recent hospital based studies upon outpatient department (OPD) attendees suffering from AD have established a low prevalence of 0.42% and 0.55% in northern and eastern parts of India respectively.[7,8] In south India, a further lower prevalence of 0.01% was observed in a hospital based study conducted at Pondicherry (2001-2002).[9] In another south Indian study, Kumar *et al.*, noted a prevalence of 2.8%.[10] In a hospital-based study on various eczema conducted in south Karnataka (2009-2011), AD was found to be in 34% patients.[11]

From the above discussion it is evident that clinical features of AD may be variable. India in general is a low-prevalence country for atopic disorders. However, as the incidence of atopy is increasing worldwide, Indian population is also experiencing the same rising trend of this group of disorders. Hence, it is relevant for the dermatologists to know common clinical features of AD in a given population.

This study aims to establish the frequency of minor criteria for the diagnosis of AD in a section of south Indian children attending a tertiary health care centre in north Karnataka.

OBJECTIVE OF THE STUDY

To estimate the frequency of minor diagnostic criteria of Hanifin and Rajka in children with atopic dermatitis.

REVIEW OF LITERATURE

Definition:

The term atopy is derived from the Greek word 'atopos', meaning strange or unusual.[12] "Atopic dermatitis is an itchy, chronic or chronically relapsing inflammatory skin condition that often starts in early childhood (usually before 2 years of age). The rash is characterized by erythema, itchy papules/papulovesicles (occasionally vesicles in infants) which may become excoriated and lichenified, and typically has a flexural distribution."[4]

Epidemiology:

The world-wide overall prevalence of AD is around 20%.[1,4] Prevalence in children is 0.7-26% and in adults is 1-3%.[13] In India, AD prevalence has been roughly estimated to be around 0.98%.[14] Slight male preponderance has been reported in many studies.[5,7,8] Aggravation of the symptoms in both winter and summer is observed.[7,8,14] In ISAAC phase 3 study, it is observed that frequent consumption of fruits, vegetables and high fish intake are protective against AD whereas fast food consumption leads to increase risk of AD.[15]

Etiopathogenesis:

Intrinsic AD versus extrinsic AD:

- Intrinsic AD (non-allergic AD): Patients exhibit normal levels of total immunoglobulin E (IgE) along with lack of allergen specific IgE.[16]
- Extrinsic AD (allergic AD): Patients exhibit elevated levels of total serum IgE and occurrence of allergen specific IgE.[16]

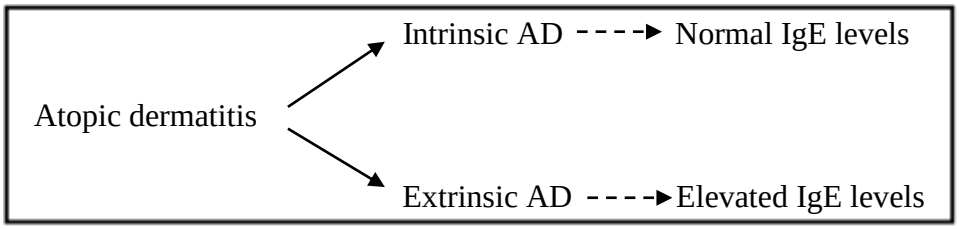

Figure 1: Intrinsic AD versus Extrinsic AD

Atopic March: Refers to "the progression within an individual from AD to other atopic diseases including allergic rhinitis and asthma".[4]

Figure 2: Atopic march

The complex interaction between skin barrier defects, immunological factors, environmental factors and genetic factors leads to development of AD.[17]

I. Defects in barrier function of skin can occur due to the following:[18]

a) Defect in filaggrin (FLG) gene expression:

Loss-of-function mutation of the gene encoding epidermal barrier protein filaggrin is an important predisposing factor for AD. Filaggrin helps in cross-linking of keratin intermediate filaments to form compact bundles and thereby maintains the barrier function of the skin. Therefore, loss of function mutation causes increased transepidermal water loss (TEWL). The substances formed when filaggrin degrades result in formation of natural moisturizing factor which moisturizes stratum corneum and maintains the pH of skin.[18] Only about 50% of all children with moderate to severe AD exhibit mutations in filaggrin gene.[19] This association is

much lesser in those with mild AD.[18] Filaggrin gene mutation is associated with allergic rhinitis, palmar hyperlinearity, allergic contact sensitization, early onset of the disease, food allergies (IgE facilitated) and development of asthma in atopic patients. Null mutation of this gene leads to ichthyosis vulgaris.[20]

b) Deficiency of ceramides in skin:

A type of lipid, ceramide is essential for retaining water in the stratum corneum. Low levels of ceramides correlate with increased TEWL in AD individuals, which shows their importance in cutaneous permeability barrier.[18] Significant deficit in the key lipid components of the skin barrier along with enhanced activity of the enzyme sphingomyelin deacylase result in reduction of ceramide production.[21] Significant decrease in the level of ceramides is observed in both lesional as well as non-lesional areas of the skin of patients with AD. However in infants with AD, reduction is seen only in the lesional skin, which points to the fact that maybe diminution in ceramide occurs as a post-inflammatory event. As opposed to filaggrin, no null mutation has been described in genes related to ceramide in patients with AD.[18]

c) Increased activation of endogenous skin proteases:

Human kallikrein (KLK)-related peptidases like KLK14, KLK7, and KLK5 are fundamental proteolytic enzymes responsible for desquamation of corneocytes. The action of the above mentioned proteases are reliant on pH of skin and therefore, when the pH is raised, their activity is augmented. Also enzyme inhibiting the proteases such as

Lymphoepithelial Kazal-type 5 Serine Protease Inhibitor (LEKTI) regulates action of these peptidases. LEKTI is encoded by the gene Serine Protease Inhibitor Kazal-type 5 (SPINK5). Mutation in SPINK5 gene leads to Netherton syndrome wherein features like AD-like dermatitis, asthma, food allergy along with significantly raised levels of serum IgE are seen. This gene is recognised to be linked with AD. These factors imply that overactivation of endogenous skin proteases and the successive corneocyte desquamation can stimulate AD-like dermatitis.[18]

II. At the immunological front, both adaptive and innate immune system abnormalities are observed in AD.[20] Various cells residing in the skin like T cells, keratinocytes, dendritic cells (DCs), mast cells, macrophages, monocytes and granulocytes are required for development of eczema in individuals with AD.[18]

Both T-helper-1 (Th1) and T-helper-2 (Th2) mediated immune responses are noticed during the progression of AD. During the acute stage of AD, Th2-predominant response is seen while a change in the Th1-Th2 balance occurs during chronic stage with Th1 cytokine profile being prominent.[13] In chronic lesions, interleukins (IL) such as IL-5 and IL-12 expression is pronounced while expression of IL-4 and IL-13 is reduced. Infiltration of Th17 cells occurs significantly in acute lesions. This leads to enhanced manufacturing of IL-6 and IL-8 by IL-17 which in turn are responsible for modulation of fibroblast function.[18] Th2, Th22, and Th17 cytokines primarily drive acute phase of disease, while Th1, Th2, and Th22 cytokines are important during the chronic phase.[22]

DCs contain receptor for the protein thymic stromal lymphopoietin (TSLP), which plays a crucial part in favouring Th2-response mediating the development of AD.[18,22] Th2 cells decrease the expression of antimicrobial peptides such as β-defensins, cathelicidins, calprotectins and inducible nitric oxide synthetase causing increased susceptibility to infections.[22,23] The polymorphisms in various pattern recognition receptors like TLR2, NOD1 and CD14 (expressed by keratinocytes) occurring in patients with AD are linked to enhanced infection predisposition, severe disease and sensitization to allergy.[22]

Activation of eosinophils and its chemotaxis (mediated by eotaxin) is induced by IL-5 (a Th2 cytokine). Raise in the blood levels of IL-5 and eotaxin are seen during flares of the disease. Also, raised quantities of cytokines related to eosinophils namely, eosinophil cationic protein and major basic protein in the lesions of AD indicate degranulation of eosinophils in skin.[18]

An important defect in the immunoglobulin observed in AD is elevated IgE synthesis which is seen in around 80% of the patients. Presence of dermatitis alone corresponds to slight increase in the serum IgE levels with absence of hypersensitivity towards environment allergens. Whereas, simultaneous occurrence of asthma or allergic rhinitis corresponds to higher levels of total IgE in the serum.[13]

III. The development of AD is influenced by various environmental factors, namely microbiome exposure, aeroallergens, climate, diet, and others.[18]

a) Role of infections:

There are two hypotheses which are indicated in the pathogenesis of AD:

- *The 'Outside-Inside' hypothesis:* This states that defective skin barrier provides a portal for the entry of the microbes and the allergens.[24,25]
- *The 'Inside-Outside' hypothesis:* This states that to an insignificant level of allergens there is a disproportionately high response mounted due to abnormally sensitive immune system seen in AD patients.[25]

Hygiene hypothesis: This states that immune system stimulation by microbes of various types (especially lipopolysaccharide endotoxin possessing ones like *Escherichia coli*) at an early age is vital in developing Th1-mediated immune responses.[13] Therefore reduced exposure of child to microbes at an early age due to factor such as over-cautiousness of the parents leads to decreased stimulation of Th1-mediated immunity which enhances Th2-mediated immunity responsible for atopy. (Th1 cells are responsible for down-regulating Th2 cells and vice versa).[26,27,28] Supplementation of probiotics in the mother during later stages of pregnancy and breastfeeding supposedly improves the microbiome and may decrease risk.[29]

The skin of majority of AD patients shows *Staphylococcus aureus* (*S.aureus*) colonization which predisposes to infection and also aggravates the eczematous process.[20,23,30] *Malessezia* is also associated with exacerbation of eczema.[13]

b) Aeroallergens: Factors such as house dust mite (HdM), grass pollen and animal dander are attributed to symptoms of AD.[31] Presence of specific IgE antibodies against these factors in AD patients results in development/exacerbation of eczema.[32] Disintegration of corneodesmosomes by cysteine proteases produced by HdM leads to disruption of barrier function.[21]

c) Climate: Various climatic factors like humidity, ultraviolet (UV) exposure and temperature influence development of dermatitis in AD.[18] Increased temperature and high UV radiation exposure have protective role in AD.[18,33] Patients show flaring up of lesions in the winter season as a result of deceased exposure to sun. Dry climate is responsible for exacerbation of lesions as it leads to dry skin which increases itching.[33]

d) Role of diet: Allergy to certain food items can be seen in upto 30% of the children affected with AD.[12] Although, most of these children outgrow the allergy during first few years of life.[34] Around 90% of allergic responses occur to items like egg, peanut, wheat, soy, and crustacean shellfish.[1,12] This might be the result of presence of micro-organisms or other elements in unprocessed milk. Also increased consumption of fish is considered to be protective due to high n-3 polyunsaturated fatty acids (n-3 PUFA) content which is anti-inflammatory.[35]

e) Other factors:

   i. Acidic pH of the skin (acid mantle) aids the barrier function. Usage of soaps and detergents elevates the pH of skin. This causes overactivity

of skin proteases which leads to hyperdesquamation and thereby contributing to eczema.[36]

ii. Pets (especially dogs) and farm animals are considered as favorable factors against development of AD. Whereas, no conclusive reports are available regarding cats.[35]

iii. Maternal smoking habits and increased outdoor pollution may be associated with increased risk.[18,35]

IV. Genetic factors:

Recent understanding of the genetic foundations of AD verifies the association between barrier protein mutations and the disease.[37] Null mutations of FLG gene is considered to be the commonest genetic risk factor associated with AD.[38] Polymorphism in gene which codes high affinity IgE receptor FCR1 is also strongly associated.[13]

Atopy history in the mother has greater influence over development of atopy in child than the father's.[39] Monozygotic twins display greater concordance rate than dizygotic twins. The area of greatest link is observed on chromosome 1q21.3 which contains filaggrin gene. Some of the other important related loci are chromosome 5q31.1 and chromosome 11q13.5.[38]

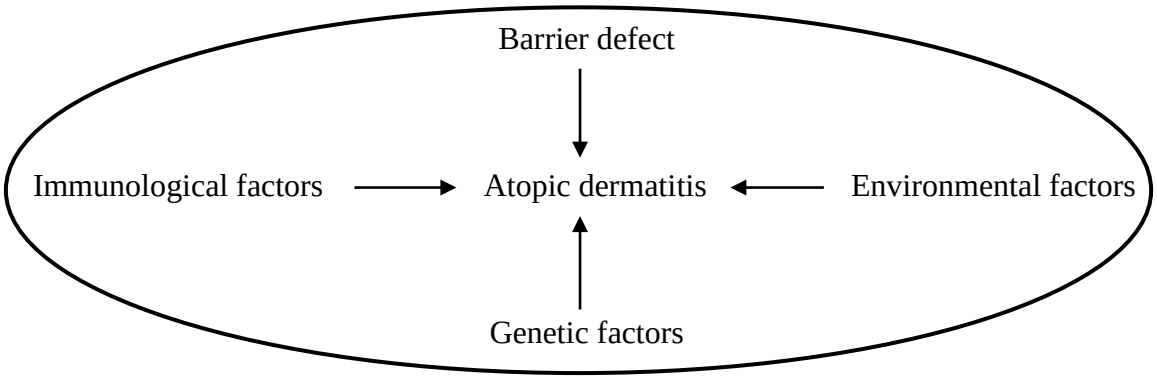

Figure 3: Atopic dermatitis pathogenesis

Clinical features:[1,4,5]

AD comprises of wide range of clinical features. These can be broadly described under 4 headings:

- The Atopic itch
- The Atopic dry skin
- The Atopic eczema
- The stigmata of Atopic Dermatitis

***Atopic itch*:** It is a persistent feature and is the hallmark of the disease. It may cause sleep disturbance, irritability and distress. Aggravating factors are sweating, bathing, emotional distress, exercise and wearing woolen clothes. It leads to scratching, excoriations, prurigo papules, eczematous skin lesions and lichenification.

***Atopic dry skin*:** It is due to increased loss of water through epidermis. Also decrease in the lipid content especially ceramide is one of the contributing factors.

Atopic dermatitis: It is divided into infantile, childhood and adult phases:

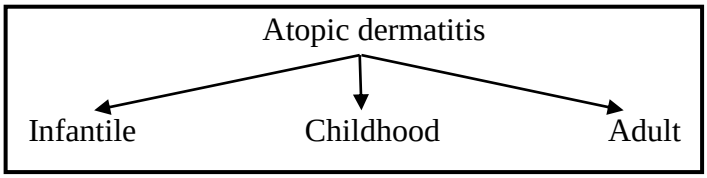

Figure 4: Phases of atopic dermatitis

Infantile phase:- Lesions present may be erythema and edematous papules over the face. The napkin area is relatively spared. Extensor areas of the knees and elbows are affected once the child begins to crawl.

