

Facultad de Medicina



UNIVERSIDAD NACIONAL AUTÓNOMA DE MÉXICO FACULTAD DE MEDICINA

PROGNOSTIC FACTORS IN MEXICAN PATIENTS WITH PATCHY AND OTHER TYPES OF ALOPECIA AREATA

TESIS

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ABSTRACT

Introduction. Some clinical features have been associated with the progression and remission of alopecia areata (AA). We aim to determine possible prognostic factors in Mexican patients with AA.

Methods. This prospective study of a 1-year follow up included Mexican patients with a clinical diagnosis of AA. We evaluated disease activity with the SALT score at the first visit and 1-year follow-up; progression, no progression and remission were defined according to score changes. We used multiple linear regression model to detect factors associated with progression and remission.

Results. One hundred and four patients concluded the study. Ninety-seven patients (93.3%) had patchy AA. Fifteen patients showed disease progression and 89 no progression, from which 35 patients had remission. Body hair involvement was related to disease progression and adherence to treatment with disease remission and progression.

Conclusions. Body hair involvement is related to poor prognosis. Adherence to treatment is a modifiable prognostic factor associated with the course of AA in Mexican patients.

1. INTRODUCTION

Alopecia areata (AA) is an autoimmune disease and the second most common cause of non-scarring alopecia, behind androgenetic alopecia [1]. The prevalence of AA in general population is 0.2% and affects approximately 2% of Mexican population [2]. The main pathogenesis features are loss of "follicle immune privilege" and activation of CD8 + T cells against follicle auto antigens [4]. Disease severity is assessed by the Severity Alopecia Tool (SALT score) that evaluates hair loss extension in the scalp and body. AA is associated with genetic factors and other autoimmune diseases: systemic lupus erythematosus (SLE), vitiligo and psoriasis [3].

The course of AA is unpredictable. Eighty percent of patients with AA and low hair extension could present spontaneous remission. Some clinical features reported to increase disease severity are: chronic disease activity, extensive hair loss, concomitant autoimmune disease, atopic dermatitis, and ungueal involvement [1]. However, factors that influence course and prognosis in patients under treatment are controversial. Studies of prognostic factors in Mexican patients with AA under treatment have not been published. Therefore, we aim to determine possible prognostic factors in Mexican patients with AA.

2. MATERIALS AND METHODS

2.1 Patients selection

This prospective study included patients with a clinical diagnosis of AA of any age and gender attending to "Dr. Ladislao de la Pascua" Dermatology Center from February 2017 to December 2017. Then, patients were followed-up for 1 year. Patients must have disease activity, defined as the presence of at least two of the following criteria: positive pull test with gentile traction of 40-60 hair follicles from 3 different parts of the plaque and loss of > 10 hair follicles, puffy consistency of the plaque and a trichoscopy with "exclamation hair follicle sign", hair follicle dystrophy, and black dots. Exclusion criteria were loss of the follow-up and not agreement to participate.

2.2 Sociodemographic features

In the first visit, patients answered a structured interview evaluating sociodemographic features, family and personal history of AA, vitiligo, atopic dermatitis, psoriasis, SLE, thyroid disease, irritable bowel disease, rheumatoid arthritis, diabetes mellitus (DM), systemic arterial hypertension, obesity, cardiovascular disease, toxicomania, and allergies. In the second visit at 1-year follow up, we investigated a new diagnosis of vitiligo, atopic dermatitis, asthma, allergic rhinitis, urticaria, autoimmune disease, psoriasis, thyroid disease, DM, hypertension, obesity, and dyslipidemia. If positive, laboratories and treatments were recorded.

2.3 Clinical features of AA

Age at disease onset, disease duration, number of activity episodes, hair loss pattern, treatments, ungueal, and body hair involvement were registered. Iconographic control was taken according to AA Investigational Assessment Guidelines Criteria [5]. One dermatologist evaluated disease severity with the SALT score at first and 1 year later visits. Patients were divided into disease progression and no progression groups according to the SALT score changes. We defined disease progression as an increase in the 1-year SALT score compared to initial SALT score and no progression a 1-year SALT score with decrease or without changes compared to initial SALT score. Patients with a 1-year SALT score of zero were defined as remission. Adherence to treatment was evaluated by a structured questionnaire and we defined good adherence to treatment a score of 90-100% and bad adherence < 90%

2.4 Statistical Analysis

The distribution of variables was assessed using the Kolmogorov-Smirnov test. We reported abnormally distributed variables with median and ranges, normally distributed quantitative variables with mean and standard deviation, and qualitative variables with percentages. We used the U Mann Whitney test to compare abnormally distributed variables and X² to correlate disease progression, no progression, and remission groups. Variables with statistical significance were included in a multiple linear regression model. Finally, we assessed variables with statistical significance with a proportional risk model using the Cox regression model and graphing with the Kaplan-Meier curves. We considered p < 0.05 as a statistical significance. We analyzed data with SPSS version 25.

