Original Article

Non-typical morphology and localization in Turkish atopic dermatitis patients with onset before the age of 18 years

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ABSTRACT

Background: Hanifin and Rajka's criteria (HRC) are the gold standard for the diagnosis of atopic dermatitis (AD). Apart from the age-related distribution and typical morphology of the lesions as defined in one of the major criteria of HRC, patients may also show nontypical morphology and localization. **Aim:** The aim of this study was to find the frequency of nontypical morphology and localization in Turkish AD patients with onset before the age of 18 years, who were diagnosed according to HRC. **Methods:** This was a methodological study based on the analysis of patients' data derived from the checklists of HRC and precise clinical documentation of each patient. A total of 321 Turkish patients diagnosed between 1996 and 2004 with the onset of AD before the age of 18 years were allocated to the study group. **Results:** 49.5% of patients had nontypical localization of AD, the majority being infants or children who had flexural involvement rather than the typical cheek or extremity lesions. Lichenified/exudative eczematous pattern was the most frequent morphologic type (45.5%); however, 54.5% of the patients showed combined or isolated variants, e.g. nummular and seborrheic patterns, in particular. **Conclusions:** A considerable amount of Turkish patients with AD before the age of 18 years presented with nontypical morphology and/or localization according to their age group. The confirmation of our findings in a multicentric prospective study would further allow a completion and correction of the diagnostic criteria of AD for age groups.

Key words: Age groups, atopic dermatitis, diagnostic criteria

INTRODUCTION

Hanifin and Rajka's criteria[1] (HRC) are widely used for the diagnosis of atopic dermatitis (AD). Apart from the age-related distribution (infancy-related cheek involvement/childhood-related extremity involvement/adolescence- or adult-related flexural involvement) and the typical lichenified/exudative eczematous morphologic pattern as defined in one of the major criteria of HRC, patients may also have nontypical morphology and localization.[2] So far, there are no large reports on the clinical presentation of AD on Turkish patients in the literature. The aim of this methodological study was to find the frequency of nontypical morphology and localization in Turkish AD patients with onset before the age of 18 years, who were diagnosed according to HRC.

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METHODS

This methodological study was based on the analysis of patients' data by assessing the checklists of HRC and precise clinical documentation of each patient in our outpatient clinic for AD. A total of 399 Turkish AD patients were consecutively diagnosed according

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to HRC between June 1996 and January 2004. Among them, 321 (80.5%) with onset of AD before the age of 18 years were allocated to the study group. Patients were analyzed in three subgroups according to the onset at infancy (1 month–2 years), at childhood (2–10 years), and at adolescence (10–18 years).

The severity of AD was assessed according to the Langeland score.[3]

Patients with or without typical morphology and distribution were noted. Morphology of dermatitis was evaluated as follows: typical lichenified/exudative eczematous pattern or other variants such as nummular, papular, prurigo-like, follicular, seborrheic dermatitis-like, mixed patterns, and erythroderma.

Localization of dermatitis was evaluated as follows: Face/symmetrical cheek involvement, flexural sites (antecubital/popliteal/neck/wrist/ankle) with or without involvement of other parts of the body, nonflexural involvement of the extremities, seborrheic areas (scalp and retroauricular region), anogenital/diaper area, and generalized involvement. Site of onset was also recorded.

Concomitant mucosal atopic disease (allergic rhinoconjunctivitis and/or asthma bronchiale) was determined according to personal history, skin prick testing (Hal-Brial, Haarlem, Holland) and/or specific IgE levels using UniCAP/Pharmacia CAP System allergens (Pharmacia and Upjohn Diagnostics , Uppsala, Sweden) against a selection of nine aeroallergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Alternaria alternata*, *Cladosporium herbarum*, *Artemisia vulgaris*, *Secale cereale,* grass mix, tree mix, and cat hair). Family histories of AD and/or mucosal atopy in first-degree relatives were recorded.

Serum total IgE levels were determined using UniCAP/Pharmacia CAP System (Pharmacia and Upjohn Diagnostics, Uppsala, Sweden). Levels more than 150 IU/ml were regarded as high.

Data were stored and assessed using SPSS for Windows Release 11.0 version. The Chi-square was used for the comparisons. A two-tailed *P* value less than 0.05 was taken to indicate a statistically significant association. The study was assessed and approved by the institutional ethics committee.