Childhood phase:- Lichenification replaces the erythematous and edematous papules in this age group. Lesions observed are erythema, excoriation, crusting, pigmentary changes such as hyper- and hypopigmentation, and warty lichenification over the knee and elbow flexures. Although flexor wrists, neck and ankles can be affected.

Adult phase:- Lichenification of flexures and hands might be observed. Localized dermatitis occurs predominantly in this age group, especially hand, nipple and eyelid eczema is seen. Photosensitivity may occur in these individuals.

***Atopic stigmata*:**

- Dennie-Morgan fold is a linear transverse fold crossing the pupillary midline which is seen below the edge of the lower eyelids.
- Nasal crease may be prominent.
- Ichthyotic skin maybe seen in upto 50% of the patients.[40]
- In low-grade dermatitis skin may be dry and scaly.
- Hyperlinearity of the palms are frequently observed.
- In subclinical dermatitis, pityriasis alba (p.alba) which is characterized by poorly demarcated hypopigmented patch is seen.
- Horny follicular lesions (keratosis pilaris) are frequently present over outer aspect of upper arms, legs, cheeks and buttocks.
- Perifollicular accentuation and prurigo nodularis are often observed in patients with AD.
- AD affecting lips gives rise to cheilitis. Surrounding skin involvement leads to perioral dermatitis and it is complicated by lip-lick dermatitis.[41]
- "Atopic shiners" refers to the periorbital brown-grey pigmentation.[42]

- "Dirty neck" appearance due to hyperkeratosis and hyperpigmentation is commonly seen.
- Perioral, periorbital, and perinasal pallor can give rise to "headlight sign".
- White dermographism (When a site is stroked with a blunt instrument, it causes blanching of skin at that area) occurring due to vasoconstriction of the capillaries is also one of the stigmata.
- Periorbital dermatitis and perianal dermatitis due to xerosis may be seen.[41]
- Hertoghe's sign which is thinning of lateral eyebrows is sometimes present.

Atopic hand eczema: Non-specific hand dermatitis in the form of dry and scaly eczematous lesions especially over the dorsal surface of hands is seen.[40] Also eczema with vesiculation and lichenification is commonly observed.[4]

Many patients complain of induction or/and aggravation of itch on sweating and usage of woolen clothing.[4]

Development of eczematous lesions secondary to environmental/food allergens and other environmental factors as discussed previously under etiopathogenesis is seen.

Viral infections: Patients with AD show tendency for the following:

- Eczema herpeticum: Also known as Kaposi's varicelliform eruption. It is defined as the "acute disseminated herpes simplex virus (HSV) infection in a patient with atopic dermatitis, often associated with systemic symptoms."[43]
- Eczema coxsackium: Refers to development of infection due to coxsackie virus (hand-foot-mouth disease) in areas affected with AD. It is characterized

by presence of pustules and erosions over eczematous lesions in typical sites of childhood dermatitis.[41]

Bacterial infections: There is an increase in the risk of development of staphylococcal infections in patients with AD. The various associated infections are impetigo (most common), folliculitis, abscess (especially caused by methicillin-resistant strain of *S.aureus*), along with cellulitis.[23]

Ocular involvement: Specific ocular conditions such as keratoconus, anterior subcapsular cataract and keratoconjunctivitis are seen in association with AD and have been included in minor criteria of Hanifin and Rajka.[40]

Diagnostic Criteria for Atopic dermatitis:

Over a period of time many criteria have been available to aid in diagnosing AD. In 1977, Hanifin and Rajka proposed a set of features to diagnose AD which they later modified in 1980.[44] Hanifin and Rajka criteria is the most commonly used criteria followed by the U.K. Working Party's diagnostic criteria and the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire.

Hanifin and Rajka Criteria (1980):[40,44]

Major Criteria (Must have 3 of the following)	*Minor Criteria (Must have 3 of the following)*
1. Pruritus 2. Typical morphology and distribution ➢ Facial and extensor involvement in infancy ➢ Flexural lichenification in adults 3. Chronic or chronically relapsing dermatitis 4. Personal or family history of atopic disease (e.g., asthma, allergic rhinitis, atopic dermatitis)	1. Xerosis 2. Ichthyosis/ hyperlinear palms/ keratosis pilaris 3. IgE reactivity [immediate skin test reactivity, Radioallergosorbent assay test (RAST) positive] 4. Elevated serum IgE 5. Early age of onset 6. Tendency for cutaneous infections (especially *S.aureus* and *Herpes simplex*) 7. Tendency to nonspecific hand/foot dermatitis 8. Nipple eczema 9. Cheilitis 10. Recurrent conjunctivitis 11. Dennie-Morgan infraorbital fold 12. Keratoconus 13. Anterior subcapsular cataract 14. Orbital darkening 15. Facial pallor/ facial erythema 16. Pityriasis alba 17. Anterior neck folds 18. Itch when sweating 19. Intolerance to wool and lipid solvents 20. Perifollicular accentuation 21. Food hypersensitivity 22. Course influenced by environmental and/or emotional factors 23. White dermographism or delayed blanch

Table 1: Hanifin and Rajka's criteria for atopic dermatitis

Other criteria are:[3]

- Kang & Tian diagnostic criteria (1989)
- Schultz-Larsen criteria (1992)
- U.K. Working Party's diagnostic criteria (1994)
- ISSAC questionnaire (1995)
- Japanese Dermatology Association criteria (1995)
- Criteria of Diepgen (1996)
- Millennium diagnostic criteria (1998)
- Danish Allergy Research Centre criteria (2005)

Clinical scoring tools:

Quality of life (QOL) of AD patients can be negatively affected due to the bothersome factors like itch, grade of the lesions, site of lesion, etc. Therefore, evaluating severity of the condition is an important aspect in clinical practice for better management. At present, no gold standard is set for severity assessment of AD.[45]

Few important scoring systems used are:[46]

1. SCORing Atopic Dermatitis (SCORAD)[47] → Most commonly used[46]
2. Eczema Area and Severity Index (EASI)[48]
3. Patient-Oriented Eczema Measure (POEM)[49]
4. Six Area, Six Sign Atopic Dermatitis (SASSAD)[50]
5. Investigator Global Assessment (IGA)[46]
6. Three-Item Severity score (TISS)[51]

Course and prognosis:

Majority of the patients show early onset of the disease, with around 60% exhibiting the features before age of 1 year and 90% before 5 years of age.[52] The disease may be persistent, intermittent or remitting.[4] There is a decrease in the severity of disease with increase in patient's age.[17] The greatest predictors for persistent disease are severity of the disease and atopy history in the family.[4] Mutations in filaggrin gene are linked with increased degree of persistence of AD.[17]

Poor prognostic factors are:[4,17]

- Onset of development of AD at an early age
- Severe AD in childhood
- Personal history of concurrent asthma, allergic rhinitis or hay fever
- Family history of AD, asthma or hay fever
- Presence of elevated serum IgE levels

Investigations:

Various tests available with context to AD in view of identifying related allergy or sensitization are:[4,46]

1. Skin prick test[53,54]
2. Serum specific IgE test (E.g., RAST) → For assessing type I reactions
3. Total serum IgE levels
4. Atopy patch test[54,55] → For assessing type IV reactions

Treatment:

***Non pharmacological*:**

Bathing: It helps in hydration of the skin and in removing crusts, irritants like sweat and allergens. In case of bacterial superinfection, it helps in mechanical elimination of the bacterial contaminants.[56] Bathing once a day with warm water for shorter time period (eg, 5-10 minutes) is recommended. "Soak and smear" technique i.e., soaking in plain water for about 20 minutes and subsequently applying anti-inflammatory agents without drying the affected regions in case of considerably inflamed areas not responsive to plain anti-inflammatory therapy should be advised.[57] Syndets or non-soap cleansers which are fragrance-free, hypoallergenic and have a pH of 5.5 are preferred.[56,57] Bleach bath (body below neck is soaked in a tub filled with about 150 litre of water and adding half a cup of 6% household bleach) is helpful in reducing staphylococcal colonization and thereby decrease AD severity.[56]

Wet-wrap therapy: This technique is utilized during severe flares. Here, the topical agent is applied over the skin and is followed by covering with two layers which can be left on from several hours to a day. The first/inner layer consists of wetted gauze, tubular bandage or cotton suit, whereas, the second/outer one is a dry layer. This therapy helps by forming a physical barrier, increasing the penetration of the topical formulation and locking in moisture.[57]

Clothing: Soft, smooth, loose, full sleeved cotton clothes should be used. Coarse irritating fabrics should be avoided.[56]

Environment: In hot weather, air conditioners/ desert coolers/ fans should be used to minimize sweating as it can aggravate AD. Swimming should be avoided in acute flares as it can cause dry skin or increase cutaneous inflammation.[56]

Aeroallergens: HdM act as nonspecific irritant as well as allergen. Damp dusting, vacuuming and wet mopping are few measures against them.[56]

Moisturizer: It helps to restore deranged epidermal barrier function by restoring skin barrier lipids.[56] It forms an important constituent in prevention of flares and maintenance.[57] It should be applied within 5 minutes of bath when skin is still wet.[56] Liberal and frequent application of emollients is recommended during acute flare.[57] Oily cream-type moisturizers are used more in AD. Vegetable oils like coconut oil and sunflower oil are also helpful.[56] "Prescription emollient devices (PEDs) are a newer class of topical agents designed to target specific defects in skin barrier function observed in AD. They include preparations having distinct ratios of lipids that mimic endogenous compositions and creams containing palmitoylethanolamide, glycyrrhetinic acid, or other hydrolipids. They are generally recommended for 2 or 3 times daily use depending on the specific agent".[57]

Pharmacological:

Topical measures:

Topical corticosteroids (TCS): These anti-inflammatory agents are used when the lesions do not respond to adequate skin care and consistent usage of moisturizers only. They help by reducing acute and chronic signs of AD, along with decreasing itching. TCS are used to treat active inflammatory lesions. Short course of TCS are used during acute flares for rapid control of symptoms.[57] Once or twice daily application is recommended. Medium-to-high potency steroids are preferred during acute flares and should be continued till eczema

resolves when it is gradually stopped or substituted with lesser potency TCS.[56] In case of long-term treatment, the least potent corticosteroid which is effective is useful in reducing the side effects.[57] "Proactive" approach i.e., intermittent (once or twice per week) application of TCS to areas which are maximum prone for relapse even in the absence of active lesions is recommended to increase the symptom-free interval.[56]

Topical calcineurin inhibitors (TCI): Tacrolimus (0.03% and 0.1%) ointment and pimecrolimus (1%) cream are the two TCIs available. They are used in treating both active inflammatory disease and prevention of relapse. They do not exhibit adverse effects associated with TCS.[57] Tacrolimus 0.03% ointment and pimecrolimus cream are used in patients aged ≥2 years, while tacrolimus 0.1% is approved only for ≥16 years of age.[56,57] Twice daily application is recommended. Decrease in relapse is seen with proactive application of TCI over recurrent sites of lesions upto 2-3 times a week.[57]

Topical antimicrobials and antiseptics: Not generally recommended except in those with secondary bacterial infection where bleach bath and intranasal mupirocin is advised.[57]

Newer topical therapies:

- Phosphodiesterase 4 Inhibitors: Crisabarole 2% (20 mg per gram) ointment is a novel United States Food and Drug Administration (US-FDA) approved agent for patients aged 2 years and above with mild-to-moderate disease. A thin layer should be applied twice daily to the affected region.[58] It is tolerated well with minimal side effects such as burning or stinging sensation.[59,60]
- Janus kinase (JAK) inhibitors: Tofacitinib 2% ointment has shown to reduce itching in clinical trials. However, it has not been approved yet.[61]
- Nonsteroidal anti-inflammatory agent: Tapinarof is a novel agent undergoing clinical trial which may be helpful in AD.[37]

Systemic measures:

Oral antihistamines: Histamine-1 (H1) receptor antagonists act against H1 receptor mediated features like vasodilation, edema and erythema. They are used to control itching. First generation antihistamines cross the blood-brain barrier due to their lipophilic nature and thus cause sedation. This property is used to improve the quality of sleep in the patient. Therefore first generation antihistamines given for short period and intermittently are advised in AD. Second generation antihistamines do not cross the blood brain barrier and have less sedating effects.[62]

Systemic antimicrobials: Use of systemic antimicrobial in case of non-infected AD is not recommended and is reserved only for patients exhibiting features of microbial infection.[63]

Systemic corticosteroids: They have only a limited role in the management of severe exacerbations of AD. These are used in short courses during acute flare. Dose has to be tapered over several weeks to prevent steroid withdrawal and thereby leading to acute eczema flares. Long term usage of systemic corticosteroid leads to significant adverse effects.[62]

Cyclosporine (CsA): CsA is an immunosuppressive drug which acts by inhibiting T-cell function. Therefore, in AD it is useful by its action against Th2 response during acute phase and Th1 response during chronic phase.[62] It is an efficient drug for severe AD refractory to topical treatments.[63] CsA reduces itching, clinical extension of lesions and improves the QOL of AD patients.[62] Recommended dosage is 3-6 mg/kg/day. It should be tapered or discontinued once the lesions resolve.[63]

Azathioprine (AZA): It is a purine analog which preferentially affects B-cells and T-cells and is used in case of recalcitrant AD. AZA is found to be helpful in improving QOL

and manifestations of AD. Dosage ranges from 1-3 mg/kg/day depending on levels of enzyme thiopurine methyltransferase. In children, doses from 2.5 mg/kg/day upto 4 mg/kg/day can be given. Upon clearance of lesions, drug should be tapered and stopped, followed by maintenance with moisturizers and topical therapies.[63]

Methotrexate (MTX): One of the off-label indications of MTX is AD. It is recommended in treatment of severe and refractory cases. Average duration for maximum response is around 10 weeks.[63]

Mycophenolate mofetil (MMF): AD is an off-label indication for MMF and is preferred in refractory AD. However, data regarding its usage in AD is insufficient.[63]

Other systemic therapies (including available and under trial):[60,64]

Target	Drug
Interferon ɣ (IFN- ɣ)	Interferon ɣ (IFN- ɣ)[63]
Anti-IgE	Omalizumab
Anti-IL-4/13	Dupilumab[65]
Anti-IL-13	Tralokinumab, Lebrikizumab
Anti-IL-17A	Secukinumab
Anti-IL-31/31 Receptor	Nemolizumab
Anti-IL-12/23	Ustekinumab
Anti-IL-22	Fezakinumab[66]
Phosphodiesterase-4 (PDE4) inhibitor	Apremilast
Anti-TSLP	Tezepelumab[67]