3. RESULTS

One hundred and twenty patients were included in the study and 16 patients were unable to return to the Dermatology Center (13.3% loss of patients). Sociodemographic and clinical features are shown in table 1.

3.1 Diseases clinical features

Most of the patients had patchy AA (93.3%) and low initial SALT score (median 7 points, range 100). The mean age at disease onset was 24.8 ± 15.8 years old. Patients with patchy AA showed a mean age at disease onset of 25.55 ± 15.5 years old and median disease evolution of 3.15 (range 1-27), 69% one episode, and 78% good adherence to treatment. These clinical features were not statistically different compared to other types of AA.

Body hair involvement was found in 15 patients with patchy AA (15.5%), 1 patient with totalis AA (25%), 1 patient with ophiasis AA (50%), and 1 patient with universalis AA (100%) without statistically significant differences (p=0.08).

Fifteen patients had disease progression and 89 patients no progression. Eighty percent of patients with disease progression had patchy AA, median disease

duration of 2 years (range 23), mean age at disease onset of 16.4 \pm 13.2 years, 53.3% had body hair involvement and 59.9% good adherence to treatment. Clinical and treatment features of these groups are shown in table 2.

Thirty-five patients from no progression group had disease remission. All patients presented patchy AA, median disease duration of 1 year (range 27), mean age at disease onset of 28.1 ± 13.8 years, and low prevalence of ungueal and body hair involvement (8.6 and 5.7%, respectively). Clinical and treatment features of the remission group are shown in table 3.

In both groups, the main causes of bad adherence to treatment were: no time and forgetting to apply the treatment and irritation with topical medications. Patients with worse adherence to treatment in both groups were under treatment with topical steroids, minoxidil, and psoralens.

3.2 Factors associated with disease course

Sociodemographic features were not associated with disease progression or remission.

Comparisons of clinical features between disease progression and no progression groups showed that the earliest age at disease onset and body hair involvement were more frequent in patients with progression (p=0.02 and p<0.01, respectively). Other clinical and treatment features did not show statistically significant differences (Table 2).

Sub-analysis of progression and remission group showed significant differences with age (median 24 versus 35 years, p=0.06), age at disease onset (median 8.5 versus 31 years, p=0.01), ungueal involvement (33.3 versus 8.6 %, p = 0.03), body hair involvement (53.3 versus 5.7 %, p < 0.01), treatment with intralesional steroid (53.8 versus 17.6 %, p= 0.03), systemic corticotherapy (38.5 versus 5.9 %,

p<0.01), and topical psoralen (38.5 versus 11.8 %, p=0.04). Good adherence to treatment was more prevalent in the remission group compared to progression group (85.3 versus 59.9 %, p=0.02) (Table 3).

Factors with statistical differences between progression and no progression groups were included in a multiple linear regression model. Body hair involvement according to body score of SALT score and adherence to treatment were associated with disease progression (Table 4). Cox regression analysis showed that body hair involvement was related to disease progression during the follow up (p=0.04; OR 1.26, IC 95: 1.04 - 12.0) (Figure 1 - 2)

Finally, we included statistical relevant factors from the sub-analysis of patients with disease remission in the multiple linear regression model. Body hair involvement showed a negative association with disease remission (table 5).

4. DISCUSSION

AA is an autoimmune disease that causes significant psychological and cosmetic impact on patients. The frequency in Mexican dermatologic consult is 1% [6]. AA has a heritable basis and specific genes have been associated with disease severity and concomitant diseases. We evaluated the family history of patients with AA including inflammatory and autoimmune disease, which did not show any relevance on disease course during follow – up. Patients with disease progression had a higher prevalence of positive family history of atopic dermatitis, diabetes mellitus, systemic arterial hypertension, and thyroid disease compared to the remission group, that were not statistically significant.

The relevance of a positive family history of AA in disease course is controversial. Studies report that 10 - 51.6 % of patients with AA have a personal history of a first-degree relative with AA, which is related to age at disease onset before 30 years old [7]. In the present study, 10 - 24% of patients had a family history of AA, that did not affect the disease course. The small size of the progression and remission group and a low prevalence of this family history could explain our results.

