ORIGINAL ARTICLE

A CASE-CONTROL STUDY TO ASSESS THE ASSOCIATION OF ALOPECIA AREATA WITH THYROID DYSFUNCTION AND THYROID AUTOIMMUNITY

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Background: Several previous studies have suggested a positive association between Alopecia Areata and thyroid disorders. However, there is a paucity of such studies in our country. Our study aimed to know the frequency of thyroid dysfunction and thyroid autoimmunity in patients reporting to Dermatology Outdoors with Alopecia Areata (AA) and to compare it with normal controls. **Methods:** This was a Case-Control study conducted at the Dermatology outpatient of a tertiary care hospital in Pakistan. 102 patients with AA and 102 age and sex-matched controls were enrolled. The age of onset of the disease, the involved sites and the presence of other associated diseases were noted. Venous blood samples were taken from patients and controls for Thyroid function tests and Anti- Thyroid peroxidase antibodies (Anti-TPO Ab). The data was analyzed using Statistical Package for Social Sciences (SPSS) version 23. **Results**: The mean age of onset of the disease was 30.37±12.53. 91.2% of patients had the classic patch type of AA. The most commonly involved site was Scalp. Associated diseases were found in eight (7.8%) patients. Thyroid dysfunction was found in two patients and none of the Controls. Both the patients had Subclinical thyroid disease. The p-value was 0.157, which was not statistically significant. Thyroid autoimmunity (raised Anti-TPO Ab titre) was detected in five (4.90%) patients and none of the Controls. The *p*-value was 0.024, which was statistically significant. **Conclusion**: AA is significantly associated with Thyroid autoimmunity but there is no significant association between AA and clinical or subclinical thyroid disease.

Keywords: Alopecia areata; Clinical thyroid disease; Subclinical thyroid disease; deranged thyroid function tests; Thyroid autoimmunity; Anti-TPO antibodies

Citation: Habib A, Ansari MM, Basra AA, Nazeer H, Ahmed A, Shaheen S. A case-control study to assess the association of alopecia areata with thyroid dysfunction and thyroid autoimmunity. J Ayub Med Coll Abbottabad 2023;35(4):640–4.

DOI: 10.55519/JAMC-04-12361

INTRODUCTION

Alopecia areata (AA) is a common, immune-mediated, non-scarring hair loss affecting the scalp or any hair-bearing surface.[1–3] It is caused by a T-cell-mediated autoimmune mechanism occurring in those individuals who are genetically predisposed. The environmental factors act as possible triggers of the disease.[1,4,5] The disease affects both sexes equally and has a prevalence of approximately 0.1–0.2%.[1–3] Although the disease can begin at any age, the peak age of onset is between the second and fourth decades.[1,3] The clinical presentation of alopecia areata varies from small, well-circumscribed patches of hair loss which usually recover spontaneously, to a diffuse involvement of the scalp or the entire body where the prognosis for hair regrowth is poor.[1,3] Based on the severity, various well-known clinical subtypes of AA have been described. The prognosis for hair regrowth is poor in more severe clinical subtypes.[1,2]

Alopecia areata is associated with various autoimmune diseases, particularly thyroid dysfunction and vitiligo.[1,5-7] The prevalence of thyroid disease is increased in patients with AA.[1,2,5] Thyroid dysfunction may manifest as overt thyroid diseases, by abnormal thyroid function tests or by the presence of anti-thyroid auto-antibodies.[7–9]

Several previous studies have suggested a positive association between AA and thyroid disorders.[7–10] However, there is a paucity of such studies in our country.[8,11] We conducted a study on patients reporting to the Dermatology outpatient department of a Tertiary Care Hospital in South Punjab, Pakistan. Our study aimed to know the frequency of thyroid dysfunctions and thyroid autoimmunity in patients reporting to Dermatology outdoors for the first time with new onset AA and to compare it with normal controls.