Table 2: Systemic biologics and small molecules used in AD

Dupilumab: US-FDA approved agent for moderate-to-severe AD in patients aged 12 years and older. Route of administration is subcutaneous injection. In adults, it is given at an initial dose of 600 mg (two 300 mg injections) followed by a dose of 300 mg every alternate week.[67] Dosage in adolescents is as follows:[68]

Body Weight	Initial Dose	Subsequent Doses (every alternate week)
less than 60 kg	400 mg (two 200 mg injections)	200 mg
60 kg or more	600 mg (two 300 mg injections)	300 mg

Table 3: Dupilumab dosage in adolescents for atopic dermatitis

Phototherapy:

Phototherapy in various forms like natural sunlight, narrowband (NB) ultraviolet (UV) B (NBUVB) therapy, broadband (BB) UVB therapy, UVA therapy, psoralen plus UVA (PUVA) therapy, UVA with UVB (UVAB) therapy, and Goeckerman therapy are useful in AD. Of these different options, NB-UVB is the most commonly recommended. Dosage is determined based on minimal erythema dose and/or Fitzpatrick skin type. Phototherapy is generally recommended as the treatment modality in children who show poor response to multimodal topical therapy.[63]

Kanwar *et al.* conducted a study to evaluate the diagnostic significance of the minor features of AD in children aged 3 months to 12 years. Out of the 50 study subjects, 82% had Dennie-Morgan fold, xerosis was seen in 80%, p.alba in 78%, 74% patients had early age at onset, 66% had itching when sweating. Out of the 23 features, the following were found more frequently in the patients than the controls: keratosis pilaris, Dennie-Morgan infraorbital folds, tendency toward cutaneous infections, facial pallor or erythema, palmar hyperlinearity, p.alba, course influenced by environmental or emotional factors, xerosis, nonspecific hand-foot dermatitis, nipple eczema, orbital darkening, onset at early age, itching induced by sweating, and intolerance to wool. The frequency of cheilitis, accentuation of the perifollicular region, recurrent conjunctivitis and white dermographism did not differ significantly between the study and the control group.[69]

Dhar *et al.* conducted a prospective study in North India over a period of 7.5 years, in which classical distribution, dry skin, infraorbital fold and its chronic/relapsing nature were observed to be helpful in differentiating the cases from the controls. They found that in the infantile AD group, facial involvement was seen in 79%, flexural involvement in 42%, and both flexors and extensors were involved in 5.7%. In the childhood AD group, corresponding figures were 74.5%, 35.5%, 56.32%, and 8.24% respectively.[7]

In another study conducted by Dhar *et al.* conducted on 100 children with atopic dermatitis in Eastern India, they observed that most cases had age of onset either at 1-2 years of age or above 3 years. Prevalence was found to be only 0.55% which was lesser than in the west. Out of 100 patients, 39 had flexural lesions, while 38 and 20 children had extensor and facial lesions respectively. Involvement of both flexors and extensors were seen in 3 children. Personal and family history of atopy were seen in 54% and 65% each. Children showing

seasonal variation were 67% of which exacerbation during summer was seen in 40%, winter exacerbation in 15% and 12% showed exacerbation in rainy season.[70]

Nagaraja *et al.* in their study evaluated frequency and significance of minor clinical features of Hanifin and Rajka in 100 children aged below 12 years. They observed that certain features like ichthyosis, cheilitis, eczema of the nipples, anterior neck folds, p.alba, and intolerance to certain food items were non-specific. Whereas, other features such as xerosis, presence of Dennie-Morgan fold, onset at early age, increased tendency to cutaneous infection, itch associated with sweating, white dermographism, facial erythema and intolerance to wool/lipid solvents were significant.[71]

Sarkar *et al.* in their clinico-epidemiological study including 125 children below 12 years of age (26 infants and 99 children) made an observation that mean age at onset was 4.5 months in infants and 4 years in children. Positive family history of atopy was seen in 42.30% of infants as compared to 35.35% of children. In childhood AD group, 7% of patients exhibited a positive personal history of atopy. Extensors were involved in 26.9% of infants and 37.4% of children, whereas, flexor involvement was seen in 15.4% of infants and 45.4% of children. Facial involvement was noted in 80.8% and 66.7% of infants and children respectively. Winter exacerbation was seen in 62% of the patients while only 17% had summer worsening. Pruritus was a common feature in all the cases. Xerosis and early age at onset were two other frequent features.[72]

Dhar *et al.* conducted a study to evaluate the history of atopy in children with AD. Children between 3 months and 12 years of age were included in this study. They found comparatively lower rates of personal and family history of atopy than the previous studies with personal history of atopy being positive in 18.5%, family history in 40%, and both personal and family history together in 7.7% of the patients.[73]

From review of literature it is evident that minor clinical features play an important role in diagnosing AD. Since there are no definite diagnostic modalities available to diagnose AD with certainty, recognising the presence of minor clinical features provides an easy basis for diagnosis and thus treatment of AD in clinical settings. However, the presence of features varies from region to region. Thus, it is important to know the prevalence of the individual features for easy recognition of the condition.

Hence, this hospital-based study is undertaken to determine the frequency of these minor features among a section of south Indian children with AD attending a tertiary health care centre in north Karnataka.

METHODOLOGY

Source of data

Children suffering from atopic dermatitis attending the outpatient department of Dermatology, Venereology and Leprosy of B.L.D.E (deemed to be university) Shri. B.M. Patil Medical College, Hospital and Research Centre, Vijayapura, were enrolled for the study.

Period of study

The study was conducted during the period of November 2017 to August 2019.

Study design

Hospital based cross-sectional study.

Method of data collection

A total of 174 patients suffering from atopic dermatitis aged ≤16 years, irrespective of gender, were enrolled for the study. Informed consent was taken from parents of all the study subjects.

There is no consensus definition for rural population in India. Following census 2011,[22] urban population has been well defined. Based on that, rural population was taken as follows for this study:

1. Any area without municipality, corporation, cantonment board or notified town area committee.

2. Places with following:
    i) Population of <5000
    ii) Density of population <400/sq.km or <1000/sq.mile
    iii) Majority of the working population engaged in agricultural activities.

Inclusion criteria

Patients aged 16 years and below, suffering from atopic dermatitis.

Method

Detailed history with respect to the present age, age of onset of disease, pruritus, chronicity of the disease, personal and/or family history of atopy, tendency toward cutaneous infections and nonspecific hand/foot dermatitis, recurrent conjunctivitis, itch when sweating, intolerance to wool and lipid solvents, food hypersensitivity, influence of environmental and/or emotional factors on course of disease was recorded from the parents in scheduled proforma.

Clinical examination was done and signs with skin lesions were recorded in the proforma enclosed.

Ophthalmological evaluation to see for presence of keratoconus and anterior subcapsular cataract was performed by ophthalmologist.

Blood test to assess serum IgE level was conducted at laboratory.

Investigations

Serum IgE level is one of the minor criteria in Hanifin and Rajka's criteria for AD. Hence it was the only laboratory investigation assessed in this study.

Statistical analysis

All characteristics were summarized descriptively. For continuous variables, the summary statistics of mean ± standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries and diagrammatic presentation. Data were analyzed using SPSS software v.23.0 and Microsoft office 2007.

Ethical clearance

Institutional ethical clearance was obtained for the study

RESULTS

A hospital based cross sectional study was conducted from November 2017 to August 2019. A total of 174 children aged ≤16 years with atopic dermatitis were included in the study.

Sex distribution:

Of the 174 patients enrolled in the study, 88 (50.6%) were males and 86 (49.4%) were females. Male to female ratio was 1.02:1.

Sex	Number	Percentage
Male	88	50.6
Female	86	49.4
Total	174	100

Table 4: Distribution of cases according to sex

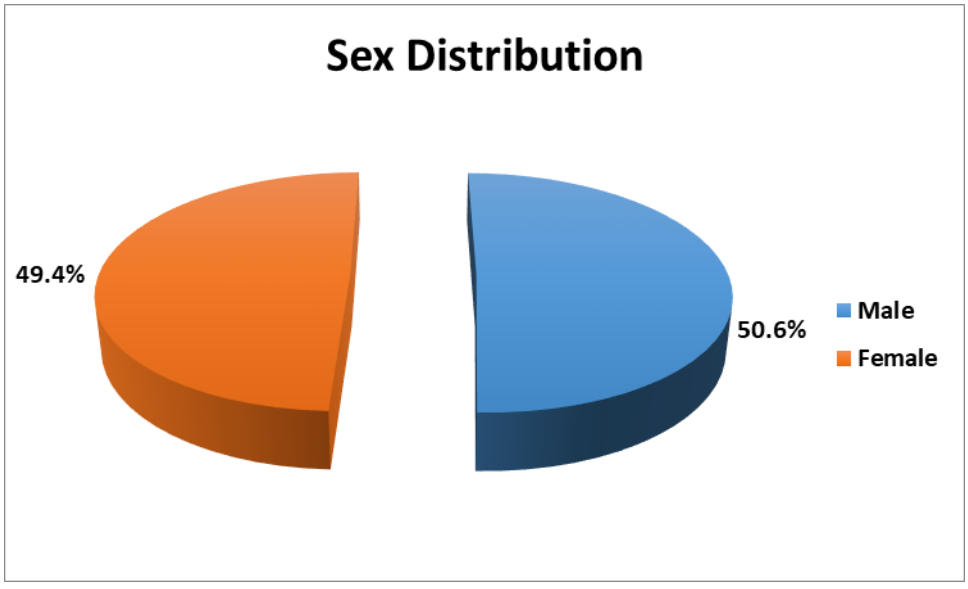

Figure 5: Distribution of cases according to sex

Age distribution

Children aged 16 years and below with atopic dermatitis were included in the study. The Mean age (±SD) of the study population was 4.6 (±3.9) years. The maximum number of patients were in the age group 2 to 12 years i.e., 104 patients (59.8%).

Age (Years)	Number	Percentage
<2	63	36.2
2-12	104	59.8
12-16	7	4
Total	174	100

Table 5: Distribution of cases according to age

	Min	Max	Mean (year)	SD
Age	01 month	16 years	4.6	3.9

Table 6: Mean age of cases

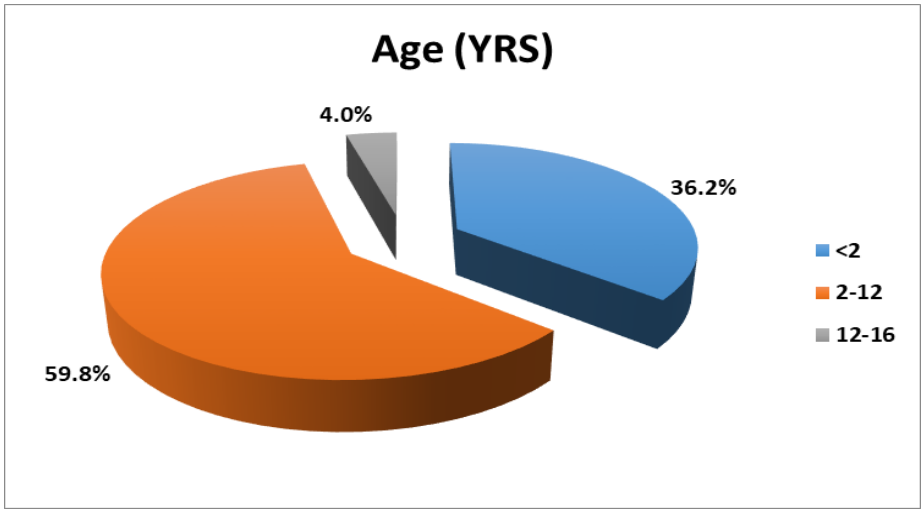

Figure 6: Distribution of cases according to age

Distribution of cases according to major criteria

Pruritus was present in 149 of the 174 cases (85.6%). Morphology and distribution of lesion-wise majority had facial and extensor involvement (124 cases, 71.3%) followed by flexural lichenification in 51 patients (29.3%). Of the 174 patients, chronic or chronic relapsing dermatitis was seen in 62 (35.6%) and personal or family history of atopic disease in 96 (55.2%).

MAJOR CRITERIA		**Number**	**Percentage**
Pruritus		149	85.6
Typical morphology and distribution	Facial and extensor involvement	124	71.3
	Flexural lichenification	51	29.3
Chronic or chronically relapsing dermatitis		62	35.6
Personal or family history of atopic disease		96	55.2

