Original Article

Is Atopic Dermatitis a Risk Factor for Thyroid Autoimmunity? – A Cross-Sectional Study from a Tertiary Care Center in India

Abstract

Background: Because of the counter-regulation of Th1 and Th2 cells, Th1-type autoimmune diseases like thyroid autoimmunity and Th2-mediated allergic diseases like atopic dermatitis (AD) should occur in mutually exclusive populations. However, thyroid autoimmunity has been associated with chronic urticaria, and atopy is considered a cause of both AD and urticaria. **Objectives:** To assess the frequency of thyroid autoimmunity in children with AD and to study the correlation between the clinical severity of AD using the SCORing Atopic Dermatitis (SCORAD) score, and biochemical parameters of serum immunoglobulin E (IgE), absolute eosinophil count, and vitamin D levels. **Materials and Methods:** A hospital-based cross-sectional study was conducted, recruiting children (0–18 years) with AD. Patients on drugs affecting thyroid dysfunction and those with sick euthyroid syndrome or an immunodeficiency disorder were excluded. Clinical severity was assessed using SCORAD, and the thyroid profile, anti-thyroid peroxidase antibodies, antinuclear antibody (ANA), absolute eosinophil count, serum IgE, and vitamin D levels were measured. **Results:** Thyroid autoimmunity was diagnosed in 18.9% (10/53) of children. There was a significant correlation between SCORAD and serum IgE (r = 0.432, P = 0.002) and absolute eosinophil count (r = 0.575, P = <0.001). There was a negative correlation between SCORAD and vitamin D levels (r = -0.373, P = 0.006). **Conclusions:** Thyroid autoimmunity may be associated with AD, and a high index of suspicion is essential. Vitamin D also should be supplemented in children with AD as it is frequently found to be low, especially in severe cases. Multi-center case-control studies are required to determine the prevalence of thyroid autoimmunity in children with AD.

Keywords: *Atopic dermatitis, biomarkers, thyroid autoimmunity*

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Introduction

Atopic dermatitis (AD) is a chronic, relapsing, inflammatory skin disease that primarily affects young children and has a lifetime prevalence of approximately 20%.[1] Because of the counter-regulation of T-helper 1 (Th1) and T-helper 2 (Th2) cells, it is expected that Th1-type autoimmune diseases such as thyroid autoimmunity and Th2-mediated allergic diseases like AD should occur in mutually exclusive population of patients.[2] However, thyroid autoimmunity has been regularly associated with chronic urticaria, and atopy is considered a cause of both AD and acute as well as chronic urticaria.[2] Additional lymphocyte subsets such as Th17 cells and soluble factors such as IL-9 and regulatory T-cells (T reg) have been identified as a common link between atopy and autoimmunity.[3-5]

There is a paucity of literature with regard to the prevalence of thyroid function impairment and thyroid autoimmunity in Indian children with AD. Hence, we conducted this study with the primary objective of assessing the frequency of thyroid autoimmunity in children with AD. In addition, we studied the correlation between the clinical severity of AD using the SCORing Atopic Dermatitis (SCORAD) score and biochemical parameters of serum immunoglobulin E (IgE), absolute eosinophil count, and vitamin D levels.

Materials and Methods

A hospital-based cross-sectional study was conducted over a period of one year in the department of dermatology and STD in a tertiary care center in India. The study was approved by the institutional ethics and scientific committee. All children diagnosed with AD based on the UK Working Party

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Diagnostic Criteria, aged 0–18 years, were recruited, after obtaining informed consent from their guardians. Patients on drugs affecting thyroid dysfunction, such as lithium, severely ill patients with sick euthyroid syndrome, and those with an immunodeficiency disorder were excluded from the study. Clinical and demographic data of all patients was recorded in a proforma. SCORAD was assessed, and blood samples were withdrawn for thyroid profile, anti-thyroid peroxidase (anti-TPO) antibodies, antinuclear antibody (ANA), absolute eosinophil count, serum IgE, and vitamin D levels. Thyroid autoimmunity was diagnosed by anti-TPO antibody serum levels more than twice normal (fully automated chemiluminescence immunoassay analyzer machine) and an abnormal thyroid profile (Roche e-411 fully automated immunoassay analyzer).

Data were entered in Microsoft Excel and analyzed using SPSS version 25.0. Correlation was determined using Pearson correlation coefficient and linear regression.

Results

A total of 62 children with AD were presented to our department during the study period. The guardians of 9 children were unwilling for investigations, and these children were, therefore, excluded from the study. Of the 53 children who underwent blood tests, there were 26 males and 27 females, with a mean age of 7.8 ± 5.9 years. The clinical profile of the cases are shown in Table 1.

