Egypt J Pediatr Allergy Immunol 2023; 21(1):9-17, DOI: 10.21608/ejpa.2023.294363.

Original article

Thymus gland assessment in infants and children with atopic dermatitis

Background: *Atopic dermatitis (AD) is one of the most common inflammatory skin conditions and is characterized by a significant activation of T cell in lesional and even non-lesional skin. The thymus is a key organ concerned with T cell immune response in early life. We sought to investigate the thymic size in infants and young children with atopic dermatitis and its relation to disease severity.* ***Methods:*** *We conducted a controlled cross-sectional study on a group of 50 preschool children aged 4 years or less with physician-diagnosed AD in comparison to 50 healthy matched children. They underwent thymic index assessment by ultrasonography and complete blood counting with manual differential.* ***Results:*** *Thymic indices of our patients ranged between 0.52 and 34.7 cm3 with a median (IQR) value of 2.7 (2.0 to 9.8) cm3. Relevant values of the control group did not vary statistically (p=0.014) from those of the patients [6.50 (2.40 to 10.80) cm3]. After adjustment for age, sex and weight percentile, there was no statistically significant relation between the thymic index and AD (odds ratio = 1.017, 95% CI = 0.988 to 1.047, p= 0.254). The thymic indices of patients correlated positively and significantly with their oSCORAD indices (p=0.001), and the latter correlated positively with the absolute lymphocyte counts (p= 0.002). Boys had higher frequency of response to treatment of AD as compared to girls (p=0.005). The poor response to treatment was associated with younger age at onset (p=0.003) and high oSCORAD index (p=0.001).* ***Conclusion:*** *Thymic indices were comparable between AD patients and healthy controls, but the thymic size was positively correlated to disease severity. The positive correlation of oSCORAD to thymic size and lymphocyte count reflects the underlying immune dysregulation in AD. Our findings are limited by the sample size and the cross-sectional study design.*

Key words: atopic dermatitis; SCORAD, thymus, children.

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Received: October 2022
Revised: November 2022
Accepted: January 2023

INTRODUCTION

Atopic dermatitis (AD) is one of the most common inflammatory skin conditions, predominantly affecting infants and children. It affects 15% to 25% of children and 4% to 7% of adults. It is characterized by pruritus, eczematous lesions, and skin dryness. It involves immune (innate and adaptive) hyper responsiveness of the skin, epidermal barrier disruption, genetic predisposition and environmental factors leading to chronic skin inflammation.[1]

Although atopic dermatitis (AD) often starts in infancy and early childhood, detailed tissue profiling of early-onset AD in children is lacking, hindering the therapeutic development for this population. The clinical manifestations of the disease can be apparently uniform; however, it actually presents a great degree of underlying heterogeneity owing to the variety and complexity of the mechanisms of pathogenicity.[2]

AD is characterized by a strong activation of T helper 2 (TH2) immune responses in lesional and even non-lesional skin. However, other TH cells, such as TH22, TH17, and TH1, might also play a role in the pathogenesis of certain subtypes of AD and different disease phases.[3]

Redistribution of memory T cells into the circulation in AD patients not only leads to disease exacerbation through T-cell skin infiltration but also spread beyond the skin to initiate the atopic march, which includes food allergy, asthma, and allergic rhinitis. Thus, skin sensitization during early-onset pediatric AD is considered the initiating step of the atopic march, and its characterization might help develop approaches that can prevent atopic diathesis through restoration of barrier integrity and/or early immune modulation.[4]

The thymus represents the primary site for T cell lymphopoiesis, providing a coordinated set for critical factors to induce and support lineage commitment and survival of thymus-seeding cells. The thymus provides a microenvironment that supports and guides the generation of a diverse T cell repertoire, which is self-restricted and self-tolerant.[5] A cross sectional study performed by Olesen et al [6] showed increased size of thymus among children with active atopic dermatitis

compared to healthy controls. The larger size of thymus might be compatible with increased thymic activity and emission of T lymphocytes. However, no similar studies are performed in our population.

Our main objective was to investigate thymic size, in terms of thymic index, in infants and young children with atopic dermatitis in comparison to healthy matched controls. Also, we aimed to investigate the relation between thymic size and the extent and severity of atopic dermatitis.

