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Study on usage of various criterias in the diagnosis of Atopic Eczema among South Indian population

Preetham S[1,*], Raghavendra S Tophakhane[2]

[1]*Dept. of Dermatology, Venereology & Leprosy, ESI Post Graduate Institute of Medical Science and Research, Rajajinagar, Bengaluru, Karnataka, India*
[2]*Dept. of Dermatology, Venereology & Leprosy,, Karnataka Institute of Medical Sciences, Hubbali, Karnataka, India*

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ABSTRACT

Background: Atopic Eczema (AE) is a specific chronic relapsing dermatitis with varied presentations. The etiopathogenesis of AE is largely speculative and over years has led to origin of various criteria like Hanifin, Rajka's criteria (HRC), United Kingdom working party's diagnostic criteria (UKWPDC) and millennium diagnostic criteria (MDC). These have originated in western countries and is used among Indian population without much validation studies.
Objective: To validate HRC, UKWPDC and MDC in the diagnosis of AE among Indian population.
Materials and Methods: A case-control study including 50 cases of AE and 30 age matched controls who are presenting to the DVL OPD of a tertiary teaching hospital. Defined case proforma was prepared highlighting the criteria's of HRC, UKWDPC and MDC posing as a questionnaire to the cases/subjects. Total Serum IgE levels were estimated. Sensitivity, specificity, Positive predictive value (PPV), Negative predictive value (NPV) and Relative value were calculated for all criteria.
Results: The Sensitivity, specificity, PPV and NPV was 100% for HRC and UKWPDC whereas there was a compromise in the specificity (32.5%) and lower relative value of (22.5%) for MDC. Some minor features of HRC and MDC criteria showed lower validity compared to major features.
Conclusions: Though many upgradations are going on in HRC, UKWPDC it could still be considered and used as a diagnostic criterion considering the high sensitivity, specificity and accuracy for diagnosis of AE.

1. Introduction

Atopic Eczema (AE) is a specific chronic relapsing dermatitis of infant, adolescent and adults with a characteristic distribution of lesions and a personal and/or family history of any of the triad of AE, atopic allergic rhinitis or atopic allergic asthma. Atopy (out of place)term was introduced by Coca & Cooke in the year 1923.[1,2] Atopic dermatitis was first proposed to be used by Wise & Sulzberger in the year 1930.[3]The etiopathogenesis of AE is still largely speculative and now "Atopic Eczema" is a most acceptable terminology of the era after many revisions. Many pioneers have not been able to correctly understand the etiopathogenesis and therefore they have their own views. These scholars had particular hesitation in making a direct diagnosis of AE as many other disorders clinically mimicked AE like Wiskott-Aldrich syndrome, Netherton's syndrome, Job's syndrome, selective IgA deficiency, agammaglobulineamia and ataxia telangiectasia.[1] Wuthrich coined the term "intrinsic atopic eczema" to segregate those phenotypes of AE but without detectable specific-allergen IgE, which is one of the minor criteria in HRC.[4] This also gave rise to some other terminologies like non-atopic flexural eczema, non-allergic AE, non- allergic atopic eczema/dermatitis syndrome (AEDS),[5] when world allergic organization (WAO) intervened to mean atopy and atopic diseases as only when there is documented specific IgE or a positive skin prick test.[1] In fact Bos JD went a step further

* *Corresponding author*.
E-mail address: preetham.1975s@gmail.com (Preetham S).

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in collectively naming these disorders as "ATOPIFORM DERMATITIS"[4,6] for intrinsic AE {non-allergic, non-IgE mediated, constitutional dermatitis /eczema (AEDS)} and AE for extrinsic AE who have atopy.

All these confusions arose because of no proper diagnostic yard stick whether clinical or investigational.[7] HRC had proposed their criteria[8] for uniformity, but was not then ratified by specialists for diagnosis nor tested for repeatability. It was helpful in hospital settings but not deducible to general population as many variables like varied clinical presentations, different diagnostic criterias, ethnicity, environmental exposure played their role.[9] The major criteria were the reliable and routinely present feature. The minor criteria were inconsistent and found in controls too.[10]

In the meanwhile, Williams and colleagues put forth a consensus of UKWPDC in the aim of simplifying the process of coming to a diagnosis of AE which was tried and tested in toto[11] and some researchers did find it not useful.[12] The millennium diagnostic criteria (MDC)[13] is very lucid and actual to the clinical point that they have adjusted the criteria of HRC and taken UKWPDC into consideration and proposed an adjusted criteria. Keeping these things into consideration we conducted this study to validate HRC, UKWPDC and MDC in the diagnosis of AE among Indian population.