Several factors have been reported to determine disease severity in AA. Previous studies have found that low hair loss during activity episodes is related to a spontaneous remission, with 80% of patients with complete regrowth in 1 year. Therefore, ophiasis or totalis AA show a high prevalence of progression [8]. In our study, we did not find any relation between progression and type of AA in the multiple linear regression model. Similar results have been reported in a recent study [9].

We found that disease onset at an early age and AA types with extensive hair loss were more prevalent in patients with progression compared to no progression group, with similar results reported previously [10-11]. Lyakhivitsky et al found that patients with early age at disease onset had a higher prevalence of disease severity [10]. However, some authors have not found these associations [9] and remains controversial.

In our study, body hair involvement was the most important prognostic factor associated with disease progression. This clinical feature has been related to extensive hair loss, progression, relapses, and a recalcitrant disease [1]. Vaño-Galvan et al described clinical features associated with bad prognosis in 80 patients with universalis AA and 52 patients with totalis AA. They found that universalis AA and family history of AA were the most important factors associated with a bad prognosis (OR 4.77, IC 95: 0.6-31 and OR 3.73, IC 95: 0.7-42.8, respectively) [12]. These results have been reported by other studies [13]. In the present study, body hair involvement was present in all types of AA. We proposed that this clinical feature could be an independent prognostic factor associated with progression in Mexican patients with AA. To our concern, studies describing the molecular mechanisms and clinical relevance of body hair involvement in patients

with AA have not been published. This prognostic factor could be considered in the therapeutic approach and future research of patients with recalcitrant AA in Mexico and other countries.

Treatment of AA has been under active research in the last decade and numerous novel therapeutic options have been published, especially for recalcitrant AA. However, corticotherapy is still one of the most useful treatments for AA. Our patients with disease progression had more prevalence of systemic corticotherapy in comparison with no progression patients, probably related to extensive hair loss and no response to other treatment modalities. We found that corticotherapy and adherence to treatment were not statistically related to disease progression. However, when we considered disease remission from no progression group, we found a higher prevalence of good adherence to treatment in the remission group compared to the progression group. Good adherence to treatment showed a negative statistical correlation with disease progression in multiple linear regression model. Patient orientation about clinical and treatment features of AA could improve adherence to treatment and prognosis [14]. Besides, we have reported that depression, anxiety, and suicide affect the guality of life and prognosis of patients with AA [15]. We propose that a good orientation, treatment adaptability according to patients occupations, and listening to their requirements in dermatologic consultation could increase the probability to reach remission.

5. CONCLUSIONS

Body hair involvement is related to poor prognosis. Adherence to treatment is a modifiable prognostic factor associated with the course of AA in Mexican patients.

6. ACKNOWLEDGMENT

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7. STATEMENT OF ETHICS

This study was approved by local ethics committee according to Helsinki declaration. Informed consent was obtained from all patients.

8. DISCLOSURE STATEMENT

The authors have no conflicts of interest to declare

9. FUNDING SOURCES

No funding sources was employed in this study

10. AUTHORS CONTRIBUTION

Dr. Erick Alejandro Jiménez-Herrera conceived the idea of the manuscript, and contributed to the analysis and interpretation of data and drafting the manuscript.

Dra. Zamira Rios-Garza contributed to include patients in the study, interview patients and acquisition of data for statistical analysis

Dra. María Luisa Peralta-Pedrero contributed to methodological design, analysis of data and final approval of the version to be published.

Dr. Fermin Jurado-Santa Cruz developed the theorical formalisms and conception of the work and revised and approved the final version of the work.

Dra. Martha Morales-Sánchez was responsible for study design, implementation and enrollment of participants; analyzed and interpreted the data, reviewed the first draft and approved the final manuscript.

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12. TABLES

	Initial evaluation (n= 120)	Final evaluation (n= 104)	p value		
Sociodemographic features					
Sex Female, n (%) Male, n (%)	70 (58.3) 50 (41.7)	44 (42.3) 60 (57.7)	0.71		
Age, median (range)	25.5 (75)	25.5 (75)	0.75		
Clinical features	1	1			
Type of AA Patchy, n (%) Ophiasis, n (%) Totalis, n (%) Universalis, n (%)	112 (93.3) 2 (1.7) 4 (3.3) 2 (1.7)	97 (93.3) 2 (1.9) 4 (3.8) 1 (1)	0.98		
Disease duration, median years (range)	1 (27)	1 (27)	0.98		
Age at disease onset, mean years <u>+</u> SD	24.8 <u>+</u> 15.4	24.8 <u>+</u> 15.8	0.98		
Initial SALT score, score (range) Body score B0, n (%) B1, n (%) B2, n (%)	6.5 (100) 98 (81.7) 18 (15) 4 (3.3)	7.0 (100) 86 (82.7) 15 (14.4) 3 (2.9)	0.27 0.44		
Nail score N0, n (%) N1, n (%) N1a, n (%)	104 (86.7) 12 (10) 4 (3.3)	90 (86.5) 11 (10.6) 3 (2.9)	0.95		
No. episodes 1 episode, n (%) 2 episodes, n (%) 3 episodes, n (%) ≥4 episodes, n (%)	82 (68.3) 28 (22.3) 5 (4.1) 5 (4.1)	73 (70.1) 21 (20.2) 5 (4.8) 5 (4.8)	0.71		
Ungueal involvement, n (%)	20 (16.7)	18 (17.3)	0.51		