METHODS

We conducted a controlled cross-sectional study over one-year. The study was carried out in the Pediatric Allergy, Immunology and Rheumatology Unit and Outpatient Clinic of the Children's Hospital, Ain Shams University, and it included 2 groups of subjects:

Patients' group (n=50): Infants and children ≤ 4 years of age with physician-diagnosed AD, based on Hanifin and Rajka criteria,[7] with or without other forms of allergy. They were enrolled consecutively after exclusion of personal/family history of chronic illness other than allergy. We also excluded children on systemic immunosuppressive treatment or having one or more of the ten warning signs of primary immune deficiency of the Jeffrey model foundation[8] including those with a history suggestive of DiGeorge syndrome (neonatal tetany, abnormal facies, or congenital heart disease).

Control group (n=50): Age and gender matched healthy children with no personal or family history of allergic or immunological disorders. They were enrolled from the Outpatient Clinic of the Children's Hospital, Ain Shams University.

Sample Size: Using (PASS11) program, setting power at 80%, alpha error at 5%, and revising results from a previous study that showed that thymus index was an average 32% higher in patients with AD compared with healthy control,[6] a sample size of 100 patients (50 per group) was collected.

Ethical Considerations

Informed written consent was obtained from parents of enrolled children before enrollment and after explanation of the aim of the study. The study has been approved by the Local Ethics Committee of the Department of Pediatrics, Ain shams university, and also has been approved by the Research Ethics Committee of Faculty of Medicine, Ain shams university (approval number: FMASU 1701/2020).

Study Measurements

Clinical evaluation for symptoms and signs of AD (dryness, erythema, edema, exudation, papules, vesicular papules, scales, crusting, lichenification), and presence of secondary infection, disfigurement, or functional limitation. We also recorded the age of onset of symptoms, distribution and duration of AD and its response to treatment, presence of other forms of allergy (asthma, allergic rhinitis or rhino-conjunctivitis, symptoms of food allergy) and family history of allergic disorders. Children's growth parameters were compared to age matched WHO growth charts for weight and length.[9]

Objective SCORing AD (oSCORAD) index:

We used the oSCORAD clinical tool to assess the extent and severity of AD. It measures the extent of AD, by applying the rule of nine to estimate the area of the patient's inflammatory lesions, which can range from 0 to 100 %. The intensity part of the oSCORAD index consists of six items: erythema, edema/papulation, excoriations, lichenification, oozing⁄crusts and dryness. Each item can be graded on a scale 0–3, with each item is chosen in the most representative lesion. The oSCORAD index formula is: A⁄5 + 7B⁄2. In this formula A is defined as the extent (0–100) and B is defined as the intensity (0–18). The maximum score is 83. Ten bonus points were given in cases with severe disfiguring visible lesions in the face or hands or functional limiting lesions. Thus, in worst cases, the maximum score reaches 93.[10]

Laboratory investigations:

Complete blood count (CBC) was performed by Coulter LH 750 cell counter (Coulter, Electronics, Hialeah, FL, USA), with examination of peripheral blood smears stained with Leishman stain for manual differential white cell count.

Radiological evaluation of the thymus gland for patients and controls:

Thymus ultrasound and estimation of thymus index (volume) in cm^3 was done according to Hasselbalch formula,[11] using real time ultrasonography that was performed by one experienced investigator using a 7-12 MHz linear transducer (GE Logic 9 set), USA.

Statistical methods

Statistical analysis was done, and data were analyzed using IBM© SPSS© Statistics version 26 (IBM© Corp., Armonk, NY) and MedCalc® Statistical Software version 20 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021).

Categorical variables were presented as counts and percentages and intergroup differences were compared using the Pearson chi-squared test or

Fisher's exact test. Ordinal data were compared using the chi-squared test for trend. Non-normally distributed continuous variables were presented as median and interquartile range and differences were compared with the Mann-Whitney test (for two-group comparison) or the Jonckheere-Terpestra trend test (for multiple-group comparison). The Conover test was used for post hoc pairwise comparison. Correlations were tested using the Spearman or Kendall rank correlation. The correlation coefficients (Spearman's rho or Kendall's tau b) were interpreted as follows: <0.2 = very weak, 0.2 to 0.39 = weak, 0.4 to 0.59 = moderate, 0.6 to 0.79 = strong, ≥0.8 = very strong.