MATERIAL AND METHODS

We conducted a case-control study for which we prospectively recruited 204 participants (102 patients with Alopecia Areata and 102 age and sex-matched controls) at the Dermatology departments of Combined Military Hospital, Bahawalpur from July 2022 to May 2023. Approval was taken from the

Hospital Ethical Committee. The sampling technique was non-probability consecutive sampling. The sample size was calculated using OpenEpi software, with a 95% confidence interval and a five percent margin of error, taking the frequency of thyroid disorders in alopecia areata patients reported previously at 7.1%.[8] All the patients belonging to either sex and any age, attending the Dermatology outpatient departments of the hospital with newly diagnosed Alopecia Areata were enrolled after taking an informed consent. Detailed history was taken and clinical examination was performed for each subject Diagnosis of Alopecia areata was essentially clinical. Each patient was interviewed in detail and a thorough physical examination was performed to determine the age, gender, age of onset of the disease, the clinical type of the disease, family history, involved sites and the presence of other associated diseases.

A total of 102 patients who fulfilled the inclusion criteria were enrolled in the study. The inclusion criteria were as follows:

Inclusion Criteria: Patients of either gender and any age, presenting in the Outpatient Department with newly diagnosed Alopecia Areata, were included in the study.

Exclusion Criteria: Patients not willing to participate in the study, pregnant females, and any patients on treatment for Alopecia Areata (either topical or systemic) within the last month were excluded from the study. Patients having scarring alopecia or showing any signs of inflammation in the affected area were also excluded from the study. Patients with autoimmune skin diseases including, Autoimmune blistering skin conditions, Systemic sclerosis, Dermatomyositis, Psoriasis, Vitiligo, Lichen planus and Lichen Sclerosis were also excluded from the study.

A Control group of 102 age and gender-matched individuals reporting to the Dermatology outpatient departments of the hospital with unrelated skin diseases or accompanying the patients as attendants were included in the study simultaneously. Patients with autoimmune skin diseases including, Autoimmune blistering skin conditions, Systemic sclerosis, Dermatomyositis, Psoriasis, Vitiligo, Lichen planus and Lichen Sclerosis were not enrolled as Controls. Recruitment of Cases and Controls was done using a nonprobability, convenience sampling technique. None of the Cases or Controls declined to participate in the study as it was a single-encounter study.

Venous blood samples were taken from patients and controls for Thyroid function tests (TFTs) and anti-thyroid peroxidase antibodies (Anti-TPO Ab). Thyroid function tests (TFT) included measurement of serum thyroid stimulating hormone (TSH), serum total triiodothyronine (T3) and total thyroxine (T4) levels. Normal values for thyroid stimulating hormone (TSH) ranged from 0.4 to 4.5 mIU/L, for T3 from 1.1 to 2.7 nmol/L and for T4 from 8–21 pmol/L. Serum T3, T4 and TSH concentration were analyzed by electrochemiluminescence immunoassay method using Cobas E 441random access autoanalyzer (Roche Diagnostics, USA). For quality control, Preci Control Universal was used. We defined thyroid dysfunction as any thyroid hormone level 10% above or 10% below of reference ranges. This included patients with clinical thyroid disease and patients with abnormal thyroid function tests (subclinical thyroid disease). The patients with raised anti-thyroid peroxidase auto-antibodies titres were said to have thyroid autoimmunity.

Data were analyzed using SPSS version 23. Frequency and percentages were computed for qualitative variables while mean and standard deviations were calculated for numerical variables. Pearson's Chi-square test was used to compare the categorical data between the groups. The *p*-value of < 0.05 was set as the cut-off value for significance.

RESULTS

102 patients with Alopecia Areata and 102 age and sex-matched controls were enrolled in the Case and Control groups. Out of 102 Cases, 80 (78.4%) were male and 22 (21.6%) were females. Male to female ratio was 3.636. The mean ages of the Case and Control groups were 31.09±13.011 with an age range of three years to 63 years. The mean age of male patients was 32.99±12.271 (age range from three to 63 years) while the mean age of female patients was 24.18±13.567 (age range from three years to 40 years). The mean age of onset of the disease was 30.37±12.526 (range 3 years to 61 years. The mean age of onset of male patients was 32.28±11.693 (age range from three to 61 years). While mean age of onset of the disease in female patients was 23.45±13.276 (age range from three years to 40 years).

