Utility of Dermoscopic Evaluation in Predicting Clinical Response to Diphencyprone in a Cohort of Patients with Alopecia Areata

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ABSTRACT

Background: Alopecia areata (AA) is a chronic and inflammatory disease of the hair follicle, causing nonscarring alopecia. While the various types of treatment have been investigated, the definite cure for AA has not been established yet. Objectives: The objective of this study is to evaluate the clinical and dermoscopic features of patients with AA to identify the factors with prognostic values in diphenylcyclopropenone (DPCP) response rate. Methods: Eighty patients with AA were included, and baseline hair loss was calculated based on the severity alopecia tool (SALT) score. The characteristic dermoscopic features of AA were evaluated by two skilled dermatologists separately at baseline, 12 and 24 weeks afterward. Results: The mean SALT score in the 1st, 12th, and 24th week was 77 ± 24.7, 80 ± 27, and 71 ± 35.6, respectively, which were not significantly different over this time period (P = 0.085). SALT score correlated negatively with the short vellus hair/field (r = −0.361, P = 0.02), broken hair/field (r = −0.317, P = 0.044), and tapering hair/field (r = −0.388, P = 0.012) in the 1st week. Forty-one patients continued treatment courses over 24 weeks. Six patients had good response, 11 achieved partial response, and 24 had no hair regrowth. Statistically significant correlation was observed between treatment response and duration of disease (P = 0.04), frequency of relapses (P = 0.033), type of alopecia, and number of black dots (P = 0.028). The mean for all dermoscopic findings showed descending process during our three follow-up sessions which was statistically significant for black dot (P = 0.015) and broken hair (P = 0.006). Conclusion: The number of black dot per field initially was negatively correlated to DPCP therapy and the frequency of dermoscopic findings reduced during the treatment process.

Key words: Alopecia areata, dermoscopy, diphenylcyclopropenone

INTRODUCTION

Alopecia areata (AA) is a chronic, inflammatory, autoimmune disease of the hair follicle, causing nonscarring hair loss. The AA prevalence is approximately 0.1%–0.2% in the general population with the lifetime risk of 1.7% for an individual.

Characteristic dermoscopic features in AA are as follows: black dots (BD) (cadaverous hairs), yellow dots (YD), short vellus hair (SVH), tapering hair (TH) (exclamation mark hairs), and broken hair (BH).

Although invasive methods such as punch biopsy used to be a diagnostic procedure to confirm AA, currently with the help of dermoscopy, such procedures are rarely required. Dermoscopy is a noninvasive diagnostic method, providing the clinician a larger field of view (×10 magnification). While the various types of treatment have been investigated, the definite cure for AA has not been established yet.
Topical sensitizers are effective treatment options for resistant AA or cases of hair loss extending more than 50% of the scalp. Diphenylcyclopropenone (DPCP) and squaric acid dibutylester are topical sensitizers with efficacy of about 60%, but the exact mechanism of action of DPCP and the factors affecting the clinical response to it are not clearly understood.

In this study, we aim to evaluate the clinical signs and dermoscopic features of patients with AA to identify factors with positive or negative prognostic values in DPCP response rate. Hopefully factors which are more predictive of therapeutic success can be recognized and an ideal treatment which can reduce the financial and psychological burden of AA disease will be planned.

**METHODS**

We conducted a cohort study authorized by local research ethics committee of Tehran University of Medical Sciences. All patients with AA attending to Alopecia clinic of Razi hospital who were candidate for DPCP therapy (alopecia more than 25% or who were unresponsive to conventional therapies) were included in this study.

An informed consent was obtained from each patient.

The inclusion criteria were patients with clinically and/or histologically confirmed AA who were candidate for DPCP therapy (alopecia more than 25% or who were unresponsive to topical and intraleisional therapies) and had initial sensitization response to DPCP 2% solution. The exclusion criteria were current pregnancy or lactation, liver function failure, systemic immunosuppressive or steroid therapy in the past 6 months, history of any topical treatment during the recent month, failed to develop initial response to DPCP 2% solution, and history of malignancies and blood dyscrasia.