TABLE 1. Sociodemographic and clinical features of patients with AA at the initial evaluation and loss of patients in the follow-up.

Body hair involvement, n 24 (20) (%)	20 (19.2)	0.59	
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Table 2. Clinical features of the progression and no progression groups.

N = 104	Progression (n=15)	No progression (n=89)	p value
Type of AA Patchy, n (%) Ophiasis, n (%) Totalis, n (%) Universalis, n (%)	12 (80) 2 (13.3) 1 (6.7) 0 (0)	85 (95.5) 0 (0) 3 (3.4) 1 (1.1)	0.03
Age at disease onset, mean years <u>+</u> SD	16.4 <u>+</u> 13.2	26.4 <u>+</u> 15.8	0.027
Disease duration, median years (range)	2 (23)	1 (27)	0.29
Body hair involvement, n (%)	8 (53.3)	12 (13.4)	< 0.01
Ungueal involvement, n (%)	5 (33.3)	13 (14.6)	0.086
No. episodes 1 episode, n (%) 2 episodes, n (%) 3 episodes, n (%) ≥4 episodes, n (%)	11 (73.3) 3 (20) 0 (0) 1 (6.7)	62 (69.7) 18 (20.2) 5 (5.6) 4 (4.5)	0.363
Treatment Topical steroids, n (%) Intralesional steroids, n	9 (69.2)	66 (77.6)	0.507
(%) Systemic steroids, n (%) Topical psoralens, n (%) Phototherapy, n (%) Retinoids, n (%)	7 (53.8) 5 (38.5) 5 (38.5) 1 (7.7) 0 (0)	22 (25.6) 7 (8.1) 15 (17.4) 3 (3.5) 3 (3.5)	0.081 0.002 0.080 0.475 0.496

Adherence to treatment			0.43
100%	5 (33.3)	42 (47.1)	
90%	4 (26.6)	34 (38.2)	
89 – 60%	4 (26.6)	12 (13.4)	
59 - 30%	1 (6.6)	0 (0)	
29 -10%	0 (0)	1 (1.1)	
<10%	1 (6.6)	0 (0)	

Table 3. Sociodemographic and clinical features of the progression and remission groups.

N = 50	Progression (n=15)	Remission (n=35)	p value**
Sociodemographic features	1	1	
Sex	12 (80)	15 (42.0)	0.12
Male, n (%)	12 (80) 3 (20)	15 (42.9) 20 (57.1)	
Age, median years (range)	24 (44)	35 (41)	0.06
Family history			
AA, n (%)	3 (20)	10 (28.6)	0.53
Atopic dermatitis, asthma, allergic rhinitis and urticaria, n (%)	1 (6.7)	0 (0)	0.33
Diabetes Mellitus, n (%)	8 (53.3)	0 (0)	0.53
Systemic arterial hypertension, n	7 (46.7)	0 (0)	0.76
(%)	2 (13.3)	0 (0)	0.93
Thyroid disease, n (%) Autoimmune diseases, n(%)*	4 (26.6)	3 (8.5)	0.61
Personal history			
Vitiligo, n (%)	0 (0)	3 (8.6)	0.24
Atopic dermatitis, asthma, allergic rhinitis and urticaria, n (%)	3 (20)	3 (8.6)	0.26
Thyroid disease, n (%)	1 (6.7)	0 (0)	0.12
Diabetes Mellitus, n (%)	0 (0)	0 (0)	1
Systemic arterial hypertension, n	0 (0)	0 (0)	1
(%)	1 (6.7)	4 (11.4)	0.61
Dyslipidemia, n (%) Autoimmune diseases, n (%)*	1 (6.7)	0 (0)	0.12
Smoking			
Active, n (%)	3 (20)	9 (25.7)	0.67
Inactive, n (%)	2 (13.3)	6 (17.1)	0.73