2. Materials and Methods

This was a case-control study conducted in the DVL OPD of a tertiary care referral hospital. A total of 80 subjects were examined, 50 being AE cases and 30 age matched controls. Two senior dermatologists and a pediatrician in a case of a child agreed to the final diagnosis of AE cases. Of the 50 AE cases 33 were males and 17 females. Study population constituted diverse religious background but homogenous ethnicity. Defined case proforma was prepared highlighting the criteria's of HRC, UKWDPC and MDC posing as a questionnaire to the cases/subjects. Personal and family history with special reference to atopy was inquired in upto two generations. Minor criteria of HRC which included immediate type 1 skin test reactivity, impaired cell mediated immunity, delayed blanch (white dermographism) were not assessed. Detailed muco-cutaneous & systemic examination was done in all subjects. Total Serum IgE levels were estimated using THERMO FISHER SCIENTIFIC INVITROGEN IgE Human ELISA kit among all the participants of the study. The study proposal was submitted to the Institutional ethical committee and Ethical clearance was obtained for the study. Informed consent was obtained from all the study subjects.

2.1. Statistical analysis

Data collected was entered on MS Excel and data was analysed using EPI-INFO-06 statistical software. Descriptive statistics were analysed as proportions for frequencies and mean and standard deviation for continuous measures. Sensitivity, specificity, PPV, NPV and Relative value were calculated for all criteria under HRC, UKWPDC and MDC. Difference in the proportions in each criteria was checked using chi square test at a significance level of $p < 0.05$. Accuracy of each criteria with its 95% confidence levels was also calculated.

3. Results

Table 1 shows the age and gender distribution of cases and controls. The mean age of cases is 9.10±10.95 years and for controls is 8.93±10.1 years. There is no statistical difference in gender and age distribution between cases and controls suggesting the groups were comparable. (Cases: $X^2 = 0.0374$, p=0.98, Controls: $X^2 = 0.0037$, p =0.95). Atopic Eczema cases were mostly males (66%) in this study.

Table 2 shows the validity results for the major and minor criteria of HRC. It was seen that all the criteria showed high sensitivity and specificity which was statistically significant for classical eczema distribution. It was also observed that the chronic relapsing dermatitis has a false positivity of 14% and accuracy of 91.2% ($p<0.001$) as compared to 100% of the other major criteria of HRC.

It was observed that the following minor criteria's were found to significant i.e; Dennie-Morgan infra orbital fold, aggravation to environmental factors, susceptibility/tendency to infections, early age of onset, xerosis/dry skin, hyperlinear palms, increased total serum IgE levels.

The sensitivity percentages of use are (in descending order %): dry skin/ xerosis (100), elevated total serum IgE (90), tendency/susceptibility to infections (86), aggravation by environmental factors (74), hyperlinear palms (72), early age of onset (62), Dennie-Morgan infra orbital fold (62). The p values were found to be statistically significant.

The false positives percentages were higher in infra orbital darkening, anterior sub-capsular cataract, keratoconus (each 100), nipple eczema (98), anterior neck folds (94), recurrent conjunctivitis (90), tendency to non-specific hand & foot dermatitis (82), aggravation by food (78), facial erythema & cheilitis (76), aggravation by sweat only (74.3), keratosis pilaris (70), perifollicular accentuation (66), ichthyosis (60).

The serum total IgE has a false negativity of 30%, specificity (70%), PPV (83.3), NPV (80.8). The validation statistical figures of UKWPDC are as shown in the table 3. Except the age of onset <2yrs all other variables had high sensitivity and specificity and it was statistically significant. However, the age of onset <2yrs do not comply, with false

positivity of 88% and it was not statistically significant (p=0.07)

The validation statistical figures of MDC are as shown in the table 4. Mandatory criteria in MDC indicate that the serum total IgE has a sensitivity of (90%), specificity (70%), false negativity of 30%, PPV (83.3), NPV (80.8). In our study serum IgE was elevated in 22(44%) of cases. The mean and standard deviation IgE among cases was 186.8±170.5 IU and that among controls was 24.7±19.3 IU and this difference was found to be statistically significant.