RESULTS

The age range of 321 patients (175 females, 146 males; female/male = 1.2) was 6 months–61 years (median: 7; interquartile range: 12) with an age of onset range of 1 months–18 years (median: 1.5; interquartile range: 5.8). AD started at infancy (1 month–2 years) in 55.2%, at childhood (2–10 years) in 30.5%, and at adolescence (10–18 years) in 14.3% of patients. In 72.9% of the patients, AD started under the age of 5 years. The duration of the disease ranged from 6 months to 48 years (median: 35.3, interquartile range: 72).

AD was mild in 51.7% of patients, moderate in 39.6% and severe in 8.7%. There was no significant statistical difference regarding AD's severity between patients with onset of AD before and after the age of 2 years. Besides, no correlation was found between AD's severity and gender of patients.

Localization

Body-site distribution of AD is shown in Table 1. The main involved sites were flexures in 239 patients (74.5%), being most frequently antecubital/popliteal flexural areas in 217 patients (67.6%).

Additionally, 52.7% of the patients with flexural eczema were infant or childhood cases. A total of 159 patients (49.5%) had nontypical localization of AD

Table 1: Localization of atopic dermatitis in patients with onset before 18 years of age

Localization	No. (*n* = 321)	(%) of patients
Flexural	239	(74.5)
Typical flexural (antecubital/popliteal)	217	(67.6)
Neck	135	(42.1)
Wrist/ankle	33	(10.3)
Face	189	(58.9)
Typical face (symmetrical cheek)	108	(33.7)
Diffuse face involvement	33	(10.3)
Eyelids	72	(22.4)
Lips	121	(37.7)
Extremity	174	(54.2)
Extensors (knee, elbow)	49	(15.3)
Trunk	151	(47.0)
Hand	97	(30.2)
Seborrheic areas (scalp/retroauricular)	83	(25.9)
Foot	36	(11.2)
Nipple	17	(5.3)
Anogenital	14	(4.4)
Diaper area	9	(2.8)
Generalized	17	(5.3)
Erythroderma	2	(0.6)

As patients can have multiple site involvement, the total number of patients in each localization is over 321

according to their age group, 93.1% of them being infants or children who had flexural involvement rather than the typical cheek or extremity lesions.

On the other hand, typical symmetrical cheek involvement was observed in 108 cases, 90.7% of them being infants, 7.4% children, 1.9% adolescents.

Regarding site of onset, flexural (mainly antecubital/popliteal) onset of AD was seen in the majority of cases (n = 130, 40.5%), followed by face (symmetrical cheek involvement) (n = 95, 29.6%), and extremity extensors (n = 33, 10.3%). The most frequent initial localization was the flexural areas in those with onset of AD at childhood and at adolescence (62.3 and 58.7%, respectively). As a striking finding, the second most frequent initial localization was flexural involvement (23.7%), following the typical symmetrical cheek involvement (49.7%) in those with onset of AD at infancy. A total of 103 patients (79.2%) with flexural eczema as the initial AD lesion were those with onset of AD at infancy or childhood. Patients showing typical cheek involvement as the initial lesion of AD were almost exclusively those with onset of AD at infancy (93.6%). Only 6.4% of patients with typical cheek involvement were those with onset of AD at childhood.

Hand lesions were reported in a total of 97 cases (30.2%). It was seen in 26.5% of infant, 31.6% of childhood and 41.3% of adolescent patients.

Anogenital lesions were seen in 14 (4.4%) of our cases, with the majority being infants (64%).

Morphology

A typical lichenified/exudative pattern was the most frequent morphologic type of dermatitis (45.5%), followed by a mixed type (44.9%) comprising combinations of mainly lichenified/eczematous pattern with other patterns of dermatitis, mainly nummular pattern.

A total of 175 patients (54.5%) had the nontypical morphologic variants such as nummular (21.2%), seborrheic dermatitis-like (21.2%), papular (18.7%), follicular (8.7%), and prurigo-like (4.6%) patterns mainly in combination with the lichenified/exudative pattern. Among them, 31 patients (9.6%) had the following isolated morphologic variants: 17 patients (5.3%) had nummular pattern alone, whereas 7 patients (2.2%) had papular, 4 patients (1.2%) prurigo-like, and 3 patients (0.9%) follicular pattern alone.