Table 7: Distribution of cases according to major criteria

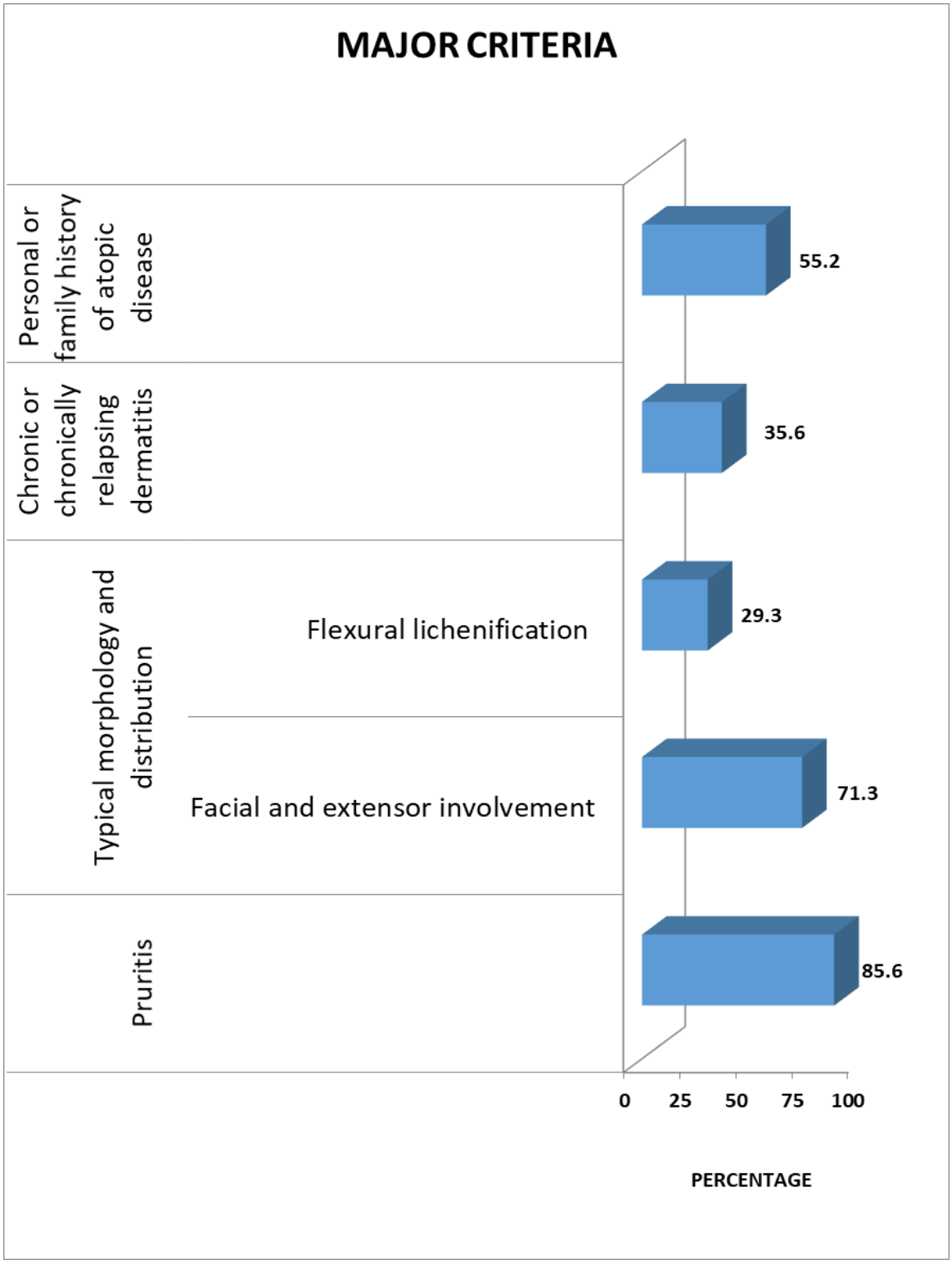

Figure 7: Distribution of cases according to major criteria

Distribution of cases according to minor criteria

The most common minor criteria observed among the subjects was Dennie-Morgan infraorbital fold i.e., in 125 (71.8%) of the 174 cases. The other common minor criteria observed were hyperlinear palms (67.8%), xerosis (67.2%), pityriais alba (57.5%), and perifollicular accentuation (47.7%). Early age of onset was seen in 118 children (67.8%). Among the 174 cases, 143 were tested for serum IgE levels out of which 92 cases showed elevation. The remaining 31 patients were not willing for the test. Ophthalmological examination of 111 cases aged 2 years and above revealed ‘high reading with no keratoconus, in 2 cases while 3 were labelled as ‘keratoconus suspect’. Nipple eczema, recurrent conjunctivitis, food hypersitivity and white dermographism were not observed in any of the patients. Tests for IgE reactivity were not conducted in any patients due to non-compliance.

MINOR CRITERIA		Number	Percentage
Xerosis		117	67.2
Ichthyosis		20	11.5
Hyperlinear palms		118	67.8
Keratosis pilaris		7	4
Elevated serum IgE level		92	52.9
Early age of onset		118	67.8
Tendency for cutaneous infections		5	2.9
Tendency to nonspecific hand/foot dermatitis		8	4.6
Nipple eczema		0	0
Cheilitis		13	7.5
Recurrent conjunctivitis		0	0
Dennie-Morgan infraorbital fold		125	71.8
Keratoconus	High reading, No Obvious Keratoconus	2	1.1
	Keratoconus Suspect	3	1.7
Orbital darkening		12	6.9
Facial pallor		37	21.3
Facial erythema		17	9.8
Pityriasis alba		100	57.5
Anterior neck folds		11	6.3
Itch when sweating		14	8
Intolerance to wool and lipid solvents		4	2.3
Perifollicular accentuation		83	47.7
Food hypersensitivity		0	0
Course influenced by environmental and/or emotional factors		14	8
White dermographism		0	0

Table 8: Distribution of cases according to minor criteria

IgE reactivity tests were not performed in any of the patients. Serum IgE level was tested in 143 cases. Examination for keratoconus and anterior subcapsular cataract was done in 111 of 174 patients. Anterior subcapsular cataract was not observed in any of the examined 111 subjects.

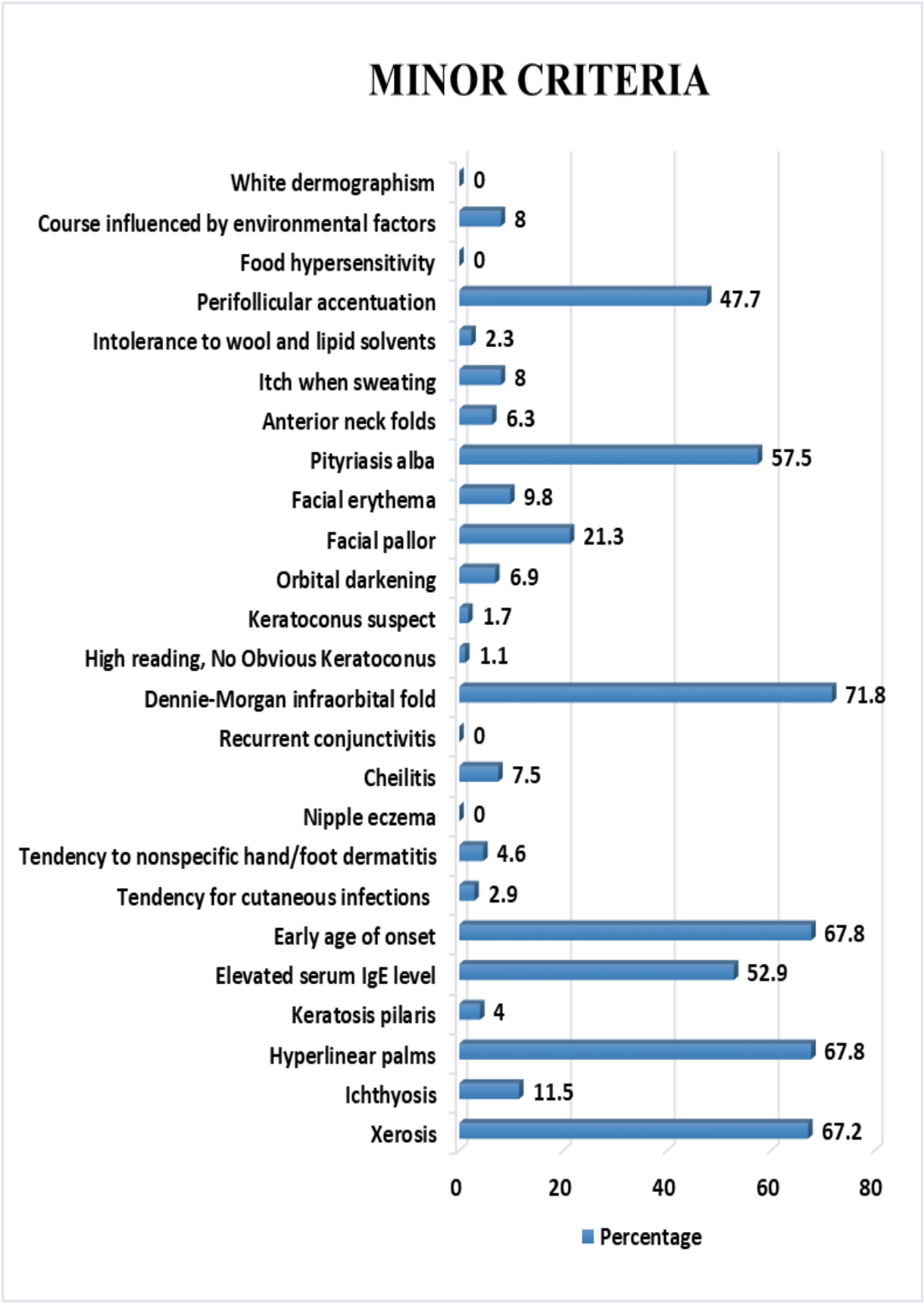

Figure 8: Distribution of cases according to minor criteria

Distribution of lichen spinulosus among cases

On examining the 174 participants of our study for presence of lichen spinulosus, 18 cases (10.3%) were found to exhibit the lesions.

LICHEN SPINULOSUS	Number	Percentage
Present	18	10.3
Absent	156	89.7
Total	174	100