The following demographic data were documented: Age, sex, age of onset, duration of the disease, family history of AA in the first-degree relatives, number of relapses, type of alopecia (totalis, universalis, ophiasis, and patchy), nail involvement, and association with other autoimmune diseases.

Severity of hair loss was calculated based on severity alopecia tool (SALT) score for all patients at the beginning of their entrance (top of scalp = 40%, posterior = 24%, and each lateral = 18%). In cases of ophiasis and patchy alopecia, hair “PULL Test” was performed in two alopecic patches by a dermatologist and was reported as positive or negative.

Characteristic dermoscopic features of AA being evaluated in this study are BD, YD, SVH, TH, and BH. Two dermatologists evaluated all the patients for the presence of dermoscopic features of AA separately at the beginning of the DPCP therapy, and reevaluated them 12 and 24 weeks afterward. Response rate was considered as good response (>50% terminal hair regrowth), partial response (0< regrowth ≤50%), and no response (no regrowth). Dermoscopic features of AA were observed by 3N dermoscope at two dermoscopic fields (from DermLite company, CA, IL, USA) (magnification ×10). An iPhone 6S smartphone was attached to the dermoscope, enabling the dermatologist to take photographs of dermoscopic field by mobile device camera.

To evaluate dermoscopic features, two dermoscopic fields were selected for each patient based on the type of Alopecia. In cases of totalis alopecia, field 1 was 5 cm above ear helix, and field 2 was 5 cm posterior to antihelix in occipital area, at the side where it is supposed to be treated by DPCP. In cases of patchy alopecia, two dermoscopic fields were selected from central site and at 3 o’clock position of the most extended alopecic patch. In cases of ophiasis alopecia, two dermoscopic fields were selected from central site and superior margin of the most extended ophiasis patch in bilateral occipital and temporal areas.

All dermoscopic variables in each field were evaluated and counted by two dermatologists. If there was a conflict between their documents, a third opinion was requested from another dermatologist. Finally, for each dermoscopic variable, the mean number of two fields that were counted by two dermatologists was calculated and documented for the final analysis.

Those patients who had initial sensitization response to DPCP 2% solution (developing allergic contact dermatitis 36–48 h after DPCP application at a test site) were treated with DPCP 0.0001% solution. Patients had follow-up visit sessions every 1 or 2 weeks and the dose of DPCP could be raised gradually by our dermatologists. The DPCP course of therapy was at least 24 weeks. We also sent the patients to the medical photography unit of … hospital to record clinical hair growth improvement after each session.

Each patient was reevaluated by dermoscopic features and clinical signs (SALT score and treatment response) in 12 and 24 weeks.
Data analysis was performed using the SPSS software version 24 (SPSS Inc., Chicago, IL, USA). The Chi-square test was used for qualitative data. Mann–Whitney was used for quantitative data. The correlation between two qualitative data was compared by means of nonparametric Spearman's rho test. A statistically significant difference was considered by a \( P < 0.05 \).

RESULTS

Patients

Eighty patients with AA were included in this study. Diagnosis was established clinically for all patients except for one who needed biopsy for diagnosis to be confirmed. Of 80 patients, 41 patients continued the treatment courses over 24 weeks, and patients were excluded from the study for the following reasons: 26 patients discontinued DPCP therapy before follow-up session 2 and 9 patients before follow-up session 3, 2 patients failed to attend follow-up sessions, and for 2 patients cignolin therapy was added after initial DPCP treatment. Patients' demographic data are shown in Table 1.

The mean age was 25.4 ± 15.4 years, which found to be positively and significantly correlated to the age at disease onset (\( P < 0.001 \)), duration of the disease (\( P = 0.007 \)), and YD in 1\(^{st} \) (\( P < 0.001 \)), 12\(^{th} \) (\( P < 0.001 \)) and 24\(^{th} \) (\( P < 0.001 \)) weeks of treatment.