In the Principal criteria of MDC typical distribution and morphology of eczema lesions (infant, childhood or adult type), pruritus had sensitivity and specificity of 100% which was statistically significant (p<0.001). Chronic or chronically relapsing dermatitis showed sensitivity of 86%, specificity of 100%, PPV 100% and NPV 81.01% (p<0.001).

Among the MDC circumstantial Additional Criteria the sensitivity was found to be highest in cheilitis, xerosis, anterior neck fold and photophobia. The Dennie- Morgan infra orbital fold showed a sensitivity 62% and specificity 100%. The p-value were statistically significant for xerosis, Dennie- Morgan infra orbital fold, p alba, intolerance to wool and lipid, facial pallor and perifollicular accentuation.

Table 5 shows the overall validity statistics of all the three criteria. The Sensitivity, specificity, PPV and NPV was statistically significant in all three and was highest for HRC and UKWPDC. MDC had sensitivity of 90%

4. Discussion

Atopic Eczema has been an onerous disease to conceptualise. The myriad presentations, no definitive diagnostic test has added more to the issue. This also accounts for the varied prevalence. The search for a tool for easy diagnosis then rested on some uniform clinical point of reference. The work by HRC in 1980 was a turning point which envisaged the way of making a diagnosis for this enigma. Their suggestion of minimum three major and three minor criteria for diagnosis of AE was a gold standard yard stick.[9] It has good sensitivity in OPD/ hospital settings. But some studies have scorned to establish the specificity of minor features[14,15] and have questioned basic major feature too.[16]

The study by Navya P et al[17] found Dennie-morgan infraorbital folds, palmar hyperlinearity, xerosis, p alba, perifollicular accentuation, serum IgE of significance similar to our study. Kanokvalai Kulthanan et al found xerosis, early age of onset ,elevated serum IgE of significance in concurrence with our study but not with Immediate Type I reactions to test antigens, nipple eczema, recurrent conjunctivitis, perifollicular accentuation, white dermographism which were of clinical significance in their study.[18]

Mevorah et al found Dennie-Morgan infraorbital folds, keratosis pilaris, palmar hyperlinearity, anterior neck folds of no significance.[19] Kang & tian did not find Dennie-Morgan infraorbital folds, keratoconus, conjunctivitis, anterior subcapsular cataract, nipple eczema and cheilitis of diagnostic significance.[20] Kanwar et al too found anterior neck folds, cheilitis, perifollicular accentuation, recurrent conjunctivitis, white dermographism, nipple eczema of no significance.[14] Nagaraja et al found food intolerance, nipple eczema, p alba, anterior neck folds, ichthyosis and cheilitis nonspecific though some minor features had specific age-group dependency.[15]

Clinicians have been using this HRC for diagnosis and found helpful too, but none inscripted about validity of major and minor criteria corroborated by the physician's diagnosis.[16,19] The HRC which was mostly used in hospital settings where mostly severe cases presented, explained certain features of presence (hyperlinear palms, keratoconus, anterior neck folds) which were not found by those when used in community settings where mild to moderate cases prevailed . Minor features like hyperlinear palms, infra-orbital folds, peri-orbital pigmentation can be found sporadically in the general population where age, sex, race, ethnicity play a role and also cause discrepancies.[14,19]

Schultz -larsen et al and others went on to advise that the HRC could not reciprocate well for population - based studies.[20,21] Some criteria have no accurate definition (p alba).[20] Some occur infrequently (keratoconus).[17] Some are non-specific (white dermographism).[22] Some criteria which were invasive couldn't be easily reproduced , more so in children. Objective tests such as raised serum IgE, positive skin-prick test have high research value for clinching atopy but impractical for community settings. Total serum IgE levels are considered non-specific for a particular phenomenon,[23] but could help as a diagnostic invasive test for this condition which could portray more than a surrogate but an imminent specific feature of significance.[24] The specific raised serum IgE levels hold more strength in that matter.[25]

In 1994 Williams et al, set HRC as a gold standard, as did some other researchers separately and conducted a study. Their idea was to have a set of criteria which suited most ethnic populations and was supposed to be sensitive, specific, non-invasive and reproducible in both hospital and community settings. This came to be known as UKWPDC which needed that patient must and should have itchy skin condition and minimum three of the following: history of asthma or hay fever, history of generalized skin rash, history of flexural involvement, onset of rash below two years of age and visible flexural dermatitis.[11]