Receiver-operating characteristic (ROC) curve was used to examine the discriminative value of continuous variables. The area under the ROC curve (AUC) was interpreted as follows: AUC < 0.6 = fail, 0.6 to 0.69 = poor, 0.7 to 0.79 = fair, 0.8 to 0.89 = good, ≥ 0.9 = excellent. Multivariable binary logistic regression analysis was used to examine the relation between thymic index and eczema as adjusted for effect of possible confounding factors. Bonferroni correction was used to adjust the level of significance for repeated or subgroup comparisons. To keep type I error at <0.05, p <0.01 was considered statistically significant.

RESULTS

Patients were 31 males (62%), 19 females (38%) with ages ranging from one month to four years. The most common clinical findings related to AD were dryness (100%) followed by lichenification (86%), and erythema (80%) with lower frequency of exudation (18%), vesiculopapular eruption (8%) and edema (2%); tables 1-2. Laboratory and radiological findings included eosinophilia in 8 (16%) patients, lymphopenia in 28 (56%) patients and lymphocytosis in 4 (8%) patients. Out of the fifty patients, 30 (60%) were on topical corticosteroids only as treatment for AD; 6 (12%) received local antibiotics and topical corticosteroids; 10 (20%) received add-on topical calcineurin inhibitor (pimecrolimus cream), and 4 (8%) patients received intermittent courses of systemic corticosteroids.

The thymic indices of our patients ranged between 0.52 and 34.7 cm^3 with median (IQR) of 2.7 (2.0 to 9.8) cm^3. Thymic indices seemed lower among cases than controls, but the difference did not reach statistical significance (p=0.014) (table 3). Using multivariable binary logistic regression analysis for assessing thew relation between thymic indices and eczema, after adjustment for age, sex and weight percentile, revealed insignificant statistical relation between the thymic index and AD (odds ratio = 1.017, 95% CI = 0.988 to 1.047, p= 0.254). Associated respiratory allergies were significantly higher among those aged above 2 years (figure 1). Boys had better response to AD treatment compared to girls in our series (x^2=8.019, p=0.005) while other clinicodemographic data, thymic indices and laboratory parameters did not vary with gender.

The non-responders to treatment had a younger age of onset of AD (p=0.003) and higher oSCORAD index (p=0.001) in comparison to partial or complete responders. The latter groups had comparable thymic indices (p=0.295); table 4. Cases of atopic dermatitis with and without secondary infection were comparable in terms of their demographic, clinical and laboratory parameters, and thymic indices.

The patient's thymic indices correlated positively with the oSCORAD index (p=0.001) (figure 2) but did not correlate with the other studied clinical and laboratory data. Also, the oSCORAD index correlated positively with the lymphocyte count (p=0.002) (figure 3). An oSCORAD index of ≤ 24.6 could predict complete response to treatment for AD with sensitivity of 81% and specificity of 79% (area under the ROC curve (AUC) was 0.831; p<0.001). It is also noted that an oSCORAD index ≤ 30.5 could predict any response to therapy, whether partial or complete, with an area under the ROC curve (AUC) of 0.862 and sensitivity of 63%, and specificity of 100%, (p=0.001) with over-all accuracy of 68%.

Table 1. Demographic and anthropometric data of the AD patients (n=50)

Variable		Value
Age (months)	**Median (IQR)**	36.0 (18.0 to 46.0)
	Range	(1 to 48)
Age at onset of AD (months)	**Median (IQR)**	14 (6 to 24)
	Range	(1 to 36)
Age category, N (%)		
≤2 years		19 (38.0%)
>2 years		31 (62.0%)
Sex, N (%)		
Females		19 (38.0%)
Males		31 (62.0%)
Weight percentile, N (%)		
<3rd		2 (4.0%)
3rd-50th		35 (70.0%)
>50th-97th		11 (22.0%)
>97th		2 (4.0%)
Height percentile, N (%)		
<3rd		3 (6.0%)
3rd-50th		37 (74.0%)
>50th-97th		9 (18.0%)
>97th		1 (2.0%)