The mean age at disease onset was 17.8 ± 12.8 years, which was negatively correlated to relapse (\( \rho = -0.344, \ P = 0.028 \)) and was positively correlated to YD in 1\(^{st} \) (\( P = 0.001 \)), 12\(^{th} \) (\( P = 0.017 \)), and 24\(^{th} \) (\( P = 0.003 \)) week of treatment.

The average disease duration was 7.6 ± 9 years, which showed a significant positive correlation with age (\( P = 0.007 \)), frequency of relapses (\( P < 0.001 \)), and treatment response (\( P = 0.025 \)).

Nail involvement

Nail involvement was seen in 46.34% of patients (pitting > ridging > trachyonychia > onycholysis > leukonychia). SALT score in 1\(^{st} \) week was significantly different considering nail involvement (\( P = 0.035 \)). This means the extent of hair loss in those patients with nail involvement (mean SALT score = 86.8%) was significantly higher than those without (mean SALT score = 68.4%).

Alopecia types

Male patients were found to have extensive hair loss (66.7%), whereas females were more likely to have limited hair loss (69.2%). Among these two categories of alopecia subtypes, there was a statistically significant difference between the mean number of SVH per field in 1\(^{st} \) week (26.8 [ranging 0–200] in complete and 28.8 [ranging 0–155] in incomplete hair loss group, \( [P = 0.022] \)), duration of disease (\( 3 \pm 2 \) years in complete and \( 10 \pm 10 \) years in incomplete hair loss group, \( P = 0.011 \)), and response (\( P = 0.04 \)).

Severity Alopecia Tool Score

The mean SALT score in the 1\(^{st} \), 12\(^{th} \), and 24\(^{th} \) week were 77 ± 24.7, 80 ± 27, and 71 ± 35.6, respectively, which were not significantly different over this time period (\( P = 0.085 \)). SALT score correlated negatively with the SVH per field (\( \rho = -0.361, \ P = 0.02 \)), BH per field (\( \rho = -0.317, \ P = 0.044 \)), and TH per field (\( \rho = -0.388, \ P = 0.012 \)) in the 1\(^{st} \) week.

Pull Test

PULL test was evaluated in 26 patients with incomplete hair loss (10 was positive). PULL test was positively correlated to BH per field in 1\(^{st} \) week (5.7 ± 8 in positive PULL test group and 1.15 ± 2 in negative PULL test group, \( P = 0.013 \)) and TH per field in 1\(^{st} \) week (0.09 ± 0.3 in positive PULL Test group and 0.85 ± 1.1 in negative PULL test group, \( P = 0.014 \)).

Response

Six patients had good response, 11 patients achieved partial response, and 24 patients had no hair regrowth.

Statistically significant correlation was observed between treatment response and duration of disease (\( P = 0.04 \), the longer duration of disease the more response rate to DPCP therapy), frequency of relapses (\( P = 0.033 \), those cases with higher frequency of relapses had better treatment response), type of alopecia (cases with incomplete alopecia achieved better treatment response than complete ones), and number of BD [Table 2].

Dermoscopic findings

The frequency of five dermoscopic features at 1\(^{st} \) week is including: BD in 39 (95.10%), YD in 30 (73.2%), SVH in 30 (73.2%), BH in 23 (56%), and TH in 7 (17%) of cases. Although the frequency of BD was higher than YD, the
mean for YD per Field was higher than BD per Field (66 vs. 44). The mean for all dermoscopic findings showed descending process during our three follow-up sessions which was statistically significant for BD ($P = 0.015$) and BH ($P = 0.006$) [Figures 1-4].

The number of BD in the 1st week was inversely associated with DPCP response ($P = 0.028$). The number of YD in the 1st, 12th, and 24th week was significantly associated with age and age at disease onset, in which patients with higher age and age at disease onset had more YD per field. The number of SVH in 1st week was inversely associated with initial ($P = 0.02$), 12 weeks ($P = 0.04$), and 24 weeks ($P = 0.018$) SALT scores. This finding implies that the presence of SVH represents less severe AA disease. The number of SVH in 1st week was also significantly associated with type of alopecia ($P = 0.022$), which was more likely in cases with incomplete hair loss than complete ones [Figure 2].