This was also considered by most other workers which they thought to explain the etiopathogenesis of AD lucidly. This UKWPDC also has flaws which proposed authors themselves enunciate that it can't properly be applied

Table 1: Demographic data of the study subjects

Variables	Cases (n=50)			Controls (n=30)			p value*
Age group(yrs)	>2	2-12	>12	>2	2-12	>12	
Age in Years, n(%)	17 (34)	19 (38)	14 (28)	10 (33.3)	11 (36.6)	9 (30)	0.98
Age in years (Mean ± SD)		9.10 ± 10.9			8.93 ± 10.1		
Male, n (%)		33 (66)			20 (66.7)		0.95
Female, n (%)		17 (34)			10 (33.3)		

*Chi Square statistics $(X)^2$, p-value not significant.

Table 2: Sensitivity, specificity, PPV, NPV, RV, and p-value of individual features of HRC (major and minor criteria)

Variables	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	RV	p-value*	Accuracy (95% CI)
Major Criteria Pruritus	100	100	100	100	100	<.001*	100 (95.5-100)
Dermatitis In classical distribution	100	100	100	100	100	<.001*	100 (95.5-100)
Personal or family history of atopy	100	100	100	100	100	<.001*	100 (95.5-100)
Chronic/relapsing dermatitis	86	100	100	81.1	86	<.001*	91.2 (82.8-96.4)
Minor Criteria dry skin/ xerosis	100	100	100	100	100	<.001*	100 (95.5-100)
elevated serum IgE	90	70	83.3	80.8	60	<.001*	82.5 (72.4-90.1)
susceptibility/(tendency) to infections	86	100	100	81.1	86	<.001*	91.2 (82.8-96.4)
aggravation by environmental factors	74	100	100	69.8	74	<.001*	83.7 (73.8-91.0)
hyperlinear palms	72	100	100	68.2	72	<.001*	82.5 (72.3-90.1)
Dennie-Morgan's Infra-orbital fold	62	100	100	61.2	62	<.001*	76.2 (65.4-85.0)
early age of onset (<5yrs)	62	100	100	61.2	62	<.001*	76.2 (65.4-85.0)
hypopigmented patches/ p alba	46	100	100	52.6	46	<.001*	66.2 (54.8-76.4)
aggravation by woolens, solvents	46	100	100	52.6	46	0.001*	66.2 (54.8-76.4)
facial pallor	42	100	100	50.8	42	<.001*	63.7(52.2-74.2)
ichthyosis	40	100	100	50	40	<.001*	62.5 (50.9-73.0)
perifollicular accentuation	34	100	100	47.6	34	<.001*	58.7 (47.2-69.6)
keratosis pilaris	30	100	100	46.2	30	0.001*	56.2 (44.7-67.3)
aggravation by sweat	26	100	100	44.7	26	<.001*	53.7 (42.2-64.9)
facial erythema	24	100	100	44.1	24	0.002*	76.4 (62.5-87.2)
cheilitis	24	100	100	44.1	24	0.002*	52.5 (41.0-63.8)
aggravation by food	22	100	100	43.5	22	0.005*	
hand & foot dermatitis(tendency) non-specific	18	100	100	42.3	18	0.023*	83.7 (73.8-91.1)
recurrent conjunctivitis	10	100	100	40	10	0.088	43.7 (32.7-55.3)
anterior neck folds	6	100	100	39	6	0.239	41.2 (30.3-52.8)
nipple eczema	2	100	100	38	2	1	38.7 (28.1-50.3)
infra-orbital darkening (atopic/allergy shiners)	-	100	-	37.5	-	-	-
anterior subcapsular cataract	-	100	-	37.5	-	-	-
keratoconus	-	100	-	37.5	-	-	-

*Statistically significant p-value<0.05

Table 3: Sensitivity, specificity, PPV and NPV of individual features of the UKWPDC

Variables	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	RV	p - Value	Accuracy (95%CI)
Pruritus	100	100	100	100	100	<.001*	100 (95.4-100)
Dermatitisin classical distribution	100	100	100	100	100	<.001*	100 (95.4-100)
Onset < age of 2 years (not applied < 4 years)	12	100	100	40.5	12	0.079	45 (33.8-56.5)
Personal or family history of atopy	100	100	100	100	100	<.001*	100 (95.4-100)
Dry skin/ xerosis	100	100	100	100	100	<.001*	100 (95.5-100)
Visible flexural dermatitis	100	100	100	100	100	<.001*	100 (95.5-100)

*Statistically significant p-value <0.05

Table 4: Sensitivity, specificity, PPV and NPV for millennium diagnostic circumstantial additional criteria.