Table 9: Distribution of lichen spinulosus among cases

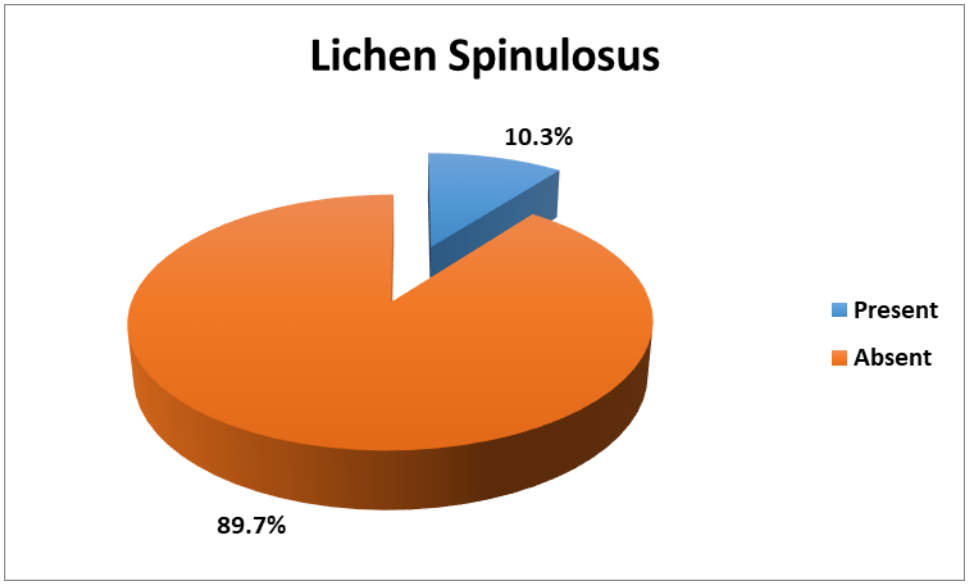

Figure 9: Distribution of lichen spinulosus among cases

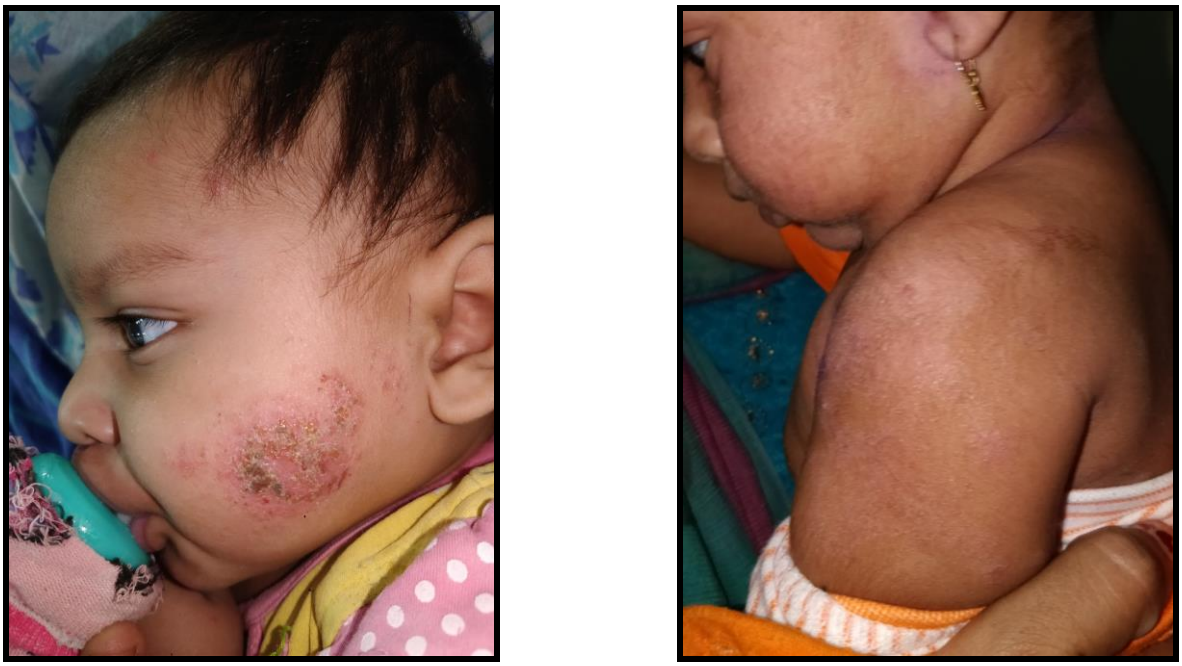

Figure 10: Facial and extensor distribution of lesions

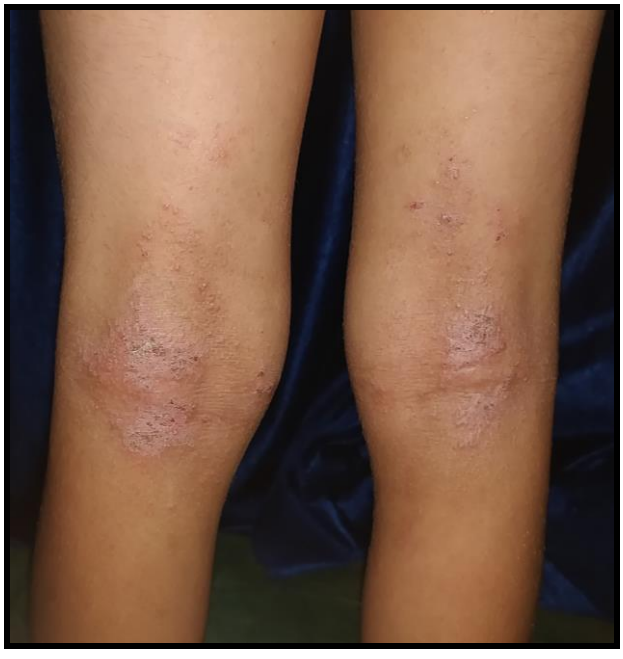

Figure 11: Flexural distribution of lesions

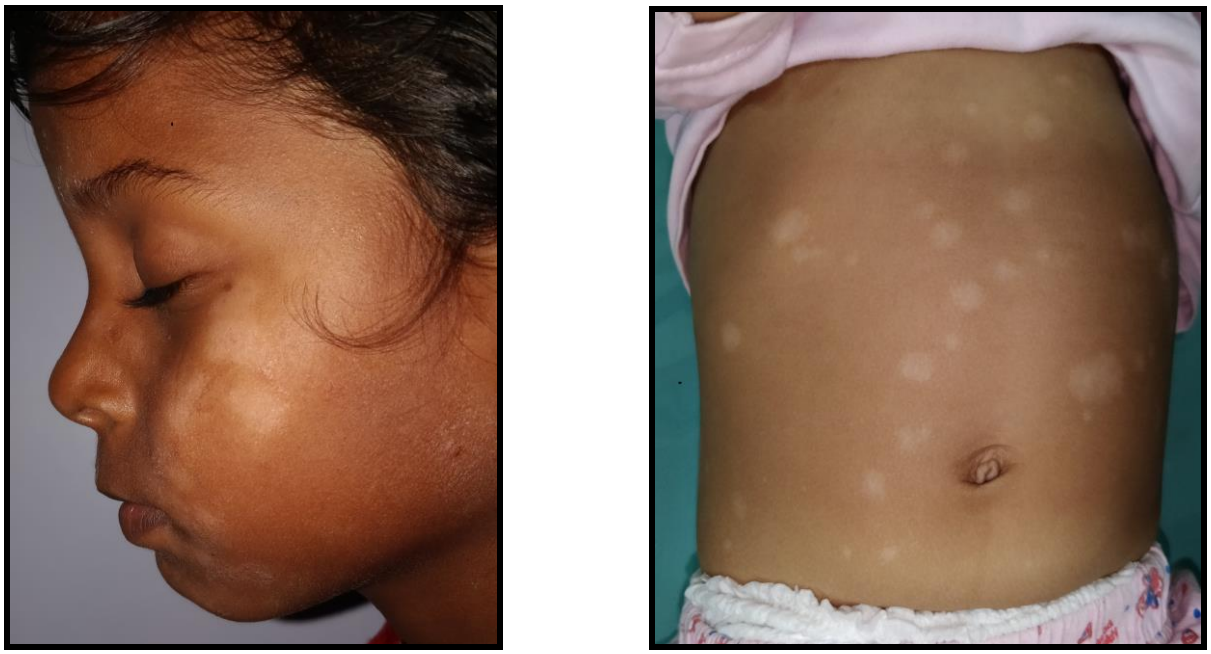

Figure 12: Pityriasis alba lesions over face and trunk

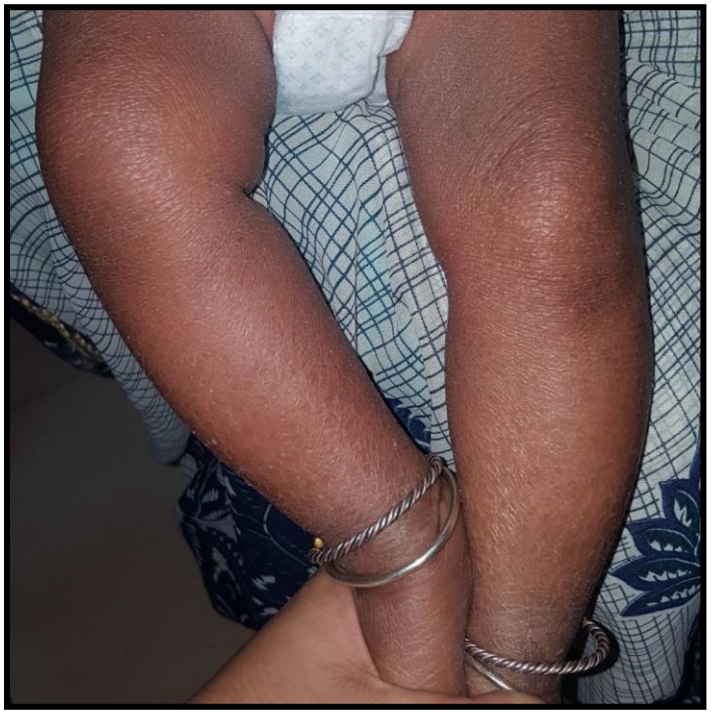

Figure 13: Xerosis over extremities

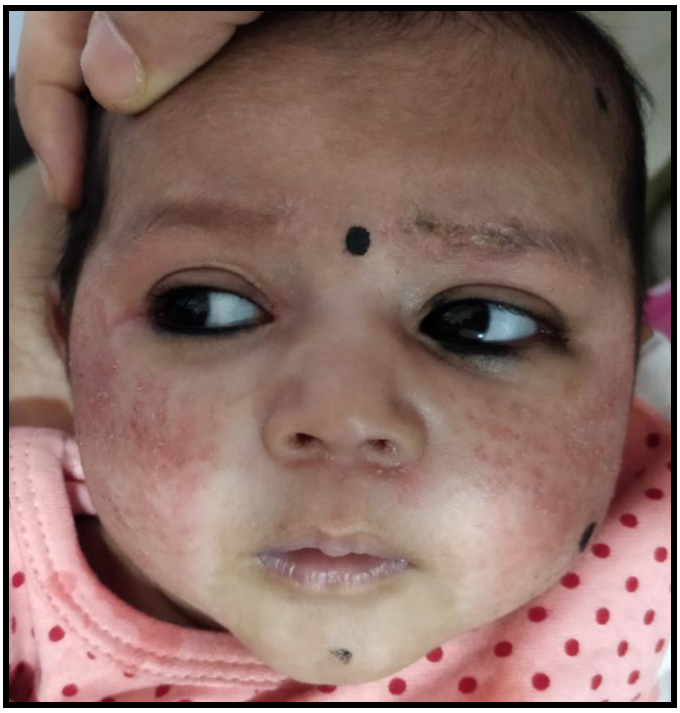

Figure 14: Facial pallor over periorbital, perinasal and perioral areas (headlight sign)

Figure 15: Dennie-Morgan infraorbital folds

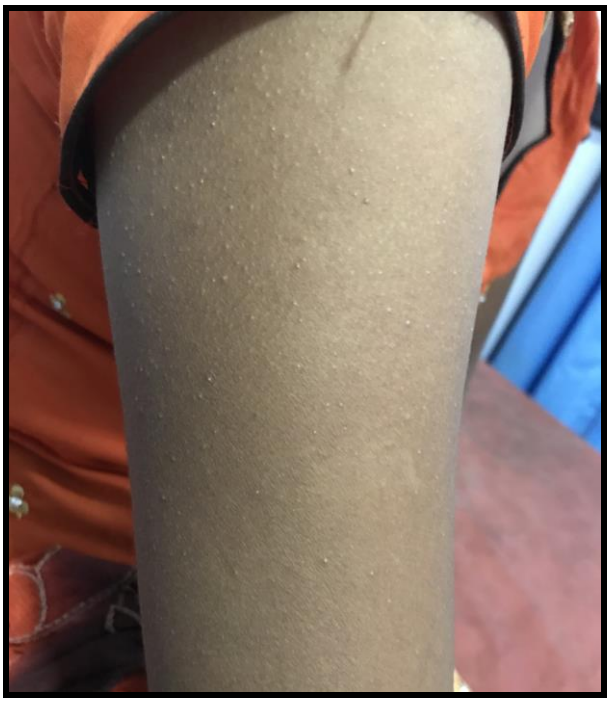

Figure 16: Keratosis pilaris lesions over arm

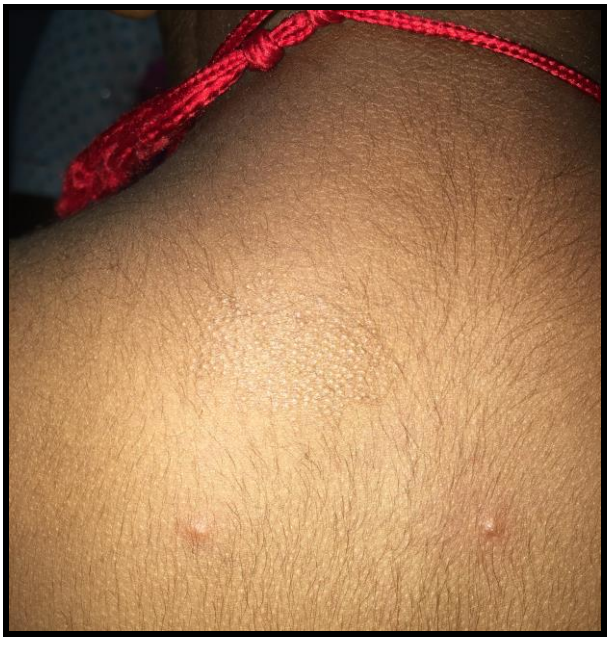

Figure 17: Lichen spinulosus lesions over upper back

DISCUSSION

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease characterized by intense pruritus. Association with other atopic disorders like, asthma and allergic rhinoconjunctivitis is commonly observed.[1] Prevalence of clinical features and intensity of symptoms of AD may vary with genetic background, climate, geographical regions, food habits, socioeconomic status, availability of health care facilities and many other factors.[3]

Various diagnostic criteria are available for the diagnosis of AD. The most important and commonly used ones are; Hanifin and Rajka's criteria, U.K. diagnostic criteria (William *et al*., 1994) and ISAAC (International Study of Asthma and Allergies in childhood) questionnaire (1995).[3] Hanifin and Rajka's criteria is suitable for use in hospital set-up by clinicians. It consists of four major criteria and twenty-three minor criteria. Three from each category are necessary for diagnosing AD.[4]

Out of 174 cases included in our study 88 were males and 86 were females i.e., males were slightly higher than females which corresponds to the findings by other Indian studies.[69,71]

Our study included children aged 16 years and below. The youngest patient was aged 1 month while the eldest patient was 16 years old. Upon categorizing the cases depending on their age into 3 major categories i.e., ≤2 years, 2-12 years and 12-16 years, we noted that majority of the cases in our study belonged to the age group of 2-12 years i.e., 59.8% followed by 36.2% who were aged below 2 years. Mean age of the patients was 4.6 ± 3.9 years. Similar finding was observed in the studies conducted by Dhar *et al.,* and Nagaraja

et al., on children aged 3 months to 12 years in which it was 4.37 ± 3.42 years and 4.04 ± 3.42 years respectively.[73,71]

Of the 174 patients in our study, 85.6% had history of itching at the time of presentation. Various factors such as impaired barrier function, central and peripheral neural sensitization, itch-scratch-itch cycle and various mediators including serine proteases, nerve growth factor and IL-31 are responsible for pruritus in AD.[10]

Facial and extensor distribution of lesions was observed in 71.3% of the children compared to the remaining 29.3% who had flexural distribution. This increased extensor/facial involvement could be attributed to the lower age group of the subjects in our study as only children were enrolled. This is in contrast to study by Agrawal *et al.,* where the mean age group was higher (42.04 years).[11]

Chronic or chronically relapsing dermatitis was regarded as any eczema persisting for 6 weeks or more, or having similar episode in the past.[11] A total of 35.6% of the patients had a positive history of chronic or chronically relapsing dermatitis. In a study by Agrawal *et al.,* they observed that 100% of the cases had positive history. However, their study included children and adults both.[11]

In a study by Dhar *et al.,* 50.76% of the children had positive personal and/or family history of atopy.[73] A similar finding was observed in our study where 55.2% of the cases gave a positive history. We defined atopy as the presence of past/present/recurrent history of asthma ± eczema ± allergic rhino-conjunctivitis, similar to study by Agrawal *et al.*[11]

In our study, the following minor features were studied: xerosis, ichthyosis, palmar hyperlinearity, keratosis pilaris, elevation in serum IgE levels, early age of onset, tendency toward cutaneous infections and nonspecific hand/foot dermatitis, nipple eczema, cheilitis, recurrent conjunctivitis, Dennie-Morgan infraorbital folds, keratoconus, anterior subcapsular cataract, orbital darkening, facial pallor or erythema, pityriasis alba, anterior neck folds, itch when sweating, intolerance to wool and lipid solvents, perifollicular accentuation, food hypersensitivity, disease course influenced by environmental and/or emotional factors, and white dermographism. IgE reactivity was not evaluated in any of the patients as parents did not agree due to expensive nature of the tests. In addition, we evaluated the presence of lichen spinulosus as minor diagnostic clue of AD.

All of the above features were present at the time of examination except for early age of onset, itch when sweating, intolerance to wool, and disease course influenced by environmental or emotional factors. Information regarding these was obtained from the history alone.

The most common finding among minor criteria observed in our study was presence of Dennie-Morgan infraorbital folds which was seen in 71.8% of the cases. Dennie-Morgan infraorbital fold was defined as present when at least one of the creases running laterally crossed the pupillary midline, as described by Mevorah *et al.*[75] Nagaraja *et al.,* and Kanwar *et al.,* noted that 63% and 82% of the patients in their study respectively exhibited Dennie-Morgan folds.[69,71]

Palmar hyperlinearity and xerosis were also other commonly observed criteria in our study which were 67.8% and 67.2% respectively. Similar higher values of palmar hyperlinearity (54%) and xerosis (80%) were also noted by Kanwar et al., in their study.[69] The high frequency of xerosis in our study could be attributed to the dry climate in the study

region. Palmar hyperlinearity was defined by the presence of more than 5 prominent lines longer than 1 cm running across palm, similar to Bohme *et al.*[76]

Criteria such as p.alba and perifollicular accentuation were also seen in higher frequency in our study i.e., 57.5% and 47.7% respectively. This high value of p.alba is in contrast to the finding by Agrawal *et al.*[11] This difference is probably due to the higher mean age of the participants in their study, as p.alba is commonly observed in children. Kanwar *et al.,* also reported an increased frequency of p.alba in their study, although study by Nagaraja *et al.,* showed a lesser frequency. Both of the studies included children aged 3 months to 12 years.[69,71] Dermatitis enhanced around hair follicles in ≥2 areas with a diameter > 5 cm was considered as perifollicular accentuation.[76] It was comparatively seen in higher frequency in our study than in the studies by Kanwar *et al.,* and Nagaraja *et al.,* where it was around 20% in both.[69,71]

Serum IgE level was screened in 143 cases in our study as the remaining 31 did not consent for the test. Out of these 143 cases, 92 showed elevated levels compared to the rest 36.5% whose values were in normal range for their age. This finding is in conformity to that reported by Agrawal *et al.,* where raised levels of serum IgE was seen in 68.7% of the cases.[11]

Early age of onset was defined as onset of symptoms of eczema before the age of 5 years, as considered by Nagaraja *et al.,* and Bohme *et al.*[71,76] In our study, 67.8% of the children had a history of early age of onset of lesions. Kanwar *et al.,* and Nagaraja *et al.,* reported that 74% and 73% of the patients respectively had a positive history of early age of onset which was comparable to our finding.[69,71]