91.2% of patients had the classic patch type of AA. (Table-1). The most commonly involved disease site was Scalp. (Figure-1). Associated diseases were found in eight (7.8%) patients. (Table-2)

Thyroid dysfunction was found in two (1.96%) patients. None of the Cases or Controls had overt thyroid diseases. Thyroid function tests were deranged in two (1.96%) patients and none of the Controls. The p-value was 0.157, which was not statistically significant (Table-3). Thyroid autoimmunity assessed by the presence of Anti-Thyroid Peroxidase antibodies (Anti-TPO Ab) was detected in five (4.90%) patients and none of the Controls. The *p*-value was 0.024, which was statistically significant (Table-4).

Table-1: Type of disease

			Patient gender		
			Male	Female	Total
Type of Disease	Patch type AA	Count	74	19	93
		% within Patient gender	92.5%	86.4%	91.2%
	Alopecia Totalis	Count	0	1	1
		% within Patient gender	0.0%	4.5%	1.0%
	Alopecia Universalis	Count	2	1	3
		% within Patient gender	2.5%	4.5%	2.9%
	Ophiasis type AA	Count	1	1	2
		% within patient gender	1.3%	4.5%	2.0%
	Madarosis	Count	3	0	3
		% within Patient gender	3.8%	0.0%	2.9%
Total		Count	80	22	102

Table-2: Associated diseases

Associated diseases	Total
Hypertension and Diabetes Mellitus	2
Chronic kidney disease	1
Pseudoxanthoma Elasticum	1
Bronchial Asthma	1
Hypertension	1
Hyperlipidemia	1
Diabetes Mellitus	1
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Table-3: Thyroid Dysfunction

		Thyroid Function Tests		*p*-value
		Normal	Deranged	
Patient category	Cases	100 (98.04%)	2 (1.96%)	0.157
	Controls	102 (100%)	0 (0.0%)	

Table-4: Thyroid autoimmunity

		Anti-TPO antibodies titre		*p*-value
		Normal	Deranged	
Patient category	Cases	97 (95.10%)	5 (4.90%)	0.024
	Controls	102 (100%)	0 (0.0%)	

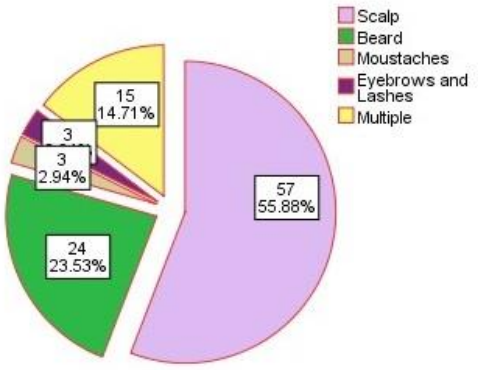

Figure-1: Body site involved

DISCUSSION

Alopecia areata (AA) results from an autoimmune T-cell-mediated destruction of hair follicles, in genetically predisposed individuals.[1–3] The hair follicle is an immune-privileged site and this immune privilege appears to be disrupted in AA.[1,2,12,13] The evidence for immunological mechanisms in the pathogenesis of alopecia areata is based on three observations. Firstly, on histology, the hair follicles in the active stage of the disease are consistently infiltrated by autoreactive T cells and the severity of the disease positively correlates with CD 8 T cell density. Secondly, the frequency of other autoimmune diseases is increased in AA and thirdly several types of circulating autoantibodies are found in many patients with AA.[1–3] Therefore it is hypothesized that autoantigens derived from hair follicles may be involved in the pathogenesis of the disease with environmental factors as possible triggers of the disease. [1,2,12,13]

Patients with AA are at an increased risk of thyroid dysfunction and thyroid autoimmunity.[1–3,5,6] Thyroid dysfunction may manifest as clinical thyroid disease or by abnormal thyroid function tests.[7–8,14,15] Although the prevalence of thyroid dysfunction is high in patients with AA, the association between thyroid dysfunction and AA is not confirmed.[7,14] Similarly there is also a lack of agreement about the association between alopecia areata (AA) and thyroid autoimmunity.[16]

Our study compared the frequency of thyroid dysfunctions and thyroid autoimmunity in patients suffering from AA with normal controls.