Thyroid autoimmunity was diagnosed in 18.9% (10/53) of children (males: 4, females: 6) based on the presence of anti-TPO antibodies. Of these, five children had a normal thyroid function test and five had an abnormal test. Mild AD, moderate AD, and severe AD were seen in four, three, and three patients, respectively. Only one patient had symptoms suggestive of thyroid disorder, and the rest were asymptomatic. There were three children with abnormal thyroid profiles but no anti-TPO antibodies. However, other antithyroid antibodies such as thyroglobulin antibody and TSH (thyroid stimulating hormone) receptor antibody levels were not measured because of the non-availability of these tests at our center. Of the ten children with thyroid autoimmunity, nine had elevated serum IgE and one child did not get herself tested for IgE. ANA was negative in all children with thyroid autoimmunity.

Based on SCORAD, mild (<25), moderate (25–50), and severe diseases (>50) were seen in 20 (37.7%), 22 (41.5%), and 11 (20.8%) patients, respectively. The mean SCORAD was 34.7 + 17.6 (range: 11.3–74.9). There was a significant correlation between SCORAD and serum IgE (r = 0.432, P = 0.002) and absolute eosinophil count (r = 0.575, P = <0.001). There was a negative correlation between SCORAD and vitamin D levels (r = -0.373, P = 0.006) [Table 2]. Serum IgE and vitamin D levels also had a negative correlation, although not statistically significant (r = -0.191, P = 0.179, n = 51).

Table 1: Clinical profile of children with atopic dermatitis

	Clinical parameters	Number of children (%)
Age of onset	By 1 year	15%
	By 5 years	26.4%
Season of onset	Winter	50.9%
	Summer	49.1%
Aggravating factors	Contact allergens	18.7%
	Food allergens	9.4%
	Airborne allergens (dust/cement)	13.2%
	Seasonal exacerbation	9.4%
	Woolen clothing	18.7%
	Others (sweating, sun exposure)	7.4%
Mucosal allergy	Bronchial asthma	47.2%
	Allergic rhinitis	11.3%
	Allergic conjunctivitis	15.1%
Family history of atopy		49%
Clinical type	Acute eczema	28.3%
	Subacute eczema	30.2%
	Chronic eczema	18.9%
	Follicular eczema	3.8%
	Mixed forms (having lesions suggestive of acute, subacute, chronic, or follicular eczema)	18.8%
Sites involved	Face	56.6%
	Trunk	52.8%
	Flexural aspect of limbs	79.2%
	Extensor aspect of limbs	43.4%

Table 2: Pearson correlation coefficient between SCORAD and serum IgE, absolute eosinophil count, and vitamin D levels

Parameter	*r* (95% confidence interval)	*P*
Serum IgE (*n*=51)	**0.432** (0.178, 0.632)	0.002
Absolute eosinophil count (*n*=50)	**0.575** (0.353, 0.736)	<0.001
Vitamin D (n *n* =52)	**-0.373** (-0.586, -0.111)	0.006

The significant correlations are highlighted in bold (P<0.05)

Discussion

AD is a pruritic, chronic, relapsing inflammatory skin disease that usually begins in early childhood and is characterized by itchy papules, papulovesicles, erythema, excoriations, and lichenification, which occur typically in a flexural distribution.[6] AD is diagnosed clinically based on the history, morphology and distribution of lesions, and other clinical signs. There are various formal sets of criteria for the same, such as the Hanifin and Rajka criteria, the Danish Allergy Research Centre Criteria, the Schultz-Larsen criteria, and the UK Working Party's

Diagnostic criteria.[7] The specificity of the UK Working Party's Diagnostic criteria ranges from 90.4% to 98.3%, and the sensitivity ranges from 10% to 95.5%.[8]

Th2 cells seem to play a crucial role in the pathogenesis of AD. Th2 cytokines, IL-4 and IL-13, are increased in the skin of early lesional AD patients and also down-regulate filaggrin expression.[6,9] AD is well known to be associated with other atopic conditions. There is increasing evidence of an association with several non-atopic conditions as well, such as autoimmune conditions mediated by Th1 cells, such as autoimmune thyroid disorders, Crohn's disease, ulcerative colitis, coeliac disease, alopecia areata, vitiligo, certain cancers, cardiovascular diseases, infections, and neuropsychiatric disorders, although their relationship with AD is not fully understood.[10-12] Autoimmune diseases occur because of multi-factorial etiology; however, one of the accepted causes is that an infection or exposure to a cross-reactive antigen leads to an immune dysregulation with a Th1 response, thereby causing inflammation and autoimmunity.[2] IgE-mediated autoimmunity has also been implicated in the pathogenesis of inflammatory disorders like AD and other autoimmune conditions. IgE auto-antibodies have been detected against >140 self-binding antigens in AD, against TPO in chronic spontaneous urticaria, and also in Grave's disease, among others.[13]