BH and TH in the 1st week were inversely correlated with initial SALT score ($\rho = -0.361$, $P = 0.02$ and $\rho = -0.338$, $P = 0.012$, respectively) indicating that the presence of them represents less severe AA disease, but they were significantly associated with pull test ($P = 0.013$ and 0.014, respectively) demonstrating higher AA activity [Figure 2].

### Table 1: Demographic and clinical data

| Demographic data                                      | Number of patients (n=80) |
|-------------------------------------------------------|---------------------------|
| Patients with complete DPCP courses (included)        | 41                        |
| Patients with incomplete treatment courses (excluded) | 39                        |
| Sex of those completing treatment course, n (%)       |                           |
| Female                                                | 23/41 (56.09)             |
| Male                                                  | 18/41 (43.9)              |
| Age (years), mean±SD (range)                          | 25.1±5.4 (3-61)           |
| Age at disease onset (years), mean±SD (range)         | 128±17.8 (1-59)           |
| Disease duration before treatment (years), mean±SD (range) | 7.6±9 (3 months-30 years) |
| Pattern of hair loss, n (%)                           |                           |
| Universalis                                           | 8/41 (19.53)              |
| Totalis                                               | 7/41 (17.07)              |
| Ophiasis                                              | 3/41 (7.31)               |
| Patchy                                                | 23/41 (56.09)             |
| Frequency of recurrence, mean±SD (range)              | 2.9±3.7 (0–15)            |
| Family history of AA, n (%)                           |                           |
| First-degree relative                                 | 7/41 (17.07)              |
| Second-and third-degree relative                      | 8/41 (19.53)              |
| Autoimmune disorders, n (%)                           | 12/41 (29.2)              |
| Male (%)                                              | 11.1                      |
| Female (%)                                            | 43.4                      |
| Nail changes, n (%)                                   | 19/41 (46.34)             |
| Response rate (%)                                     |                           |
| Good response, $50\% < \text{terminal hair regrowth}$ | 6                         |
| Partial response, $0 < \text{regrowth} \leq 50\%$    | 11                        |
| No response, no regrowth                              | 24                        |
| Dermoscopic findings, n (%)                           |                           |
| Black dots                                            | 39/41 (95.10)             |
| Yellow dots                                           | 30/41 (73.20)             |
| Short vellus hair                                     | 30/41 (73.20)             |
| Broken hair                                           | 23/41 (56.00)             |
| Tapering hair                                         | 7/41 (17.00)              |

DPCP – Diphenylcyclopropenone; SD – Standard deviation; AA – Alopecia areata

### Table 2: Association between disease duration and response rate

| Salt score variation | Mean n | SD | Median | Minimum | Maximum |
|----------------------|--------|----|--------|---------|---------|
| No regrowth          | 5.492 24 | 7.6202 | 2.000 | 0.3 | 30.0 |
| $< 50\% \text{regrowth}$ | 10.617 12 | 11.3557 | 5.500 | 0.4 | 29.0 |
| $50\% \leq \text{regrowth}$ | 11.000 5 | 8.3367 | 8.000 | 3.0 | 23.0 |
| Total                | 7.663 | 41 | 9.0577 | 3.500 | 0.3 | 30.0 |

SD – Standard deviation

11th, 12th, and 24th week was significantly associated with age and age at disease onset, in which patients with higher age and age at disease onset had more YD per field. The number of SVH in 1st week was inversely associated with initial ($P = 0.02$), 12 weeks ($P = 0.04$), and 24 weeks ($P = 0.018$) SALT scores. This finding implies that the presence of SVH represents less severe AA disease. The number of SVH in 1st week was also significantly associated with type of alopecia ($P = 0.022$), which was more likely in cases with incomplete hair loss than complete ones [Figure 2].
DISCUSSION