Table 2. Clinical presentation of AD in the studied sample

Pattern of AD, N (%)	N (%)
Persistent	18 (36.0%)
Seasonal	32 (64.0%)
Clinical findings, N (%)	
Dryness	50 (100.0%)
Lichenification	43 (86.0%)
Erythema	40 (80.0%)
Crustation	36 (72%)
Exudation	9 (18.0%)
Vesiculopapular eruption	4 (8.0%)
Edema	1 (2.0%)
Complication, N (%)	
Secondary infection	6 (12.0%)
Disfigurement/Limitation	0 (0.0%)
oSCORAD index, median (IQR) Range	28.2 (20.1 to 36.8), 14 to 53
Response to treatment, N (%)	
Nil	7 (14.0%)
Partial	27 (54.0%)
Complete	16 (32.0%)

AD=atopic dermatitis, n= number, oSCORAD= Objective Scoring Atopic Dermatitis

Table 3. Variation of clinical and investigational data among AD patients and controls

Variable	Cases (N=50)	Controls (N=50)	X^2/U	p value
Sex, F/M	19/31	26/24	1.980	0.159
Age (months), median (IQR)	36.0 (18.0 to 48.0)	33.6 (7.2 to 45.0)	1159.500	0.530‡
Weight percentile, n (%)			2.368	0.124§
<3rd	2 (4.0%)	1 (2.0%)		
3rd-50th	35 (70.0%)	44 (88.0%)		
>50th-97th	11 (22.0%)	4 (8.0%)		
>97th	2 (4.0%)	1 (2.0%)		
Height percentile, n (%)			0.000	1.000§
<3rd	3 (6.0%)	0 (0.0%)		
3rd-50th	37 (74.0%)	42 (84.0%)		
>50th-97th	9 (18.0%)	8 (16.0%)		
>97th	1 (2.0%)	0 (0.0%)		
Thymic index (cm^3), median (IQR)	1.65 (0.66 to 7.04)	6.50 (2.40 to 10.80)	892.500	0.014‡

§. Chi-squared test for trend, ‡. Mann-Whitney U test, df = degree of freedom, F= female, IQR = interquartile range, M=male, n= number, Pearson chi-squared test, U = Mann-Whitney U, $\chi 2$ = chi-squared statistics

Table 4. Variation of clinical, laboratory and radiological parameters according to the degree of response to AD treatment

Variable	Response to treatment						Z	P-value†
	Nil (N=7)		Partial (N=27)		Complete (N=16)			
	Median	IQR	Median	IQR	Median	IQR		
Age (months)	18.0	12.3 to 36.0	36.0	10.5 to 43.7	36.0	27.0 to 48.0	1.771	0.077
Age at onset (mo)	8.0	6.0 to 17.3	12.0	2.5 to 24.0	24.0	15.0 to 30.0	2.958	**0.003**
oSCORAD index	39.6	36.9 to 41.1	33.2	24.4 to 36.8	19.95	17.10 to 24.1	-4.468	**<0.001‡**
Eosinophils (k/mm^3)	0.70	0.45 to 0.76	0.30	0.10 to 0.50	0.25	0.14 to 0.50	-1.717	0.086
Eosinophils (%)	4.7	3.4 to 6.8	3.0	1.3 to 5.5	2.6	1.3 to 4.9	-1.309	0.191
Lymphocytes (k/mm^3)	6.2	5.6 to 6.3	5.3	4.1 to 6.4	4.7	3.7 to 5.6	-1.823	0.068
Thymic index (cm^3)	3.12	2.6 to 5.7	2.80	1.84 to 12.24	2.34	1.76 to 4.26	-1.047	0.295

†. Jonckheere-Terpstra trend test, ‡ P < 0.01 versus Nil & Partial Groups (Conover post hoc test), AD: atopic dermatitis; IQR = interquartile range, J-T = Observed J-T Statistic, Z = Z statistic

