Dermatology Practical & Conceptual

# Retrospective Analysis of the Effect of Comorbid Atopic Dermatitis on the Treatment Response to Topical Immunotherapy in Pediatric Alopecia Areata Patients

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## ABSTRACT

**Introduction:** Alopecia areata is an organ-specific autoimmune disease. In addition, treatment options are limited in pediatric patients. Topical immunotherapy treatment may be preferred, especially in pediatric patients with severe and/or refractory alopecia areata.

**Objectives:** In this study, it was aimed to examine the effect of atopic dermatitis, which is one of the poor prognostic factors in pediatric alopecia areata, on topical immunotherapy treatment.

**Methods:** The data of patients aged 18 years and younger who received at least 20 sessions of topical immunotherapy with the diagnosis of alopecia areata in our clinic between January 2018 and December 2020 were analyzed.

**Results:** A total of 139 patients were included in the study. The mean age of the patients was 10.29 years, 67 (48.20%) of the patients were female, 72 (51.80%) were male, 24 (17.26%) of the patients had mild disease, 115 of them (82.73%) had severe disease. Atopic dermatitis accompanying alopecia areata was detected in 38 of the patients. Inadequate response was obtained in 60 (43.17%) patients and adequate response was obtained in 79 (56.83%) patients with topical immunotherapy treatment. In addition, the presence of atopic dermatitis in the patient group with inadequate response to treatment was found to be statistically significantly higher than the patient group with adequate response to treatment.

**Conclusions:** Topical immunotherapy treatment was found to be effective in 56.83% of pediatric alopecia areata patients included in the study. Our study showed that questioning pediatric alopecia areata patients for atopic dermatitis before topical immunotherapy treatment can predict the response to treatment.

## Introduction

Alopecia areata is an autoimmune disease characterized by non-cicatricial alopecia of the scalp and/or body with an unpredictable course [1]. Alopecia areata affects approximately 2% of the general population throughout life [2]. The epidemiology, clinical features and treatment of childhood alopecia areata have been less studied [3].

Although the pathogenesis of alopecia areata is still unknown, the common theory in the pathogenesis is the loss of immune privilege in the hair follicle caused by immune mechanisms [4]. Alopecia areata is accepted as a tissue-specific autoimmune disease that occurs with an environmental triggering factor on the basis of genetic predisposition [5-7]. Relationships have been reported between alopecia areata and autoimmune diseases such as autoimmune thyroid diseases, vitiligo, type 1 diabetes mellitus and celiac disease [8]. It has also been reported that atopic conditions such as atopic dermatitis, allergic rhinitis, and asthma are common comorbid diseases in alopecia areata [9].

Treatment decision in alopecia areata; it is given by evaluating factors such as the age of the patient, the severity of the disease, the duration of the disease, access to treatment and the cost of treatment [10]. However, there is currently no curative treatment. Topical treatments used in pediatric alopecia areata include contact immunotherapy, cryotherapy, topical minoxidil, topical calcineurin inhibitors, topical and intralesional steroids, and topical prostaglandins. Systemic treatments used include systemic steroids, methotrexate, sulfasalazine, hydroxychloroquine and jack inhibitors. The use of systemic steroids is limited due to significant side effects, while the use of systemic JAK inhibitors is limited due to their safety profile and cost [11]. Topical immunotherapy offers the best efficacy and safety in long-term treatment in patients with treatment-resistant alopecia areata [12].

Agents used in topical immunotherapy; contact sensitizing agents such as diphenylcyclopropenone (DPCP), dinitrochlorobenzene (DNCB), squaric acid dibutylester (SADBE). Although the mechanism of action is not fully known, it is thought that they act by reducing the CD4+/CD8+ lymphocyte ratio around the follicle, directing T lymphocytes from the perifollicular area to the interfollicular area and dermis, and attracting new T lymphocytes to the treated area, which eliminates the antigenic stimulus [13].

## Objectives

The search for effective and safe treatment in alopecia areata, especially in severe and treatment-resistant pediatric patients, is still ongoing. Topical immunotherapy treatment is frequently preferred in this patient group. In this study, we aimed to retrospectively evaluate the effect of atopic dermatitis accompanying alopecia areata on the treatment of pediatric alopecia areata patients receiving topical immunotherapy.