Manifestations such as ichthyosis and keratosis pilaris were observed in 11.5% and 4% of the cases respectively in our study. More than 20 follicular, keratotic papules involving at least posterolateral aspects of upper arms or thighs defined keratosis pilaris.[76] In studies by Kanwar *et al.,* and Nagaraja e*t al.,* a comparatively higher levels of 46% and 33% respectively were observed for keratosis pilaris.[69,71] Ichthyosis was found only in 4% of the patients by Nagaraja *et al.*[71]

Facial erythema in our study was defined as erythema over cheeks without papules/scaling and facial pallor as skin pallor which is often accentuated perinasally and/or periorally.[76] In our study, facial pallor was present in 21.3% of the patients which is compatible to the findings by Nagaraja *et al*.[71] Facial erythema was noted in 9.8% of our cases and this is in contrast to the findings by Nagaraja *et al.*, where they noted 56% patient had facial erythema.[71]

Tendency for cutaneous infections described as presence of at least 2 episodes of folliculitis/ furunculosis/ impetiginisation or diagnosed herpes simplex infection in the past 1 year, was noted in only 5 of the 174 cases in our study.[76] A higher frequency was reported by both Kanwar *et al.*, and Nagaraja *et al.*, in their studies (62% and 36% respectively).[69,71] Tendency to nonspecific hand and foot eczema was defined as presence of itchy lesions on one or both hands/feet with erythema and papules/vesicles or scaling, with or without oozing, crusting, fissures, or lichenification.[76] It was also noted in fewer cases i.e., 4.6% in our study compared to the study by Kanwar *et al.*[69]

The lesser frequency of cheilitis seen in our study was in agreement with the other studies from India which were also conducted on children. The percentage of children with cheilitis in study by us, Kanwar *et al.*, and Nagaraja *et al.*, was 7.5%, 6% and 3% respectively.[69,71]

In our study, we also noted that criteria such as orbital darkening, anterior neck folds and itching when sweating occurred in fewer patients i.e., 6.9%, 6.3% and 8% respectively. Anterior neck fold(s) was defined by us as prominent horizontal skin crease(s) on anterior aspect of neck, when head is upright.[76] The finding of anterior neck fold frequency is in conformity to that reported by Nagaraja *et al.*[71] However, orbital darkening and itch when sweating both occurred in a comparatively higher frequency in other Indian studies.[69,71]

Ocular examination to diagnose keratoconus and anterior subcapsular cataract was performed by ophthalmologist in our hospital. Out of 174 cases, ophthalmological examination was done in 111 cases as the remaining children aged below 2 years were noncompliant. Anterior subcapsular cataract was not observed among any of the children examined. 'High reading but no obvious keratoconus' was noted in 2 cases while 3 were labelled as 'keratoconus suspect' on examining the children for presence of keratoconus. The parents of these 5 children were advised to follow-up once in 6 months for ophthalmological examination of their child. 'Kerataconus suspect' is defined by presence of asymmetric bowtie/ skewed radial axes pattern on videokeratography in the absence of slitlamp findings or scissoring on retinoscopy.[77] Nagaraja *et al.,* in their study did not observe keratoconus or anterior subcapsular cataract in any of the patients.[71] Keratoconus is postulated to arise as result of chronic rubbing of the eyes in AD patients.[17]

Nagaraja *et al.,* observed that intolerance to wool and lipid solvents was present in 41% of the children.[71] Also, Kanwar *et al.,* noted intolerance to wool in 28% of the children in their study.[69] In our study, history of intolerance to wool was present in only 2.3% of the cases while none gave history of intolerance to lipid solvents. This could be probably

due to the fact that majority of the patients were minimally exposed to woollen items and parents used very little soap when washing their young children.

Out of 174 cases in our study, 14 of the cases (8%) gave history of exacerbation of the lesions during winter season while none gave history of summer exacerbation. This is in contrast to other studies conducted at northern and eastern part of India where winter and summer exacerbation were comparatively higher.[8,71,72] This could be attributed to the prolonged and harsh winter and summer seen in northern and eastern India compared to the southern part.

Criteria such as nipple eczema, recurrent conjunctivitis, food hypersensitivity and white dermographism were not observed in any of the 174 cases in our study. Nagaraja *et al.,* and Sarkar *et al.,* also noted that none of the patients gave history of food intolerance which was in accordance with our findings.[71,72] Kanwar *et al.,* in their study did not find any significance of nipple eczema, white dermographism and recurrent conjunctivitis.[69] Nipple eczema was found to be non-specific in a study by Nagaraja *et al.*[71]

Apart from these 23 criteria, we also examined our cases for presence of lichen spinulosus. Lichen spinulosus is commonly observed in patients having atopic diathesis.[78] Out of the 174 patients, 18 exhibited lichen spinulosus lesions which accounted for 10.3%. However, in our study as no controls were taken, significance of lichen spinulosus in atopic dermatitis could not be established. This finding indicates that while diagnosing atopic dermatitis in a patient, lichen spinulosus could be a helpful marker.

MINOR CRITERIA		Present study	Nagaraja *et al.*	Kanwar *et al.*
Xerosis		67.2	76	80
Ichthyosis		11.5	4	-
Hyperlinear palms		67.8	23	54
Keratosis pilaris		4	33	46
Early age of onset		67.8	73	74
Tendency for cutaneous infections		2.9	36	62
Tendency to nonspecific hand/foot dermatitis		4.6	12	42
Nipple eczema		0	1	8
Cheilitis		7.5	3	6
Recurrent conjunctivitis		0	14	4
Dennie-Morgan infraorbital fold		71.8	63	82
Orbital darkening		6.9	12	32
Facial pallor		21.3	26	14
Facial erythema		9.8	56	
Pityriasis alba		57.5	34	78
Anterior neck folds		6.3	6	12
Itch when sweating		8	35	66
Intolerance to wool and lipid solvents		2.3	41	28
Perifollicular accentuation		47.7	39	22
Food hypersensitivity		0	0	-
Course influenced by environmental factors	Winter	8	29	26
	Summer	0	15	
White dermographism		0	40	12

Table 10: Comparison of minor criteria with few Indian studies (percentage values)

CONCLUSION

Atopic dermatitis is a chronic inflammatory cutaneous disease causing great morbidity and psychological stress in both patients and their parents. There are no definite diagnostic modalities available for the diagnosis of AD with certainty. To aid the diagnosis of AD, various criteria are available out of which Hanifin and Rajka's criteria is the most commonly used in the hospital set-up by clinicians.

Hanifin and Rajka's criteria consist of four major and twenty-three minor criteria. Three criteria from each category are required in making a diagnosis of AD in an individual. The frequency of minor criteria may vary population-wise.

In the present study, 174 children with atopic dermatitis who were aged 16 years and below were evaluated by us to record the features of Hanfin and Rajka's minor criteria. Ophthalmologist performed ocular examination in the patients aged 2 years and above for the presence of keratoconus and anterior subcapsular cataract. Blood tests to see for serum IgE level were conducted at laboratory. Tests for IgE reactivity were not done in any patients due to non-compliance.

The most common minor criteria in our study was Dennie-Morgan fold, observed in 71.8% of the cases. This was followed by hyperlinear palms in 67.8% and xerosis in 67.2% of the patients. The other criteria which occurred in higher frequency were p.alba (57.5%) and perifollicular accentuation (47.7%). Out of the 174 children, 74 (42.5%) exhibited early age of onset i.e., onset before 5 years of age.

Features such as nipple eczema, recurrent conjunctivitis, food hypersensitivity and white dermographism were not observed in any of the patients.

Of the 143 cases who underwent testing for serum IgE level, 92 showed elevation which denotes frequency of extrinsic AD in the study population.

Ophthalmological examination performed in 111 children revealed ‘high reading with no obvious keratoconus’ in 2 patients while 3 more were labelled as ‘keratoconus suspect’. This signifies the importance of ophthalmological examination in patients with AD. Also our study varied from other Indian studies where keratoconus was not observed in any patients.

Apart from these criteria, this study noted presence of lichen spinulosus in few of the children with AD. As no controls were included in our study, the significance of association of lichen spinulosus with atopic dermatitis should be studied with appropriate study design.

From the above discussion, it is evident that clinical features of AD may be variable. Prevalence of AD varies country-wise and within a country, region-wise. The prevalence and severity of AD are influenced by several factors like ethnic/racial factors, environmental factors, dietary habits, etc. Therefore, it is relevant for the dermatologists to have a knowledge regarding common clinical features of AD in a given population to diagnose the condition and thereby provide treatment to reduce the morbidity along with appropriate counselling.

SUMMARY

A hospital based cross sectional study to estimate the frequency of Hanifin and Rajka's minor criteria for diagnosis of atopic dermatitis in children was conducted between November 2017 and August 2019.

- A total of 174 children aged ≤16 years with atopic dermatitis were included in the study.
- Majority of the patients were in age group of 2-12 years i.e., 59.8%. Mean age of the patients enrolled in the study was 4.6±3.9 years.
- Male to female ratio in the study population was 1.02.
- Pruritus was observed in 85.6% of the patients.
- Majority of the children presented with facial and extensor involvement than flexural lichenification.
- History of chronic or chronically relapsing dermatitis was present in 35.6% of the patients.
- A positive personal and/or family history of atopy was seen in 55.2%.
- The most common minor criteria observed in our study were Dennie-Morgan infraorbital fold (71.8%), early age of onset (67.8%), palmar hyperlinearity (67.8%), xerosis (67.2%), p.alba (57.5%) and perifollicular accentuation (47.7%).
- Out of 143 cases whose serum was tested for IgE level, elevation was seen in 92.

- Facial pallor was present in 21.3% while facial erythema was present in only 9.8% of the children in present study.

- History of winter exacerbation was seen in 8% of the cases while summer exacerbation was seen in none.

- Of the 174 cases, 2.9% exhibited increased tendency for cutaneous infections and 4.6% exhibited increased tendency to nonspecific hand/foot dermatitis.

- Other criteria noted in lesser frequency in our study were ichthyosis (11.5%), itch when sweating (8%), cheilitis (7.5%), orbital darkening (6.9%), anterior neck folds (6.3%), keratosis pilaris (4%) and intolerance to wool (2.3%).

- On ophthalmological examination of 111 cases, 'high reading with no obvious keratoconus' was present in 2 cases while 3 cases were labelled as 'keratoconus suspect'. Anterior subcapsular cataract was not noted in any of the cases.

- Criteria such as nipple eczema, recurrent conjunctivitis, food hypersensitivity and white dermographism were not observed in any of the patients.

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ANNEXURE-I

ETHICAL CLEARANCE CERTIFICATE

ANNEXURE-II

PROFORMA

B.L.D.E.U'S SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, VIJAYAPURA.

Department of Dermatology, Venereology and Leprosy.

Name: SL NO:

Age: Date:

Sex: F / M IP NO/ OP NO:

Address:

Occupation of parents:

Education Status:

Major criteria

1. Pruritus
2. Typical morphology and distribution:
    a. Facial and extensor involvement
    b. Flexural lichenification
3. Chronic or chronically relapsing dermatitis
4. Personal or family history of atopic disease (asthma, allergic rhinitis, atopic dermatitis)

Minor criteria

1. Xerosis
2. Icthyosis/ hyperlinear palms/ keratosis pilaris
3. IgE reactivity (immediate skin test reactivity, Radioallergosorbent assay test positive)
4. Elevated serum IgE
5. Early age of onset
6. Tendency for cutaneous infections (especially *S.aureus* and HSV)
7. Tendency to nonspecific hand/foot dermatitis
8. Nipple eczema
9. Cheilitis
10. Recurrent conjunctivitis
11. Dennie-Morgan infraorbital fold
12. Keratoconus
13. Anterior subcapsular cataract
14. Orbital darkening
15. Facial pallor/ facial erythema
16. Pityriasis alba
17. Anterior neck folds
18. Itch when sweating
19. Intolerance to wool and lipid solvents
20. Perifollicular accentuation
21. Food hypersensitivity
22. Course influenced by environmental and/or emotional factors
23. White dermatographism or delayed blanch

ANNEXURE-III

CONSENT FORM

B.L.D.E.U's SHRI B M PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, VIJAYAPURA-586103

TITLE OF THE PROJECT : - A HOSPITAL-BASED CROSS-SECTIONAL STUDY TO ESTIMATE THE FREQUENCY OF HANIFIN AND RAJKA'S MINOR CRITERIA FOR DIAGNOSIS OF ATOPIC DERMATITIS IN CHILDREN.

PG GUIDE : -

PG STUDENT : -

PURPOSE OF RESEARCH:-

I have been informed that this project will be studied to estimate the frequency of minor diagnostic criteria of Hanifin and Rajka in atopic children.

BENEFITS:-

I understand that my participation in this study will help the investigator to estimate the frequency of various minor diagnostic criteria in children with atopic dermatitis which helps in better recognition of the clinical features and thereby contributing to the diagnosis of AD.

PROCEDURE:-

I understand that relevant history will be taken and I will undergo detailed clinical examination after which necessary investigations will be done whenever required.

RISK AND DISCOMFORTS:-

I understand there is no risk involved with this study.

CONFIDENTIALITY:-

I understand that medical information produced by this study will become a part of my hospital records and will be subjected to the confidentiality and privacy regulation of the said hospital. Information of a sensitive personal nature will not be a part of the medical records, but will be stored in the investigator's research file.

If the data are used for publication in the medical literature or for teaching purposes no names will be used and other identifiers such as photographs and audio or videotapes will be used only with my special written permission. I understand I may see the photographs, videotapes and hear the audiotapes before giving this permission.

REQUEST FOR MORE INFORMATION:-

I understand that I may ask more questions about the study at any time concerned. _____ is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of this study, which may influence my continued participation.

REFUSAL OR WITHDRAWAL OF PARTICIPATION:-

I understand that my participation is voluntary and I may refuse to participate or may withdraw consent and discontinue participation in this study at any time without prejudice. I also understand that _____ may terminate my participation in this study at any time after she has explained the reasons for doing so and has helped arrange for my continued care by my own physician, if this is appropriate.

INJURY STATEMENT:-

I understand that in the unlikely event of injury to me resulting directly from my participation in this study and if such injury were reported promptly, then medical treatment will be available to me, but no further compensation will be provided. I understand that by my agreement for my participation in this study, I am not waiving any of my legal rights.

I have explained to (patient's / relevant guardian's name) the purpose of the research, the procedures required, and the possible risks and benefits to the best of my ability in patient's own language.

_____ _____

Investigator / P. G. Guide Date

I confirm that …….……(Name of the PG guide / chief researcher) has explained to me the research, the study procedures that I undergo and the possible risks and discomforts as well as benefits that I may experience. I have read and I understand this consent form. Therefore, I agree to give my consent for my participation as a subject in this research project.