In this study, the sole dermoscopic finding that was inversely correlated to the response rate was the number of BD/field. In other words, higher frequency of them in a patient with AA suggests poor response to DPCP therapy. Besides, the mean for all dermoscopic findings showed descending process during three follow up sessions, which was statistically significant for BD and BH. Overall, we had 14.6% of cases with good response, 26.8% with partial response, and 58.5% with no response. Moreover, response rate in patients with incomplete hair loss was higher than complete hair loss cases (58% vs. 20%), revealing that initial severity of hair loss was inversely associated with response rate to DPCP therapy. Patients with universalis and ophiasis alopecia did not show any response to DPCP therapy, that means these subtypes of AA are more resistant to DPCP and also it seems that more than 6 months of follow-up is needed to evaluate whether they have any response to the DPCP therapy. Other retrospective studies showed higher response rates.[10‑14] These differences in response rate may be due to the variations in study methodologies, treatment protocol, initial severity of AA, and follow-up period, which response rate to DPCP could be higher after longer follow-up.[13]

In a study by Ganjoo and Thappa, it has shown that TH, BD, and BH are the first parameters to respond to treatment and thus imply a subsidence of disease activity.
with treatment, but YD are the least responsive. They assumed that TH, BD, and BH are the markers of disease activity, but no statistically significant association was found between disease activity and YD.[6,10] Two other studies found that pull test was positively correlated to TH, BD, and BH and negatively correlated to SVH.[6,10] In our study, pull test was positively correlated to initial number of BH and TH.

Our results showed that SALT score was negatively correlated to the number of TH, BH, and SVH/field in the first week. This means that we expect less severe AA disease in patients who have higher number of these three dermoscopic findings. In 2010, Inui et al. showed that SALT score was negatively correlated to SVH and positively correlated to BD and YD.[6] Two other studies did not find significant association between the severity of AA and dermoscopic findings.[6,10]

We found that there was a significant correlation between the age, age at disease onset, and number of YD per field at the 1st, 12th, and 24th week. This means the higher age and age at disease onset the more YD found per field. As the YD is caused by sebum and keratin accumulation which increases by age, we expect to have more YD per field in older ages and disease onset at an older age.

In our study, the most prevalent dermoscopic finding was BD (95.1%) and other findings such as SVH, YD, BH, and TH had frequency percentage of 73.2%, 73.2%, 56%, and 17%, respectively. Previous studies showed different frequency of dermoscopic findings which are depicted in Table 3.

We attribute these differences in the frequency of dermoscopic findings to the severity of hair loss in our patients. The mean hair loss percentage was 77% initially in our cases, but other studies mostly included patients with less severe involvement. As BD is associated with severity of AA based on previous studies, we believe that having BD as the most prevalent dermoscopic finding in our patients could be due to more severe cases of AA that we included.

### Limitations

We had several potential limitations in our study. First, the follow-up duration of 6 months was not long enough to fully evaluate response rate to DPCP therapy. Second, there was no control group in our study. Third, more patients are needed to evaluate the accurate efficacy of DPCP treatment in dermoscopic findings.

### CONCLUSION

Employing dermoscopic findings and clinical signs in patients with AA help us to evaluate their association with disease severity, activity, and response to treatment. In this study, we recognized that the presence of SVH represents less severe AA disease and incomplete hair loss. Besides, BD per field initially is negatively correlated to DPCP treatment response. Moreover, BH and TH were indicative of less severe AA disease, but higher AA activity.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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### Table 3: Results of previously reported studies on the frequency of dermoscopic findings in alopecia areata patients

| Authors               | YD (%) | BD (%) | SVH (%) | BH (%) | TH (%) |
|-----------------------|--------|--------|---------|--------|--------|
| Mander et al. 2013[6] | 81.8   | 66.6   | 55.4    | 40.9   | 12.1   |
| Spandana et al. 2013[10] | 57.3   | 63     | 68      | 28     | 18.6   |
| Nishant et al. 2014[10] | 89.9   | 31     | 78.4    | 12.93  | 19.8   |
| Akhilia et al. 2015[10] | 86     | 58     | 66      | 56     | 26     |
| Mahmoudi et al. 2017[10] | 84.4   | 48.4   | 62.7    | 9.52   | 30.95  |

BD – Black dots; YD – Yellow Dots; SVH – Short Vellus Hair; TH – Tapering hair; BH – Broken hair
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