## Methods

### Patient Selection

In our study, the clinical data of patients aged 18 years and younger who received at least 20 sessions of topical immunotherapy (SADBE/DPCP) treatment with the diagnosis of alopecia areata in our clinic between January 2018 and December 2020 were retrospectively analyzed. Patients with a follow-up period of less than 6 months and receiving additional treatment were excluded from the study.

### Patient Evaluation

Pre-treatment hair loss severity was evaluated according to the criteria defined in the alopecia areata research evaluation guidelines: S0: no hair loss, S1:<25%, S2:25-49%, S3:50-74%, S4:75%-99, S5:100% hair loss as classified. S1 and S2 were considered mild disease and S3, S4 and S5 were considered severe disease.

The patients response to treatment was evaluated according to the improvement in the percentage of baseline SALT score. Accordingly, good response ≥50% improvement, moderate response 25%-49% improvement, poor response 1%-24%, and the same SALT score before and after treatment were considered as non-response. Good and moderate responders were graded as adequate response, poor response, and non-responders as inadequate response, and statistics were made accordingly.

In addition, the presence of atopic dermatitis, which was determined using Hanifin Rajka diagnostic criteria, was recorded in the patients before treatment. In patients with atopic dermatitis, atopic dermatitis disease severity was graded using the SCORing Atopic Dermatitis (SCORAD) scoring system.

This study was approved by the tertiary hospital ethics committee (No. 154281; August 6, 2021). Written informed consent was obtained from all participants.

### Statistical Methods

Statistical analyses in the study were made with the NCSS (Number Cruncher Statistical System) 2007 Statistical Software package program. In the evaluation of the data, besides descriptive statistical methods (mean, standard deviation [sd], median, etc), the distribution of variables was examined with the Shapiro-Wilk test of normality. Binary groups of normally distributed variables independent t-test was used for comparison and Mann-Whitney U test was used for comparison of binary groups of variables that did not show normal distribution. Chi-square test was used in the comparison

of qualitative data and logistic regression analysis was used to determine the factors affecting response to treatment. The results were evaluated at the significance level of $P < 0.05$.

## Results

A total of 139 patients, 69 of whom received SADBE and 70 of whom received DPCP treatment, were included in the study. Sixty-seven (48.20%) of the patients were female and 72 (51.80%) were male. The mean age was 10.29 years (sd: 3.77 years) and the mean disease duration was 4.02 years (sd: 2.84 years). In addition, 44 (31.65%) patients had nail involvement (due to alopecia areata), 31 (22.3%) had a family history of alopecia areata, 31 (22.3%) had a family history of atopic disease. The mean value of the total IgE level of the patients before the treatment was 283.87 IU/ml (sd:864.28 IU/ml), and the lowest value was 0 and the highest value was 9024 IU/ml (normal value:0-100 IU/ml).

However, 38 (27.34%) patients had atopic dermatitis. When the data of 38 patients with atopic dermatitis were compared with the data of 101 patients without atopic dermatitis; no significant difference was observed between the two groups in terms of gender distribution, mean age, disease duration (years), and the presence of a family history of alopecia areata (P values, respectively: 0.378, 0.329, 0.780, 0.810). In the patient group with atopic dermatitis, the mean of total IgE values, the presence of nail involvement (due to alopecia areata), and the presence of a family history of atopy were found to be statistically significantly higher than the patient group without atopic dermatitis (P values, respectively: 0,0001, 0,036, 0,001). When the severity of the disease was evaluated according to the pre-treatment SALT scores; in the group with atopic dermatitis, mild disease was detected in 4 patients (10.53%), while severe disease was detected in 34 patients (84.47%), in the group without atopic dermatitis, mild disease was found in 20 patients (19.80%) and severe disease was found in 81 patients (80.20%). However, these evaluations were not found suitable for statistical interpretation in terms of their distribution (Table 1).