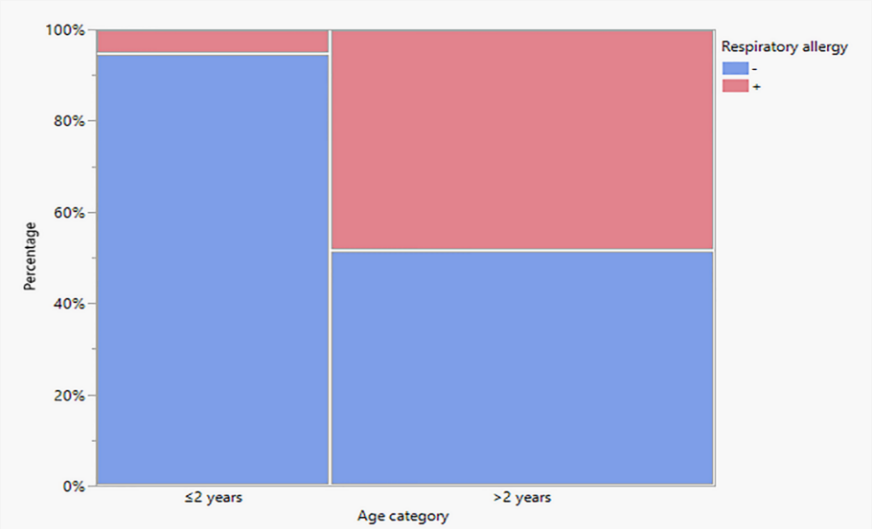

Figure 1. Prevalence of respiratory allergy with age category among studied patients (p=0.002).

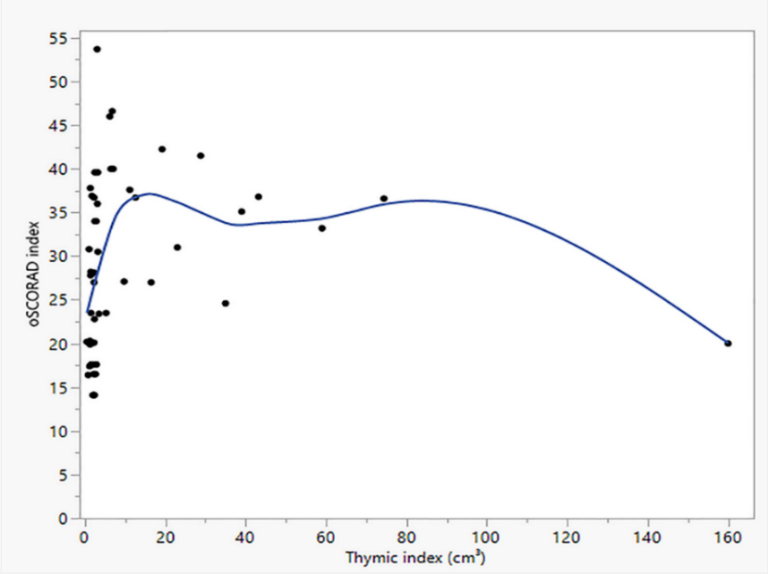

Figure 2. Scatter plot illustrating correlation between thymic index and oSCARD index. Fitted line (blue) represents the local regression smoothing trend line (p=0.001).

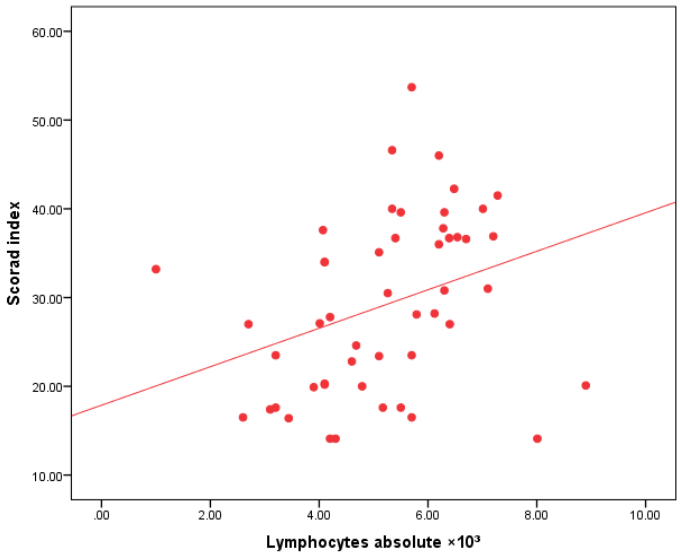

Figure 3. Correlation between oSCORAD index and absolute lymphocytes count

DISCUSSION

The thymus is essential for the establishment of a normal peripheral T-lymphocyte immune system. Its size and function are highest in infants.[6] Atopic dermatitis (AD) is associated with immune deviations such as T-cell accumulation and activation in the skin resulting in active AD.[12] We, therefore, sought to investigate the thymic size, in terms of thymic index, in infants and young children with atopic dermatitis in comparison to healthy matched subjects.