Personal/familial atopy

A personal history of mucosal atopy was present in 142 patients (44.2%). Mucosal allergic disease was detected in 63 (44.4%) comprising allergic rhinoconjunctivitis in 43 patients, allergic asthma bronchiale in 4 patients, and allergic rhinoconjunctivitis plus allergic asthma bronchiale in 16 patients. House dust mite antigens were the most relevant allergens (88.9%). AD preceded mucosal atopy or started synchronously with mucosal atopy in a majority of cases (40.1 and 41.5%, respectively).

A family history of atopy was present in 78 patients (24.3%); 38 suffered from allergic rhinoconjunctivitis alone, 20 from asthma bronchiale alone, 8 from allergic rhinoconjunctivitis plus asthma bronchiale, 6 from AD alone and 6 from AD plus mucosal atopic disease.

A total of 165 patients (51.4%) had neither personal nor family history of atopy.

Laboratory

Serum total IgE level was high in 57.5% of patients with a range from 155 to 21,000 IU/ml (median: 200, interquartile range: 638.8). Serum total IgE was significantly higher in patients with mucosal atopy than in those without mucosal atopy ($P < 0.05$; Chi-square = 6.1; OR = 1.9; 95% confidence interval = 1.1–3.4).

Frequency of Hanifin and Rajka's criteria

Frequencies of the HRC are listed in Table 2. It can be seen that 166 patients (51.7%) had three major criteria, whereas 155 patients (48.3%) had four major criteria. The number of positive minor features ranged from 3 to 17 in the whole group (mean = 7.5). Patients with less than seven minor criteria had significantly a milder disease ($P < 0.001$, Chi-square = 17.8, OR = 2.8, 95% confidence interval = 1.7–4.6). The most frequent minor criterion was xerosis (86%), followed by early onset of age (72.9%), and itch when sweating (69.5%). The number of minor features was significantly higher in patients with xerosis than in those without xerosis ($P < 0.001$; Chi-square = 16.0; OR = 3.9; 95% confidence interval = 1.9–7.9).

The frequency of the minor criteria was significantly lower in those who were younger than 2 years

Table 2: Frequencies (%) of the Hanifin and Rajka's criteria[1] in atopic dermatitis patients with onset before the age of 18 years

Diagnostic criteria	No. (%) of patients *n* = 321
Major criteria (3 or 4 are required)	
Pruritus	321 (100.0)
Typical morphology and distribution	320 (99.7)
Chronic or chronically relapsing dermatitis*	321 (100.0)
Personal or family history of atopy	156 (48.6)
Minor criteria (3 or more are required) (decreasing in frequency)	
Xerosis	276 (86.0)
Early age of onset	234 (72.9)
Itch when sweating (*n* = 311)	216 (69.5)
Dennie-Morgan infraorbital fold (*n* = 312)	199 (63.8)
Intolerance to wool (*n* = 309)	194 (62.8)
Elevated serum IgE (*n* = 254)	146 (57.5)
Keratosis pilaris (*n* = 312)	117 (37.5)
Ichthyosis	6 (1.9)
Palmoplantar hyperlinearity (*n* = 316)	94 (29.7)
Cheilitis (*n* = 320)	115 (35.9)
Orbital darkening (*n* = 309)	110 (35.6)
Course influenced by environmental/ emotional factors (*n* = 300)	104 (34.7)
Immediate (type I) skin test reactivity (*n* = 130)	78 (60.0)
Tendency toward cutaneous infections	80 (24.9)
Impaired cellular immunity (*n* = 68)	9 (13.2)
Food intolerance (*n* = 301)	85 (28.2)
Anterior neck folds (*n* = 304)	77 (25.3)
Pityriasis alba (*n* = 315)	57 (18.1)
White dermographism** (*n* = 306)	43 (14.1)
Recurrent conjunctivitis (*n* = 316)	38 (12.0)
Tendency toward nonspecific hand/foot dermatitis	98 (30.5)
Perifollicular accentuation (*n* = 306)	29 (9.5)
Nipple eczema	17 (5.3)
Facial pallor/erythema	12/34 (3.7/10.6)
Anterior subcapsular cataracts (*n* = 95)	1 (1.1)
Keratoconus (*n* = 95)	0

*At least three relapses or a chronic course of 6 months were required.
**White dermographism was investigated on non-eczematous skin

(mean: 5.6) compared with those who were older than 2 years at the time of diagnosis ($P < 0.001$, Chi-square = 37.3, OR = 6.2, 95% confidence interval = 3.2–12.1).