When the response to topical immunotherapy treatment was evaluated according to the improvement in the percentage of baseline SALT score, 37 (26.62%) of the patients had no response, 23 (16.55%) had a poor response, and 14 (10.07%) moderate response was obtained, and 65 (46.76%) had good response. When the conditions affecting the response to treatment were examined; when the data of 60 patients who responded inadequately to treatment with topical immunotherapy treatment and 79 patients who responded adequately to treatment were compared. There was no statistically significant difference between the two groups in terms of: gender distribution, mean age, distribution of treatment type (SADBE/DPCP), mean duration of disease (years), presence of nail involvement (due to alopecia areata), presence of family history of alopecia areata and mean total IgE (P values respectively: 0.092, 0.123, 0.448, 0.798, 0.271, 0.281, 0.170). The presence of family history

**Table 1. Comparison of the data of the patient group with atopic dermatitis and the patient group without atopic dermatitis.**

| | | Atopic Dermatitis (-) N = 101 | | Atopic Dermatitis (+) N = 38 | | P |
|---|---|---|---|---|---|---|
| Age (Years) | Mean±Standard Deviation | 10.49±3.90 | | 9.79±3.38 | | 0.333 |
| Gender | Male | 50 | 49.50% | 22 | 57.89% | 0.378 |
| | Female | 51 | 50.50% | 16 | 42.11% | |
| Disease duration (years) | Mean±Standard Deviation | 4.08±2.92 | | 3.84±2.67 | | 0.780 |
| | Median (IQR) | 4 (2-6) | | 3 (2-5.25) | | |
| Nail involvement (due to alopecia areata) | ( - ) | 37 | 36.63% | 7 | 18.42% | 0.04 |
| | ( + ) | 64 | 63.37% | 31 | 81.58% | |
| Family history of alopecia areata | ( - ) | 79 | 78.22% | 29 | 76.32% | 0.810 |
| | ( + ) | 22 | 21.78 | 9 | 23.68% | |
| Family history of atopy | ( - ) | 89 | 88.12% | 24 | 63.16% | 0.001 |
| | ( + ) | 12 | 11.88% | 14 | 36.84% | |
| Total IgE (IU/ml) | Mean±Standard Deviation | 133.46±310.21 | | 683.63±1516.59 | | 0.0001 |
| | Median (IQR) | 43.32 (15.7-91.77) | | 251.5 (36.92-617.55) | | |

IQR = interquartile range.

**Table 2.** Distribution of factors affecting treatment response.

| | | Inadequate response to treatment N = 60 | | Adequate response to treatment N = 79 | | P |
|---|---|---|---|---|---|---|
| Age (years) | | 9.73±3.25 | | 10.72±4.08 | | 0.123 |
| Gender | Male | 36 | 60.00% | 36 | 45.57% | 0.092 |
| | Female | 24 | 40.00% | 43 | 54.43% | |
| Type of treatment | SADBE Treatment | 32 | %3.33% | 37 | 46.84% | 0.448 |
| | DPCP Treatment | 28 | 46.67% | 42 | 53.16% | |
| Disease duration (years) | Mean±Standard Deviation | 3.88±2.63 | | 4.12±3.01 | | 0.798 |
| | Median (IQR) | 3 (2-6) | | 3 (2-6) | | |
| Nail involvement (due to alopecia areata) | ( - ) | 16 | 26.67% | 28 | 35.44% | 0.271 |
| | ( + ) | 44 | 73.33% | 51 | 64.56% | |
| Family history of alopecia areata | ( - ) | 44 | 73.33% | 64 | 81.01% | 0.281 |
| | ( + ) | 16 | 26.67% | 15 | 18.99% | |
| Patient's history of atopy | ( - ) | 39 | 65.00% | 69 | 87.34% | 0.002 |
| | ( + ) | 21 | 35.00% | 10 | 12.66% | |
| Family history of atopy | ( - ) | 44 | 73.33% | 69 | 87.34% | 0.036 |
| | ( + ) | 16 | 26.67% | 10 | 12.66% | |
| Total IgE (IU/ml) | Mean±Standard Deviation | 491.33±1267.14 | | 126.3±220.89 | | 0.170 |
| | Median (IQR) | 65.82 (11.97-395.5) | | 43.32 (22.11-135.7) | | |
| Atopic Dermatitis | ( - ) | 38 | 63.33% | 63 | 79.75% | 0.032 |
| | ( + ) | 22 | 36.67% | 16 | 20.25% | |
| SCORAD Score | Mean±Standard Deviation | 45.43±16.61 | | 23.48±13.95 | | 0.0001 |
| | Median (IQR) | 44.98 (36.58-57.13) | | 22.20 (12.8-30.55) | | |

DPCP = diphenylcyclopropenone; IQR = interquartile range SADBE = squaric acid dibutylester.

of atopy, the presence of atopy history in the patient, the presence of atopic dermatitis in the patient group with inadequate response to the treatment were found to be statistically significantly higher than the patient group with adequate response to the treatment (P values respectively: 0.036, 0.002, 0.032). In addition, the SCORAD score averages calculated in the patients with atopic dermatitis in the patient group with inadequate response to the treatment were found to be statistically significantly higher than the patient group with adequate response to the treatment (P 0.0001) (Table 2). Additionally, photographs of patients with and without atopic dermatitis before and after topical immunotherapy treatment are shown in Figures 1 and 2. (Figure 1 and Figure 2)

## Conclusions

Alopecia areata is a chronic, autoimmune disease [1,3]. Although alopecia areata can occur at any age, the majority of cases appear before the age of 40 [14].