Variables	Sensitivity (%)	Specificity (%)	PPV	NPV	Relative Value (RV)	p -value	Accuracy (95% CI)
Mandatory Criteria Serum IgE	90	70	83.3	80.8	60	<0.001*	82.5 (72.4-90.9)
Principal Criteria Typical distribution and morphology of eczema lesions: infant, childhood or adult type	100	100	100	100	100	<0.001*	100 (95.5-100)
Pruritus	100	100	100	100	100	<0.001*	100 (95.5-100)
Chronic or chronically relapsing dermatitis	86	100	100	81.0	86	<0.001*	91.2 (82.8- 96.4)
Additional Criteria: cheilitis	100	100	100	100	100	0.074	100 (91.5-100)
xerosis	100	100	100	100	100	<0.001*	100 (95.4-100)
anterior Neck Fold	100	94	25	100	94	0.655	94.1 (83.7-98.7)
photophobia	100	90	16.67	100	90	0.456	90.2 (78.5-96.7)
Dennie- Morgan infra orbital fold	62	100	100	61.2	62	<0.001*	76.2 (65.4-85.0)
p alba	46	100	100	52.6	46	0.001*	66.2 (54.8-76.4)
intolerance to wool,lipid	46	100	100	52.6	46	0.001*	66.2 (54.8-76.4)
facial pallor	42	100	100	50.8	42	0.002*	63.75 (52.2-74.2)
perifollicular accentuation	34	100	100	47.6	34	0.011*	58.7 (47.1-69.6)
palmar hyper linearity	26	100	100	44.7	26	0.05	53.7 (42.2-64.9)
itch when sweating	26	100	100	44.7	26	0.05	53.7 (42.2-64.9)
facial erythema	24	100	100	44.1	24	0.074	52.5 (41.0-63.7)
keratosis pilaris	8	100	100	39.4	8	0.551	42.5 (31.5-54.0)
nipple eczema	2	100	100	37.9	2	0.379	38.5 (28.0-50.3)
orbital darkening	0	0	0	0	0	-	0
cradle cap	0	0	0	0	0	-	0
ichthyosis	0	0	0	0	0	-	0
perleche	0	0	0	0	0	-	0
extra skin folds	0	0	0	0	0	-	0
auricular rhagades	0	0	0	0	0	-	0
anterior cataract	0	0	0	0	0	-	0
Hertoghe sign	0	0	0	0	0	-	0

*Statistically significant p-value <0.05

Table 5: Sensitivity, specificity, PPV and NPV of individual criteria

Criteria	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	RV	p- value	Accuracy
HRC	100	100	100	100	37.5	<0.01*	100 (95.4-100)
UKWPDC	100	100	100	100	37.5	<0.01*	100 (95.4-100)
MDC	90	32.5	83.3	80.7	22.5	<.001*	68.7 (57.4-78.6)

*Statistically significant p-value <0.05.

to general community and in infants. The study by Wisuthsarewong W & Viravan S used original HRC on their preset cases. They found perifollicular accentuation, history of pruritic rash, periorbital dermatitis, visible xerosis, chronicity of more than 6 months, history of flexural dermatitis by multiple logistic regression analysis as a minimum set of diagnostic criteria for diagnosis of AE, but criteria were not validated.[26]

The study by Sharma too derived a minimum set of criteria (visible flexural dermatitis, history of flexural dermatitis, pruritus, history of atopy, history of dry skin, personal history of diagnosed asthma).[27] Being short of validation, William et al assessed their efficacy and found 93%sensitivity, 78% specificity.[12] In our study it was 100% sensitivity & 37.5% specificity. When compared with UKWPDC, in our study HRC had 100% sensitivity and 100% specificity. Though both criteria don't consume much time for elucidating history, HRC is elaborate which researchers find incredulous. Time spent on the patient is worthwhile asking about history even though the H&R criteria has less specific and less sensitive pointers and has some invasive tests too.