Alcoholism, n (%)	5 (33.3)	16 (45.7)	0.42
Clinical features	1	1	1
Disease duration, median years (range)	2 (23)	1 (27)	0.29
Age at disease onset, mean years SD	16.4 <u>+</u> 13.2	28.1 <u>+</u> 13.8	0.01
Initial SALT score, score (range) Body score B0, n (%) B1, n (%) B2, n (%) Nail score N0, n (%) N1, n (%) N1a, n (%)	18 (91) 7 (46.73) 8 (53.3) 0 (0) 12 (80) 3 (20) 0 (0)	4 (15) 33 (94.3) 2 (5.7) 0 (0) 32 (91.4) 3 (8.6) 0 (0)	< 0.01 < 0.01 0.25
Final SALT score, score (range) Body score B0, n (%) B1, n (%) B2, n (%) Nail score N0, n (%) N1, n (%) N1a, n (%)	20.5 (96) 7 (46.73) 8 (53.3) 0 (0) 10 (66.7) 5 (33.3) 0 (0)	0 (0) 33 (94.3) 2 (5.7) 0 (0) 32 (91.4) 3 (8.6) 0 (0)	< 0.01 < 0.01 0.01
No. episodes 1 episode, n (%) 2 episodes, n (%) 3 episodes, n (%) ≥4 episodes, n (%)	11 (73.3) 3 (20) 0 (0) 1 (6.7)	27 (43.3) 5 (15.4) 2 (14.3) 1 (2.9)	0.80
Type of AA Patchy, n (%) Ophiasis, n (%) Totalis, n (%) Universalis, n (%)	12 (80) 2 (13.3) 1 (6.7) 0 (0)	35 (100) 0 (0) 0 (0) 0 (0)	< 0.01
Ungueal involvement, n (%)	5 (33.3)	3 (8.6)	0.03
Body hair involvement, n (%)	8 (53.3)	2 (5.7)	< 0.01

9 (69.2)	24 (72.7)	0.81
7 (53.8)	6 (17.6)	0.03
5 (38.5)	2 (5.9)	< 0.01
5 (38.5)	4 (11.8)	0.04
1 (7.7)	1 (2.9)	0.53
0 (0)	0 (0)	0.1
		0.02
5 (33.3)	21 (60)	
4 (26.6)	10 (28.5)	
4 (26.6)	3 (8.5)	
1 (6.6)	0 (0)	
0 (0)	1 (2.8)	
1 (6.6)	0 (0)	
	9 (69.2) 7 (53.8) 5 (38.5) 5 (38.5) 1 (7.7) 0 (0) 5 (33.3) 4 (26.6) 4 (26.6) 4 (26.6) 1 (6.6) 0 (0) 1 (6.6)	$\begin{array}{ccccccc} 9 & (69.2) & 24 & (72.7) \\ 7 & (53.8) & 6 & (17.6) \\ 5 & (38.5) & 2 & (5.9) \\ 5 & (38.5) & 4 & (11.8) \\ 1 & (7.7) & 1 & (2.9) \\ 0 & (0) & 0 & (0) \\ \end{array}$ $\begin{array}{c} 5 & (33.3) & 21 & (60) \\ 4 & (26.6) & 10 & (28.5) \\ 4 & (26.6) & 3 & (8.5) \\ 1 & (6.6) & 0 & (0) \\ 0 & (0) & 1 & (2.8) \\ 1 & (6.6) & 0 & (0) \end{array}$

* Psoriasis, systemic lupus erythematosus, rheumatoid arthritis, bullous diseases, vasculitis

Table 4. Multiple linear regression model for factors associated with disease progression

Variable	n	%	X ² P value	В	CI 95%	P value
Body hair involvement Present Absent	8/15 7/15	53.3% 46.7%	< 0.01	0.798	0.42 – 1.17	< 0.01
Body Score (SALT score) B0 B1 B2	7/15 8/15 0/15	46.7% 53.3% 0%	< 0.01	0.468	0.16 - 0.78	0.03

Adherence to treatment						
100%	5/15	33.3%				
90%	4/15	26.6%				
89 – 60%	4/15	26.6%				
59 - 30%	1/15	6.6%				
29 -10%	0/15	0%				
<10%	1/15	6.6%	< 0.01	-0.88	-0.15 – -0.021	0.01

Table 5. Multiple linear regression model for factors associated with disease remission

Variable	n	%	X² p value	В	CI 95%	p value
Body hair involvement						
Present Absent	2/35 33/35	5.7% 94.3%	0.013	-0.295	-0.530 — -0.059	0.015

12. FIGURES LEGENDS







Figure 2. Kaplan – Meier curves for hair body involvement