Among our series, the thymic indices were comparable between patients with AD and controls. Boralevi et al[13] in their study of 60 children with AD using the same technique of thymus ultrasound scan, reported that the thymus was smaller in cases of AD than healthy controls and explained their results, by the possible thymolytic effect of long-term treatment with topical steroids and stress among children with AD, these factors would probably lead to a reduction in the size of the thymus.[11] The size of the thymus in children with AD can be influenced by many factors of which stress from itching, lack of proper sleep, and/or the impact from application of topical steroids are particularly relevant.[14] Worth to note that, Only 4 of our patients received systemic steroids for their AD, but even the regular application of topical steroids is expected to exert some systemic side effects due to cutaneous absorption.[15] Another study, that investigated 37 children with AD versus 29 healthy controls reported that the thymus index declined with age. The decline was more significant for the healthy controls, but not for the AD children.[6]

We noticed that the oSCORAD index, which reflects the extent and severity of AD, was positively correlated with the thymic index. Although the thymic indices did not vary significantly with the presence of AD, it revealed higher expression with severity. This observation might point to the possible structural and functional changes in the thymus in relation to the severity of AD. The severity of atopic dermatitis was judged in our patients by the oSCORAD index which is totally based on physician evaluation (objective) and thus reflects the extent and intensity of affection.[11,16] However, our results are limited by the cross-sectional nature of the study, longitudinal studies might lead to more conclusive results. Also, we only evaluated the thymic size rather than function. In other words, we did not investigate the lymphocyte subsets involved in AD patients. In this context, one study by Moosbrugger-Martinz et al [17] reported thymic expansion of a specific population of T regulatory cells, exhibiting Th2 cytokine profile induced by emigrated skin-derived dendritic cells in mice model with AD.

In our study, out of the 50 patients with AD, 44% had associated allergic manifestation, mainly in the form of respiratory allergies which were particularly more frequent among patients above 2 years of age. A relevant long-term follow-up study (up to 20 years) on 252 Korean children aged between 6 to 36 months reported that many children with AD outgrow their AD symptoms but may develop respiratory allergies such as asthma and rhino-conjunctivitis later in childhood.[18]

In our study, boys with AD outnumbered girls (62% versus 38%). In a population-based case-control study of 2-year-old children from Sweden, more boys than girls had ongoing AD and positive IgE-sensitization.[19] Also, AD children younger than

4 years in central Netherlands showed male preponderance particularly marked below 2 years of age.[20]

Our AD series demonstrated eosinophilia in 16% and lymphopenia in 56%. Eosinophil numbers as well as eosinophil granule protein levels in the peripheral blood are reported to be elevated in most AD patients and appear to correlate with disease activity. These observations point to a potential important role of eosinophils in the pathogenesis of AD.[21] However, Lymphopenia in patients with AD might be secondary to corticosteroid treatment whether local or systemic. AD patients treated with the immunosuppressive drugs and corticosteroid might develop disturbance of cellular immunity.[22] However, it is essential to recheck the lymphocyte counts in the corticosteroids-free intervals, to better interpret such observation.

CONCLUSIONS

Thymic indices were comparable between AD patients and healthy controls, but within the AD patients, thymic indices varied significantly with the disease severity. The positive correlation of oSCORAD to the thymic index and lymphocyte count may reflect the underlying immune dysregulation in AD. Our study is indeed limited by the sample size and cross-sectional design. Further wider scales studies are recommended to provide better assessment of thymic size. Local reference data for thymic size and characterization of thymic function are needed and studying the thymic functions, lymphocyte subsets, and cytokine profile would provide better insight about the relation between this gland and atopic dermatitis in children.

CONFLICTS OF INTEREST

Authors declare they have no conflicts of interest

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