_____ _____

Participant / guardian Date

_____ _____

Witness to signature Date

KEY TO MASTER CHART

T.M.D	-Typical morphology and distribution
F.E.I	- Facial and extensor involvement
F.L	- Flexural lichenification
C or CR D	- Chronic or chronically relapsing dermatitis
P/FH of A	- Personal or family history of atopic disease
HP	- Hyperlinear palms
KP	- Keratosis pilaris
IgE R(ISTR/RAST)	-IgE reactivity (immediate skin test reactivity, Radioallergosorbent assay test)
S.IgE	-Serum IgE
E.A.of.O	- Early age of onset
T.C.I	- Tendency for cutaneous infections
T.N.H/F.D	-Tendency to nonspecific hand/foot dermatitis
R.C	- Recurrent conjunctivitis
DMF	- Dennie-Morgan infraorbital fold
ASC	-Anterior subcapsular cataract
OD	- Orbital darkening
P.Alba	- Pityriasis alba
ANF	- Anterior neck folds
I.W/L.S	- Intolerance to wool and lipid solvents
PA	- Perifollicular accentuation
Food HSN	- Food hypersensitivity

C.I.En/Em	- Course influenced by environmental and/or emotional factors
WD	- White dermographism
M	- Male
F	- Female
P	- Present
A	- Absent
ND	- Not done
HR, NOK	- High reading, no obvious keratoconus
KS	- Keratoconus suspect

MASTER CHART

S.No.	OP/IP No.	Name	Age	Sex	Major					Lichen Spinulosus
					Pruritis	T.M.D		C or CR D	P/FH of A	
						F.E.I	F.L			
1	349905	Praveen	12y	M	A	P	P	P	A	A
2	364729	Sweta S	8y	F	P	P	A	P	A	A
3	364821	Vijaylaxmi	7y	F	P	P	A	P	A	A
4	367192	Shivaji	1.5y	M	P	P	A	P	A	A
5	370548	Tanayya S	1y	F	A	P	A	P	A	A
6	395023	Aman.M	7y	M	A	P	A	P	A	A
7	396646	Rakshita P	6y	F	A	A	P	P	A	A
8	400444	Shreya	11m	F	P	P	A	P	A	A
9	402862	Nisha M	6y	F	A	A	P	P	A	A
10	407370	Akhil	5m	M	A	P	A	P	A	A
11	433345	Bhumika D	9y	F	P	P	A	P	A	A
12	1975	Shreya P	15m	F	A	P	A	P	P	A
13	4679	Shahista A	10m	M	A	P	A	P	P	A
14	10393	Vatsalya	11m	F	P	P	A	P	A	A
15	3104	Sneha SK	11m	F	P	P	A	P	A	A
16	42376	Prajnya	1y	F	P	P	A	P	P	A
17	41969	Rajat	4y	M	P	A	P	P	A	A
18	84126	Om B	1y	M	P	P	A	P	A	A
19	86783	Abhay B	2y	M	A	P	A	P	P	A
20	91818	B/o Prathiba	1m	F	P	P	A	P	P	A
21	97530	Avanish	8y	M	P	A	P	P	A	A
22	97614	Abhinav	2y	M	P	P	A	P	P	A
23	125124	Adarsh	2.5m	M	P	P	A	P	P	A
24	121053	Mohd.Zaki	1y	M	P	P	A	P	A	A
25	139694	Fatima Bagali	3m	F	P	P	A	P	P	A
26	165075	Vaishnavi R	2y	F	P	P	A	P	A	A
27	175725	Moh.Zuber	7m	M	P	P	A	P	P	A
28	166339	Maria B	1y	F	P	P	A	P	A	A
29	177312	Sameena K	3y	F	P	P	A	P	A	A
30	174355	Davik C	1y	M	P	P	A	P	A	A
31	184090	Varsha W	4y	F	P	P	A	P	A	A
32	187282	Pallavi B	9y	F	P	A	P	P	P	A
33	16694	Prateeksha	9m	F	P	P	A	P	A	A
34	200000	Arushi S	4y	F	P	A	P	P	P	A
35	203348	Nandini	10m	F	P	P	A	P	P	A
36	96243	Inaya P	2y	F	P	A	P	P	P	A
37	217618	Shivakumar	13y	M	P	A	P	P	P	A
38	218630	Md.Azeen D	4m	F	A	P	A	P	P	A
39	220071	Mayuresh	7y	M	P	A	P	P	P	A
40	223491	Sangram	6y	M	P	A	P	P	P	A
41	224751	Satvik M	1.5y	M	P	P	A	P	P	A
42	226033	Priyanka	3y	F	P	P	A	P	P	A
43	234628	Ratna W	2y	F	P	A	P	P	A	A
44	371749	Laxmi B	5y	F	P	P	A	P	A	A
45	248059	Divya I	3y	F	P	P	A	P	A	A
46	248147	Virta U	1y	M	P	P	A	P	P	A
47	247524	Shrushti K	6y	F	P	A	P	P	P	A
48	249317	Shravani	3y	F	P	P	A	P	A	A
49	254279	Divit	7m	M	P	P	A	P	A	A
50	256740	Trisha H	2y	F	P	P	A	P	A	A
51	258043	Abhishek K	5y	M	P	P	A	P	A	A
52	258383	Shreyas M	2m	M	A	P	A	P	P	A
53	259258	Moshina	1.5y	F	P	P	A	P	A	A
54	259316	Sannidhi B	1.5y	F	P	P	A	P	A	A
55	260603	Swaran P	5y	M	P	P	A	P	P	A

56	261477	Soujanya SM	5y	F	P	A	P	P	P	A
57	261963	Raju V	8y	M	P	P	A	P	A	A
58	263999	Siddu W	5m	M	A	P	A	P	A	A
59	265738	Sagar O	6m	M	P	P	A	P	P	A
60	267904	Prasad AK	5m	M	P	P	A	P	A	A
61	269774	Shrinath K	2y	M	P	P	A	P	P	A
62	270396	Uday C	4y	M	P	P	A	P	P	A
63	270391	Abhishek C	8y	M	P	A	P	A	P	A
64	272826	Sanvi	1y	F	P	P	A	A	A	A
65	278519	Akash R	12y	M	P	A	P	A	A	A
66	284510	Revakka P	13y	F	P	A	P	A	P	A
67	284668	Prajwal P	9y	M	P	A	P	A	P	A
68	286504	Sahan P	6y	F	A	P	A	A	P	A
69	288789	Aishwarya	10m	F	P	P	A	A	A	A
70	289671	Soundarya A	6y	F	A	P	A	A	P	P
71	292053	Sultan T	11m	M	P	P	A	A	P	P
72	292156	Shivanand S	4y	M	P	P	A	A	P	P
73	292142	Raju G	8y	M	A	P	A	A	P	P
74	294867	Yashin N	8y	M	A	P	A	A	P	P
75	295482	Neha M	4y	F	A	P	A	A	P	A
76	296146	Srikant M	6y	M	A	P	A	A	P	A
77	300971	Shreya M	8y	F	P	P	A	A	P	A
78	309984	Navyashree S	1y	F	P	P	A	A	P	A
79	311678	Netra S	3m	F	P	P	A	A	P	A
80	312030	Achit Kumar	4y	M	A	P	A	A	P	A
81	312411	Sanskriti	11y	F	P	P	A	A	A	A
82	314838	Sanvi M	5Y	F	P	P	A	A	P	A
83	317151	Nandan R	1.5y	M	P	P	A	A	P	A
84	317756	Ummehabiba	15m	F	P	P	A	A	P	A
85	326821	Pallavi VM	7y	F	P	P	A	A	P	A
86	328605	Alina K	4y	F	P	P	A	A	A	A
87	329778	Shankar P	7y	M	P	P	A	A	P	A
88	336596	Jahnavi	3y	F	P	A	P	A	A	A
89	346106	Samart G	4y	M	P	A	P	A	P	A
90	347489	Pratam	6m	M	P	P	A	A	A	P
91	354306	Basamma K	8y	F	P	A	P	A	A	A
92	356212	Mahenoor C	5y	M	P	A	P	A	P	A
93	367047	Samskriti	4y	F	P	A	P	A	P	A
94	372344	Aishwary N	11m	F	P	P	A	A	A	A
95	387357	Hammad M	3.5y	M	P	P	A	A	P	A
96	396662	Adya J	1.5y	F	P	P	A	A	P	A
97	397007	Mustan K	15m	F	P	P	A	A	P	A
98	401513	Ankita S	9y	F	P	A	P	A	P	P
99	412312	Nazish Z	3y	M	P	A	P	A	P	P
100	412811	Aradhya H	11m	F	P	P	A	A	A	A
101	419035	Preetam K	7m	M	P	P	A	A	A	A
102	425775	Sampat K	8y	M	P	A	P	A	A	A
103	434306	Preetam A	2y	M	P	P	A	A	P	A
104	44018	Pratam S	15m	M	A	P	A	A	P	A
105	3226	Md.Owais	4y	M	P	P	A	A	P	A
106	9227	Ruhan B	11m	M	P	P	A	A	A	A
107	27256	Prabhuver	1y	M	P	P	A	A	P	A
108	84277	Adya P	1.5Y	M	P	A	A	A	P	A
109	91827	Sushmita B	7y	F	P	P	A	A	P	P
110	92445	Anash N	10m	M	P	P	A	A	P	A
111	97838	Laxmi D	2y	F	P	A	P	A	A	A
112	144601	Shreyas M	1y	F	P	P	A	A	P	A
113	185593	Vikas K	11y	M	P	P	A	A	A	A
114	189427	Megha A	3y	F	P	A	P	A	P	A
115	188992	Vittal	10y	M	P	P	A	A	A	A
116	192899	Praveen	10y	M	P	A	P	A	A	A
117	195316	Shruti S	7y	F	P	P	A	A	A	A
118	197635	Prajwal P	7y	M	P	A	P	A	P	A

119	204430	Md.Afzar	3y	M	P	P	A	A	A	A
120	206818	Soujanya	8y	F	P	A	P	A	A	A
121	208124	Omkar	1y	M	P	P	A	A	P	A
122	208137	Radhika	10y	F	P	A	P	A	A	A
123	212017	Swati	11y	F	P	A	P	A	P	A
124	213060	Numra	12y	F	P	A	P	A	A	A
125	214401	Tanvi	5y	F	P	A	P	A	A	A
126	221652	Manit	10m	M	A	P	A	A	P	A
127	222129	Anita	11y	F	P	A	P	A	P	A
128	213659	Aishwarya	12y	F	P	A	P	A	A	A
129	224340	Bhimaray	11y	M	P	A	P	A	A	A
130	226026	Advik	15m	M	A	P	A	A	P	A
131	232156	Sakerbaig	6m	M	P	P	A	A	A	A
132	243813	Deepa K	4y	F	P	P	A	A	A	A
133	243811	Abhishek K	6y	M	P	P	A	A	A	A
134	62180	Renuka S	8y	F	P	A	P	A	A	A
135	253823	Mayur A	5y	M	P	P	P	A	A	A
136	261157	Shrishti	9m	F	P	A	P	A	P	P
137	271167	Shivani K	5Y	F	P	P	A	A	A	A
138	271032	Jayachandra	16y	M	P	A	P	A	P	P
139	272277	Dareppa K	11y	M	P	P	A	A	P	A
140	279071	Adarsh C	6y	M	P	P	A	A	P	A
141	280109	Vedant	3m	M	P	P	A	A	A	A
142	280009	Shrikrishna P	8y	M	P	P	A	A	P	A
143	281429	Umesh C	3y	M	P	A	P	A	A	A
144	281783	Basavaraj	10y	M	P	P	A	A	P	P
145	281969	Kaveri	7y	F	A	P	A	A	P	A
146	282840	Netravati MB	16y	F	P	A	P	A	P	P
147	283108	Hemavati P	4m	F	P	P	A	A	P	A
148	284989	Vishal G	9y	M	P	P	A	A	P	A
149	285218	Vasanti GM	4y	F	P	A	P	A	A	A
150	285235	Srinivas	8y	M	P	A	P	A	A	A
151	286057	Nirmal K	7.5y	M	P	A	P	A	P	P
152	286495	Roopa S	3y	F	P	A	P	A	P	A
153	287153	Arvin KA	6m	M	P	P	A	A	P	A
154	287419	Md. Zuber	7.5y	M	P	P	A	A	P	A
155	287764	Sanjana M	6y	F	P	P	A	A	P	P
156	287936	Manish HP	4y	M	P	A	P	A	P	A
157	289418	Arziya B	1.5y	F	P	P	A	A	A	A
158	289792	Harvish J	8y	M	P	P	A	A	A	A
159	290041	Srishti LR	1y	F	A	P	A	A	P	A
160	290293	Amira z	1Y	F	P	P	A	A	A	A
161	290527	Rukmini S	3m	F	P	P	A	A	P	A
162	291634	Sachin C	4y	M	P	P	A	A	A	A
163	293427	Srinivas	4y	M	P	P	A	A	A	A
164	298502	Sachin D	8y	M	P	A	P	A	P	A
165	294333	Preeti C	12y	F	P	A	P	A	P	A
166	294950	Md. Ali K	14y	M	P	P	A	A	A	A
167	295209	Rohit T	6.5m	M	P	P	A	A	P	A
168	296606	Aarti D	13y	F	P	P	A	A	A	P
169	296915	Sadhwini P	7m	F	A	P	A	A	P	A
170	297907	Pallavi C	7y	F	P	P	A	A	P	P
171	298353	Dhanush G	15y	M	P	P	A	A	P	A
172	298434	Girish N	3.5m	M	P	P	A	A	P	A
173	298837	Kushi B	7y	F	P	P	A	A	P	A
174	298992	Sayad DP	7m	M	P	P	A	A	A	P