Williams et al validated their criteria in one of their study[11] and found 69% sensitivity and 96% specificity, respectively. This has been the first hospital-based validation study involving all ages and sex. In our study it was 100% sensitivity and 37.5% specificity, respectively. The performance of UKWPDC was the same as HRC. Further studies on validation of UKWPDC yielded 70% sensitivity, 93% specificity, 47% PPV, 97% NPV.[28] Other studies yielded varying results considering similar parameters: Popescu et al 74% sensitivity 98.9% specificity 62.5% PPV, 99.3% NPV.[13] Gu et al 95.5% sensitivity, 97.5% specificity, 97.25% PPV, 95.94% NPV.[29] Firooz et al 10% sensitivity 98.3% specificity.[30]

The UKWPDC has three of its criteria based on history. So, they had reservations if it was used on cases below four years of age. Moreover, the IgE immune-etiopathogenesis is given a minor role. In our study we had similar advantages with HRC & UKWPDC.

Facial erythema, cheilitis, recurrent conjunctivitis, anterior subcapsular cataract, infraorbital darkening, keratoconus, anterior neck folds, aggravation by food, tendency to nonspecific hand & foot dermatitis, nipple eczema were statistically non-significant.

In our view classical eczema distribution, chronically relapsing history, Dry skin/ xerosis, early age of onset (<5yrs), susceptibility/(tendency) to infections, elevated serum IgE, Dennie-Morgan's Infra-orbital fold, aggravation by environmental factors, hyperlinear palms help in differentiating cases from control because of high relative score.

The MDC[7] mandatory criteria of increased allergen specific IgE (immunological) or hematological marker of allergy or skin/intracutaneous challenge (invasive) though sensitive and specific could be conducted more effectively in a hospital set up. As specified by them if IgE levels are raised it points towards atopy and to make a diagnosis of AE then the principal criteria would help. But in the light of new developments with respect to immunology and evaluation of the clinical features the principal criteria have been accordingly revised. The principal criteria are mostly historical though and could be carried out in an epidemiological survey or through telephonic interviews by non-dermatologists too.

In the study by Mandy E S et al[31] who by multiple logistics & regression model analysis had constituted a refined MDC, showed 81.8% sensitivity and 98.8% specificity. In our study it was 90% sensitivity and 32.5% specificity. The subjective analysis of the history could play a role in the skewing of the specificity.

The other features seen in atopic eczema cases have been taken into consideration too and categorized as circumstantial evidence. They reduce patient selection bias. Not many studies have validated MDC because of mandatory criteria being invasive, laboratory oriented and need skill to extract blood from apprehensive small babies with informed consent from guardians /parents. Also, AE being a chronic disease, immunological response of allergen-specific serum IgE tends to be a point prevalence indicator. In our study total serum IgE was elevated in 44% of cases. In the study by Kanokvalai Kulthanan et al, total serum IgE was elevated in 32.7% of the cases whose ages started from 18 years and above.[18] As atopics age to adults IgE levels increase and tend to ebb on the upper end of the normal curve[32] which could account for the lower results of IgE levels reported by them.

The study by Mandy ES et al[31] had 51% elevation of allergen specific IgE($p< 0.001$). The study by Navya P et al[17] had 64.33% elevations of serum IgE similar to Agrawal et al[33] of 68.7% (they have used the recent version of IgE detector-sandwich ELISA technique and also set 200 IU as a cut off for normal range). The lower results for IgE in our study could be due to taking 35 IU as cut off for normal.[32] The total serum IgE levels could be used as proxy if not as stand-in for correlations. Also in developing countries as ours, population are chronically exposed to communicable diseases and then IgE levels tend to stay in the upper limit of normal range because of sensitization only to rise in acute situations.[32]

The conundrum of diagnosis for AE still looms large, though current research on developing diagnostic tools is on. The MDC has served the purpose for the diagnosis of AE aptly. With the present day knowledge of the limitations in the HRC, UKWPDC and standing for its upgradations, it could then be used for diagnosis of AE along with evaluation tools gauging objective skin lesions (POEM)[34] and subjective symptoms pruritus(NRS).[35] Advances in Gene finger-printing of the recent gene technology for identifying atopy genes remains the ultimate redeemer but "out of place" for common use.

5. Conclusion

Though many upgradations are currently in vogue for HRC, UKWPDC, MDC it could still be considered and used as a diagnostic criterion because of its high sensitivity, specificity and accuracy for diagnosis of AE. The HRC, UKWPDC, MDC provides good validity among Indian population and can be used in OPD/ hospital settings.

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7. Conflicts of Interest

There are no conflicts of interest.

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Author biography

Preetham S, Assistant Professor

Raghavendra S Tophakhane, Professor

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