In addition, many diseases that accompany alopecia areata and can determine the prognosis of the disease have been reported. Considering the accompanying diseases [15] it was determined that the risk of atopic dermatitis increased especially in patients with alopecia areata younger than 10 years of age [16]. In addition, treatment options are limited in pediatric alopecia areata patients due to concerns about treatment tolerance. Topical immunotherapy treatments are one of the most frequently applied treatment methods, especially in treatment-resistant and severe pediatric alopecia areata cases.

In a study, diseases that may accompany alopecia areata in patients with pediatric alopecia areata were examined, and atopic dermatitis was detected in 17.4% of alopecia areata patients and in 2.2% of controls, and it was determined as the most common disease accompanying pediatric alopecia areata [17]. On the contrary, there is a study in the literature reporting that no difference was found between the adult and pediatric alopecia areata patients and the control group in terms of the frequency of atopic disease [18]. We found the

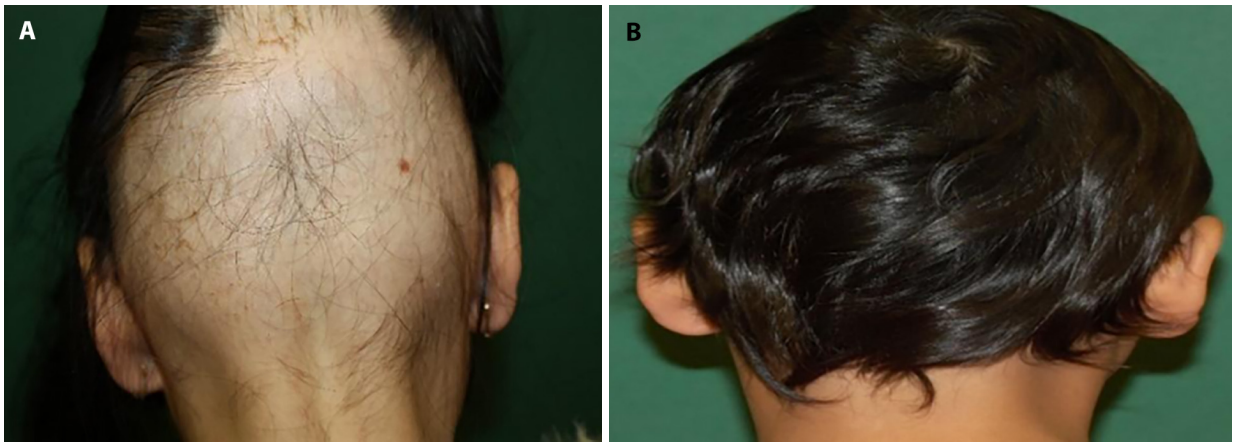


**Figure 1.** (A,B) Before (A) and after (B) topical immunotherapy treatment of a patient without atopic dermatitis

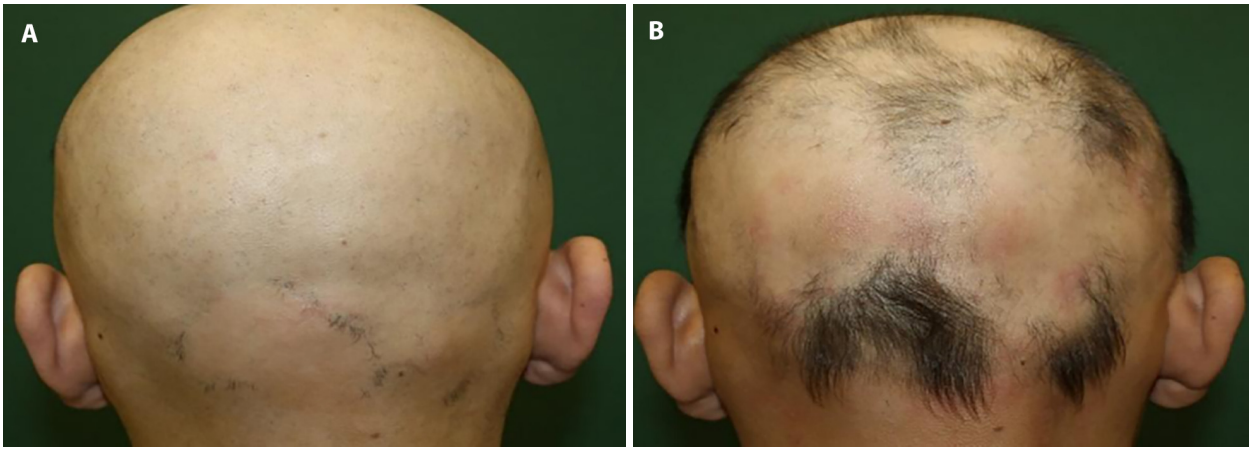


**Figure 2.** (A,B) Before (A) and after (B) topical immunotherapy treatment of a patient with atopic dermatitis

presence of atopic dermatitis in 27.34% of pediatric alopecia areata patients included in our study. However, since there was no control group in our study, this value could not be compared with the control group. While Th1 cell-mediated pathways are thought to be effective in the pathogenesis of alopecia areata, especially Th2 cell-mediated pathways are thought to be effective in the pathogenesis of atopic dermatitis. Recently, it has been shown that Th1 and Th17 cell-mediated pathways are also effective in the pathogenesis of atopic dermatitis, especially in the chronic period. The frequently reported association of alopecia areata and atopic dermatitis in the literature can be explained by these overlapping immunological pathways [19]. In many studies in the literature, the relationship between atopy and alopecia areata has been examined, but atopic diseases have been customized and their relationship with alopecia areata has not been mentioned much. Addressing this, one study found that patients with alopecia areata with atopic dermatitis and/or a family history of atopic dermatitis were statistically significantly more likely to have severe forms of alopecia areata, such as alopecia totalis and alopecia universalis, than patients without a history of atopic dermatitis [20]. In our study, we found the presence of nail involvement (due to alopecia areata), the presence of a family history of atopy, and the total IgE averages statistically significantly higher in the group of patients with alopecia areata with atopic dermatitis compared to the patient group without atopic dermatitis.