S.No.	Minor																									
	Xerosis	Ichthyosis/HP/KP			IgE R (ISTR/RAST)	Raised S.IgE	E.A.of.O	T.C.I	T.N.H/F.D	Nipple eczema	Cheilitis	R.C	DMF	Keratoconus	ASC	OD	Facial pallor/erythema		P.Alba	ANF	Itch sweat	I.W/L.S	PA	Food HSN	C.I.En/Em	WD
		Ichthyosis	HP	KP													Facial pallor	Facial erythema								
1	P	A	A	A	ND	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
2	P	A	A	A	ND	A	A	A	A	A	A	A	A	A	A	A	A	A	P	A	A	A	P	A	A	A
3	P	A	A	A	ND	A	A	A	A	A	A	A	A	A	A	A	A	A	P	A	A	A	A	A	A	A
4	A	A	P	A	ND	A	P	A	A	A	A	A	A	ND	ND	A	P	A	A	A	A	A	P	A	A	A
5	P	A	P	A	ND	ND	P	A	A	A	A	A	P	ND	ND	A	P	A	A	A	A	A	P	A	A	A
6	P	A	A	A	ND	ND	A	A	A	A	A	A	P	A	A	A	A	A	P	A	A	A	A	A	A	A
7	A	A	A	A	ND	A	A	A	A	A	A	A	P	A	A	A	A	A	P	A	A	A	A	A	P	A
8	A	A	P	A	ND	P	P	A	A	A	A	A	P	ND	ND	A	P	A	A	A	A	A	P	A	A	A
9	P	A	A	A	ND	ND	A	A	A	A	A	A	P	A	A	A	A	A	P	A	A	A	P	A	A	A
10	A	A	A	A	ND	P	P	A	A	A	A	A	P	ND	ND	A	A	A	P	A	A	A	P	A	A	A
11	P	A	P	A	ND	P	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	P	A	A	A
12	A	P	P	A	ND	P	P	A	A	A	A	A	P	ND	ND	A	A	A	A	A	A	A	P	A	A	A
13	P	A	P	A	ND	ND	P	A	A	A	A	A	A	ND	ND	A	P	A	A	A	A	A	A	A	A	A
14	P	A	P	A	ND	P	P	A	A	A	A	A	A	ND	ND	A	P	A	A	A	A	A	P	A	A	A
15	A	A	P	A	ND	A	P	A	A	A	A	A	P	ND	ND	A	A	P	A	A	A	A	A	A	P	A
16	P	A	P	A	ND	P	P	A	A	A	A	A	P	ND	ND	A	A	P	A	P	A	A	A	A	P	A
17	P	A	P	A	ND	P	A	A	A	A	A	A	P	A	A	A	A	A	A	A	A	A	A	A	A	A
18	P	P	P	A	ND	P	P	A	A	A	A	A	A	ND	ND	A	A	A	A	A	A	A	A	A	A	A
19	P	A	P	A	ND	ND	P	A	A	A	A	A	A	A	A	A	A	A	P	A	A	A	A	A	A	A
20	A	A	P	A	ND	A	P	A	A	A	A	A	A	ND	ND	A	P	P	A	A	A	A	A	A	A	A
21	P	A	P	A	ND	P	A	A	P	A	A	A	A	A	A	A	A	A	A	A	A	A	P	A	A	A
22	P	A	P	A	ND	A	P	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	P	A	A	A
23	A	A	A	A	ND	ND	P	A	A	A	A	A	P	ND	ND	A	P	A	P	A	A	A	A	A	A	A
24	A	P	A	A	ND	A	P	A	A	A	A	A	A	ND	ND	A	A	P	A	A	A	A	A	A	A	A
25	A	A	A	A	ND	A	P	A	A	A	A	A	P	ND	ND	A	P	P	A	A	A	A	A	A	A	A
26	P	A	A	A	ND	A	P	A	A	A	A	A	P	A	A	A	A	A	A	A	A	A	A	A	A	A
27	P	A	P	A	ND	P	P	A	A	A	A	A	A	ND	ND	A	A	A	P	A	A	A	A	A	A	A
28	P	A	P	A	ND	P	P	A	A	A	A	A	P	ND	ND	A	A	P	A	A	A	A	A	A	A	A
29	A	A	P	A	ND	P	P	A	A	A	A	A	A	A	A	A	A	A	P	A	A	A	A	A	A	A
30	A	A	P	A	ND	A	P	A	A	A	A	A	P	ND	ND	A	P	A	A	A	A	A	A	A	A	A
31	A	P	P	A	ND	P	P	P	A	A	A	A	P	A	A	A	A	A	P	A	A	A	A	A	A	A
32	A	A	P	A	ND	A	A	A	A	A	A	A	A	A	A	A	A	A	P	A	A	A	A	A	P	A
33	A	A	P	A	ND	P	P	A	A	A	A	A	P	ND	ND	A	A	A	A	A	A	A	A	A	A	A
34	A	P	A	A	ND	A	P	A	A	A	A	A	P	A	A	A	A	A	A	A	A	A	A	A	A	A
35	A	A	P	A	ND	A	P	A	A	A	A	A	P	ND	ND	A	P	A	P	A	A	A	P	A	A	A
36	P	A	P	A	ND	P	P	A	A	A	A	A	P	A	A	A	A	P	A	P	P	A	A	A	P	A
37	A	P	A	A	ND	A	A	A	A	A	P	A	P	A	A	A	A	A	P	A	A	A	A	A	A	A
38	P	A	P	A	ND	P	P	A	A	A	A	A	P	ND	ND	A	P	A	P	P	A	A	A	A	A	A
39	A	A	P	A	ND	A	A	A	A	A	A	A	A	A	A	A	A	A	P	A	A	A	A	A	A	A
40	P	A	A	A	ND	P	P	A	A	A	A	A	P	A	A	A	A	A	P	A	A	A	A	A	A	A
41	P	A	P	A	ND	A	P	A	A	A	A	A	P	A	A	A	A	A	P	A	A	A	A	A	A	A
42	P	A	P	A	ND	P	P	A	A	A	A	A	P	A	A	A	A	A	P	A	A	A	A	P	A	A
43	A	A	P	A	ND	ND	P	A	A	A	A	A	P	A	A	A	A	A	A	A	P	P	A	A	A	A
44	P	A	P	A	ND	ND	P	A	A	A	A	A	A	A	A	A	A	A	P	A	A	A	P	A	A	A
45	A	A	P	A	ND	P	P	A	A	A	A	A	P	A	A	A	A	A	P	A	A	A	A	A	A	A
46	P	A	P	A	ND	P	P	A	A	A	A	A	P	ND	ND	A	A	A	A	A	A	A	P	P	A	A
47	A	A	P	A	ND	A	A	A	A	A	A	A	P	A	A	P	A	A	P	A	A	A	A	A	A	A
48	A	A	P	A	ND	P	P	A	A	A	A	A	P	A	A	A	A	A	P	A	A	A	A	A	A	A
49	P	A	A	A	ND	A	P	A	A	A	A	A	P	ND	ND	A	P	A	A	A	A	A	P	A	A	A
50	A	A	P	A	ND	ND	P	A	A	A	A	A	P	A	A	A	A	A	P	A	A	A	P	A	A	A
51	P	A	A	A	ND	P	P	A	A	A	A	A	P	HR, NOK	A	A	A	A	P	A	A	A	A	A	A	A
52	A	A	A	A	ND	A	P	A	A	A	A	A	P	ND	ND	A	P	A	P	A	A	A	A	A	A	A
53	A	A	P	A	ND	ND	P	A	A	A	A	A	P	ND	ND	A	A	A	P	A	A	A	A	A	A	A
54	P	A	P	A	ND	P	P	P	A	A	A	A	P	ND	ND	A	A	A	A	A	A	A	A	A	A	A
55	A	A	P	A	ND	P	P	A	A	A	A	A	P	A	A	A	A	A	P	A	A	A	A	P	A	A
56	P	A	P	A	ND	P	P	A	A	A	A	A	P	A	A	A	A	P	A	A	A	A	A	A	P	A
57	P	A	A	A	ND	P	A	A	A	A	A	A	P	A	A	A	A	A	P	A	A	A	A	A	A	A
58	P	P	A	A	ND	A	P	A	A	A	A	A	P	ND	ND	A	A	A	A	A	A	A	A	A	A	A
59	P	A	P	A	ND	ND	P	A	A	A	A	A	P	ND	ND	A	P	A	A	A	A	A	P	A	A	A
60	P	A	A	A	ND	P	P	A	A	A	A	A	P	ND	ND	A	A	P	A	P	P	A	P	A	A	A

61	P	A	A	P	ND	ND	P	A	A	A	A	A	P	A	A	A	A	A	A	A	A	P	A	A	A
62	P	A	A	P	ND	P	P	A	A	A	A	A	P	A	A	A	A	P	A	A	A	P	A	A	A
63	P	A	A	P	ND	A	A	A	A	A	A	A	P	A	A	A	A	P	A	A	A	P	A	A	A
64	P	A	P	A	ND	P	P	A	A	A	A	A	P	ND	ND	A	P	A	A	A	A	A	P	A	A	A
65	P	A	P	P	ND	P	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	P	A	A	A
66	P	A	P	A	ND	P	A	A	A	A	A	A	P	A	A	A	A	A	P	A	A	A	A	A	A	A
67	P	A	A	P	ND	A	A	A	A	A	A	A	A	A	A	A	A	A	P	A	A	A	P	A	A	A
68	A	A	P	A	ND	ND	A	A	A	A	A	A	P	A	A	A	A	A	P	A	A	A	A	A	A	A
69	A	A	P	A	ND	P	P	A	A	A	A	A	P	ND	ND	A	P	A	A	A	A	A	P	A	A	A
70	P	A	P	A	ND	A	A	A	A	A	A	A	P	HR, NOK	A	A	A	A	P	A	A	A	A	A	A	A
71	P	A	A	A	ND	A	P	A	A	A	A	A	P	ND	ND	A	P	P	A	A	A	A	P	A	A	A
72	A	A	A	A	ND	ND	P	A	A	A	A	A	P	A	A	A	A	P	A	A	A	A	P	A	A	A
73	A	A	A	A	ND	A	A	A	A	A	A	A	P	A	A	A	A	A	P	A	A	A	P	A	A	A
74	A	A	P	A	ND	P	A	A	A	A	A	A	A	A	A	A	A	A	P	A	A	A	P	A	P	A
75	P	A	P	A	ND	P	P	A	A	A	P	A	A	A	A	A	A	A	P	A	A	A	A	A	A	A
76	P	A	P	A	ND	P	P	A	A	A	A	A	P	A	A	A	A	A	P	A	A	A	A	A	A	A
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79	A	P	P	A	ND	A	P	A	A	A	A	A	P	ND	ND	A	P	A	A	A	A	A	A	A	A	A
80	A	A	P	A	ND	P	P	A	A	A	A	A	P	A	A	A	A	A	A	A	A	A	P	A	A	A
81	P	A	P	A	ND	P	A	A	A	A	A	A	P	A	A	A	A	A	P	A	P	A	P	A	A	A
82	A	A	P	A	ND	P	P	A	A	A	P	A	P	KS	A	P	A	A	A	A	A	A	A	A	A	A
83	P	A	P	A	ND	A	P	A	A	A	A	A	P	ND	ND	A	P	A	A	A	A	A	P	A	A	A
84	P	A	P	A	ND	P	P	A	A	A	A	A	P	ND	ND	A	P	A	P	A	A	A	A	A	A	A
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86	P	A	P	A	ND	P	P	A	A	A	A	A	A	A	A	A	A	A	P	A	A	A	P	A	A	A
87	P	A	P	A	ND	P	A	A	A	A	A	A	A	A	A	A	A	A	P	A	A	A	P	A	A	A
88	P	A	P	A	ND	P	P	A	A	A	A	A	P	KS	A	A	A	A	P	A	P	A	A	A	A	A
89	A	P	P	A	ND	P	P	A	A	A	A	A	P	A	A	A	A	A	P	A	P	A	A	A	A	A
90	A	A	P	A	ND	P	P	A	A	A	A	A	P	ND	ND	A	P	A	P	A	A	A	P	A	A	A
91	P	P	A	A	ND	P	A	A	A	A	A	A	A	A	A	P	A	A	P	A	A	A	P	A	A	A
92	P	A	A	A	ND	ND	P	A	P	A	A	A	P	A	A	A	A	A	P	A	P	A	A	A	A	A
93	P	A	A	A	ND	A	P	A	A	A	A	A	P	A	A	A	A	A	P	A	A	A	P	A	A	A
94	P	A	P	A	ND	P	P	A	A	A	A	A	P	ND	ND	A	P	A	A	A	A	A	P	A	P	A
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121	P	A	P	A	ND	P	P	A	A	A	A	A	A	ND	ND	A	A	A	P	A	A	A	P	A	A	A
122	P	A	P	A	ND	P	A	A	A	A	A	A	P	A	A	A	A	A	P	A	A	A	A	A	A	A
123	P	A	A	A	ND	A	A	A	P	A	A	A	A	A	A	A	A	A	P	A	A	A	A	A	A	A

124	P	A	P	A	ND	A	A	A	A	A	P	A	P	A	A	A	A	A	A	A	A	A	A	P	A
125	P	P	A	A	ND	P	P	A	A	A	P	A	A	A	A	A	A	P	A	A	A	A	A	A	A
126	A	A	P	A	ND	A	P	A	A	A	A	A	A	ND	ND	A	A	A	P	A	A	A	A	P	A
127	P	A	P	P	ND	P	A	A	A	A	A	A	P	A	A	A	A	A	P	A	A	A	P	A	A	A
128	P	A	A	P	ND	A	A	A	A	A	A	A	P	A	A	P	A	A	A	A	A	A	P	A	A	A
129	P	A	P	A	ND	ND	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	P	A	A	A
130	P	A	A	A	ND	A	P	A	A	A	A	A	A	ND	ND	A	A	P	P	A	A	A	A	A	A	A
131	P	A	P	A	ND	P	P	A	A	A	A	A	P	ND	ND	A	P	A	A	A	A	A	A	A	A	A
132	P	A	P	A	ND	P	P	A	A	A	A	A	A	A	A	A	A	A	P	A	P	A	A	A	A	A
133	P	A	A	A	ND	P	P	A	A	A	A	A	A	A	A	A	A	A	P	A	P	A	P	A	A	A
134	P	A	P	A	ND	P	P	A	A	A	A	A	P	A	A	A	A	A	P	A	A	A	P	A	P	A
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136	A	A	P	A	ND	ND	P	A	A	A	A	A	P	ND	ND	A	A	A	A	A	A	A	P	A	A	A
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139	P	P	P	A	ND	P	A	A	A	A	P	A	P	A	A	A	A	A	A	P	A	A	A	A	A	A
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142	A	A	P	A	ND	P	A	A	A	A	A	A	P	A	A	A	A	A	P	A	A	A	P	A	A	A
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148	P	P	P	A	ND	P	A	A	A	A	P	A	P	A	A	A	A	A	A	P	A	A	A	A	A	A
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173	A	A	P	A	ND	P	P	A	A	A	P	A	P	KS	A	P	A	A	A	A	A	A	A	A	A	A
174	A	A	P	A	ND	P	P	A	A	A	A	A	P	ND	ND	A	P	A	P	A	A	A	P	A	A	A