DISCUSSION

AD is a chronic inflammatory skin disease with a varied range of presentations and lack of a proper definition. The diagnosis depends on clinical features as there are no definitive diagnostic tests. The HRC have been considered as a gold standard for the diagnosis of AD since their introduction in 1980.[1] Apart from HRC, there are more sets of criteria for AD such as the UK Working Party's criteria,[4] Millennium criteria[5] or those developed for specific ethnical patient population, e.g. Japanese dermatological association criteria[6] and Kang and Tian's criteria.[7] However, different from these criteria the HRC have been found to be useful particularly in hospital-based studies due to high sensitivity.[8,9] The major drawback of the HRC is the low specificity.[9] Inclusion of atopy (especially family history) as a major criterion[9] and lack of diagnostic significance of many of the minor criteria that were also found in control groups were regarded as the main reasons for loss of specificity of the HRC.[4,10-12]

Interestingly, nearly half of the patients had different localization of dermatitis than would be expected according to their age group in this study. These were almost exclusively infants or children with flexural lesions rather than the expected face or extremity lesions as indicated in the HRC.[1] Furthermore, flexural areas were a frequent initial localization even in those with onset of AD at infancy. For this reason, the recently modified HRC[13] would be more suitable for the diagnosis of AD, indicating that flexural involvement could be seen at any age, rather than only in adolescents or adults. On the contrary, typical cheek involvement as an initial localization of AD was seen almost exclusively in infancy.

Hand lesions that are frequently seen in adult AD patients[2] were observed in nearly one-third of the infant or childhood cases in this study. A recent report indicated that hands were frequently involved in childhood AD.[14]

Another striking finding was related with the morphology of AD. A typical lichenified/exudative pattern was most frequently seen. However, nearly 60% of the patients had the nontypical morphologic variants such as seborrheic-dermatitis like, nummular, papular, follicular, and prurigo-like, mainly in combination with the lichenified/exudative pattern. These morphologic variants are well described in the literature, with nummular pattern being the most commonly reported type in children and adults.[15,16] Orange and de Waard-van der Spek suggested adding nummular pattern to the clinical signs in young children.[15] Papular, follicular, seborrheic dermatitis-like patterns are other well-described forms of AD, especially in children,[15-18] whereas prurigo-like lesions are more frequently reported in adults.[17,18] In

the present series, seborrheic dermatitis-like pattern on scalp and retroauricular area, and nummular pattern were the most frequently observed nontypical morphologic variants.

It might be difficult to differentiate the AD of seborrheic areas (scalp/retroauricular region) from infantile seborrheic dermatitis (ISD) that might even precede or be superimposed on AD.[19] Early onset since the first months of life, greasy crusts, and absence of pruritus are the characteristic features of ISD.[19] In contrast, scalp lesions in AD are characteristically very pruritic. In case of additional flexural involvement, the most useful distinguishing feature was the increased incidence of lesions in the axillae and in the napkin area in ISD, whereas the absence of axillary involvement was suggested to be characteristic for AD.[9,20] Although usually spared in infants due to humidity under the diaper,[15] the napkin area can also be involved in AD as the skin of these patients is more susceptible to irritants like the ones in urine and feces.[21] Anogenital lesions were seen in 4.4% of our cases, with the majority being infants.

It must be stated that our results have been achieved on the basis of a specific ethnic patient population. The genetic background of Turkish patients might have led to a different clinical phenotype, i.e. large number of nontypical presentation of AD such as more flexural lesions than expected.

In the present study, patients with onset of AD before the age of 18 years had a mean number of seven minor criteria according to HRC.[1] Patients under the age of 2 years had significantly less minor criteria in this study, suggesting a time-related increase in the number of minor criteria with increasing age. At that point, a risk of underdiagnosis of AD among infants with less than three minor criteria would arise if they would be evaluated strictly according to HRC.

In conclusion, this study on Turkish AD patients with onset before the age of 18 years has shown that a considerable number of patients could have a different morphology (i.e. seborrheic dermatitis-like, nummular, papular, follicular, or prurigo-like) and/or different distribution of AD. Flexural areas were an important site of involvement in any age group. Even at infancy, AD might begin with flexural lesions in nearly one-fourth of the cases. Besides, there was a time-related increase in the number of positive minor criteria. We believe that the confirmation of our findings in a multicentric prospective study would further allow that the diagnostic criteria of AD could be completed and corrected for age groups.

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