In addition, there are many studies in the literature examining the factors affecting the responses obtained with topical immunotherapy, but the data are conflicting in terms of situations that can predict treatment responses and be used as prognostic factors. In a retrospective study, disease severity, disease duration, atopy history (especially eczema), and early development of contact dermatitis in the area where the topical immunotherapy agent applied for sensitization was applied were identified as the main factors affecting treatment responses [21]. In addition, there are very few studies evaluating the response to topical immunotherapy treatment, especially in pediatric patients, and examining the factors that may affect these treatment responses. In our study, we investigated the factors that may affect the treatment response in pediatric patients receiving topical immunotherapy treatment. And finally, the presence of atopy in the family, the presence of atopy in the patient, and the

presence of atopic dermatitis were found to be statistically significantly higher in the patient group who responded inadequately to the treatment. In addition, the SCORAD score averages calculated in the patients with atopic dermatitis in the patient group with inadequate response to the treatment were found to be statistically significantly higher than the average SCORAD score calculated in the patients with atopic dermatitis in the patient group with adequate response to the treatment.

The most important limitation of our study is the absence of a control group. The effect of the presence of atopic dermatitis on topical immunotherapy treatment in pediatric alopecia areata patients will be better understood with studies with a higher number of cases and control groups.

In conclusion, with the data we obtained in our study, we determined that atopic dermatitis, which is a disease often accompanying alopecia areata in pediatric patients, and the presence of a family history of atopy associated with it and the presence of atopy in the patient were more common in patient groups who did not respond to topical immunotherapy treatment, and these conditions were observed before topical immunotherapy treatment was started. We thought that investigating the presence of atopic dermatitis that may accompany in pediatric alopecia areata patients, and the presence of atopy in the family and in the patient may help predict the response to treatment, and that it is more difficult to obtain a good response in the treatment of these patients with topical immunotherapy, and perhaps it would be a better choice to try other treatment methods in these patients.

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