In our study, thyroid autoimmunity was found in 18.9% of the cases. Population-based studies have reported the prevalence of anti-TPO antibodies and anti-TG antibodies as 16.7% and 12.1%, respectively among adults in India.[14] A previous study from India on children found thyroid autoimmunity in 54.3% of children with type 1 diabetes, compared to only 10% in healthy controls.[15] The prevalence of thyroid autoimmunity reported for age-matched healthy children in different geographic areas range from 0.3% to 1.6%.[16,17] However, similar data from healthy children in India is sparse. In the study by Pedullá *et al*.[2] in Italy, the prevalence of thyroid autoimmunity was higher in children affected by AD (9.52%) than in those unaffected by AD and/or other atopic diseases (0%). This again suggests the possibility of atopy and thyroid autoimmunity are caused by immune dysregulation. Another study was conducted by Pedullá *et al*.[18] in 187 children with AD, 95 with acute urticaria, 40 with chronic urticaria, and two with alopecia areata, which also found a significant prevalence of thyroid autoimmunity in atopics as compared with non-atopics (11.5% vs 2.7%, $P = 0.03$, odds ratio (OR) = 4.68, 95% confidence interval (CI): 1.02–21.38) in children with AD and a significant association between thyroid autoimmunity and atopy (OR = 5.76, 95% CI: 1.71–19.35) in all children with skin disease.

Previous studies have evaluated the prevalence and severity of AD in vitamin D-deficient children. Peroni *et al*.[19] studied 37 children with AD with mild, moderate, and severe diseases using the SCORAD score and found that serum levels of vitamin D were higher in patients affected by mild AD compared to those with moderate or severe AD. Similar results were obtained by El Taieb *et al*.[20] However, there are many controversies. Whereas vitamin D may have anti-inflammatory action by inhibiting dendritic cell migration and IL-12 and IL-23 cytokine production on the one hand, on the other hand, it may also inhibit adaptive immune responses and reduce the production of Th1 cells, thereby causing an increased proliferation of allergy-associated Th2 cells.[21] A similar non-linear association was also described by Hyppönen *et al*., wherein patients with low vitamin D (<10 ng/mL) or with very high serum levels (>54 ng/mL) had significantly higher IgE levels than healthy individuals (40–50 ng/mL). A subsequent correction of serum concentrations of vitamin D reduced IgE levels significantly.[22] In our study, there was an inverse correlation between serum levels of vitamin D and clinical severity of AD ($r = -0.373$, $P = 0.006$) and serum IgE ($r = -0.191$, $P = 0.179$, n = 51).

Various biomarkers that correlate with the severity of AD, such as serum IgE, peripheral eosinophils, lactate dehydrogenase (LDH), thymus and activation-regulated chemokine (TARC), have been identified, although none are reliable individually and a combination of such biomarkers along with clinical scoring systems is more reliable.[23] A previous study from India found the highest correlation of SCORAD with LDH ($r = 0.582$; 95% CI, 0.40–0.72), followed by serum TARC ($r = 0.538$; 95% CI, 0.36–0.68), peripheral eosinophils ($r = 0.397$; 95% CI, 0.19–0.57), and serum IgE ($r = 0.331$; 95% CI, 0.11–0.52).[24] In our study, we assessed the role of serum IgE and absolute eosinophil count as biomarkers for the severity of AD and found a significant correlation between SCORAD and serum IgE ($r = 0.432$; 95% CI, 0.178, 0.632) and absolute eosinophil count ($r = 0.575$; 95% CI, 0.353, 0.736).

Conclusion

Although our study was limited to a single center, we conclude that thyroid autoimmunity may be associated with AD and a high index of suspicion is essential to avoid missing this disorder. Vitamin D also should be supplemented in children with AD, as it is frequently found to be low, especially in severe cases. Depending on the availability of biomarkers in various setups, these can be measured in addition to the clinical assessment of such patients, which will help in determining the prognosis of patients. Multi-center case-control studies are required to determine the prevalence of thyroid autoimmunity in children with AD.

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Conflicts of interest

There are no conflicts of interest.

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