Out of 102 cases, 80 (78.4%) were male and 22 (21.6%) were females. A similar male-to-female ratio has been reported previously.[17] The mean age of our patients was 31.09±13.011. Similar mean age was reported previously by Asgher R *et al*,[8] Puavilai S *et al*,[9] Rahnama Z *et al*,[18] Marahatta S *et al*,[10] Lyakhovitsky A *et al*,[19] and Chu SY *et al*.[20] A younger mean age of patients was reported previously by Shahzadi N *et al*[11] (22.28±13.00 years) and Bakry OA *et al*[21] (26.38±10.85 years).

The mean age of onset of the disease was 30.37±12.526 in our patients. The age of onset of AA reported previously was lower.[16,20]

Thyroid dysfunction is a term used for altered thyroid function tests. This includes patients with clinical thyroid disease and subclinical thyroid

disease. We found thyroid dysfunction in 2 (1.96%) Cases and in none of the Controls. The *p*-value was 0.157 and the difference was not statistically significant. Both of these cases had subclinical thyroid disease.

The prevalence of thyroid dysfunction (clinical and subclinical thyroid disease) in patients with AA, reported previously ranged from 7.1–24%.[8,16,19,21–23]

Our findings were in concordance with those of Kinoshita-Ise M *et al*.[13] but were in discordance with Popa A *et al*,[7] Marahatta S *et al*,[10] and Xin C *et al*,[14] who reported a significantly higher prevalence of thyroid dysfunction in patients with alopecia areata.

None of our patients had clinical thyroid disease. As regards clinical thyroid disease, our findings were in concordance with Puavilai S *et al*[9] but were in discordance with most of the previous studies. Previously, clinical thyroid disease was reported in 2.5%, 3.69 %, 5%, 7.2% and 8.9% by Lyakhovitsky A *et al*[19], Park SM *et al*[23], Shahzadi N *et al*[11], Chu SY *et al*[19] and Ahmad I *et al*,[22] respectively.

The prevalence of elevated anti-TPO-Ab titres has been reported to be 5%, 11.5%, 17.6%, 18.5%, 48% and 51.4% by Lyakhovitsky A *et al*[19], Rahnama Z *et al*[18], Lee S *et al*[5], Bakry OA *et al*[20] and Xin C *et al*[14] respectively. Although the prevalence of elevated anti-TPO-Ab titres in patients with AA has been extensively studied only a few case-control studies have been done to statistically establish the association between alopecia areata (AA) and thyroid autoimmunity.[16]

We found thyroid autoimmunity (as detected by elevated anti-TPO-Ab titres) in a significantly higher number of our AA patients in comparison to the Controls (*p*-value <0.05).

Our findings were in agreement with those of Díaz-Angulo S *et al*[16], Kinoshita-Ise *et al*[13], Baars MP *et al*[24] and Kasumagić-Halilović E *et al*[25] who found a significantly higher prevalence of elevated TPO-Ab titres in their patients with AA as compared to the Controls.

However, our findings were in discordance with Puavilai S *et al*[9] who did not find a statistically significant association between thyroid autoimmunity and alopecia areata.

CONCLUSION

AA is significantly associated with Thyroid autoimmunity but there is no significant association between AA and clinical or subclinical thyroid disease.

Limitations of study:

This is a Hospital-based study and gives only a rough estimate of the prevalence in the general population. Moreover, thyroid autoimmunity was only assessed by elevated titres of anti-thyroid peroxidase (TPO) titres and anti-thyroglobulin antibody (TgAb) and anti-thyroid-stimulating hormone receptor (TSHR) antibody titres were not measured.

Conflict of interest:

There is no conflict of interest in the study.

AUTHORS' CONTRIBUTION

AH: & MMA: Conception, study design, Data acquisition, data analysis, data interpretation, critical review, drafting the manuscript, and approval of the final version to be published. AAB: HN: AA: & SS: Data acquisition, data analysis, data interpretation, drafting the manuscript: critical review, approval of the final version to be published.

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Submitted: August 12, 2023	*Revised: October 23, 2023*	*Accepted: November 8, 2023*

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