J Arch Mil Med. 2016 February; 4(1): e36377. doi: 10.5812/jamm.36377

Published online 2016 February 17. **Research Article**

Alopecia Areata: The Role of Stressful Events and an Estimate of Lifetime Risk in First-Degree Relatives

Alireza Khoshdel,[1,*] Arash Shekari,[2,3] Koosha Paydary,[3] and Iraj Shekari[3]

[1]Department of Epidemiology, Faculty of Medicine, AJA University of Medical Sciences, Tehran, IR Iran
[2]Epidemiology Research Center, AJA University of Medical Sciences, Tehran, IR Iran
[3]Students' Scientific Research Center (SSRC), Tehran University of Medical Sciences, Tehran, IR Iran

*Corresponding author: Alireza Khoshdel, Department of Epidemiology, Faculty of Medicine, AJA University of Medical Sciences, Tehran, IR Iran. Tel: +98-2188337909, E-mail: alikhoshdel@yahoo.com

Received 2016 January 16; **Accepted** 2016 January 16.

Abstract

Background: Alopecia areata (AA) is a common disease in the military population; however, a few studies have calculated the lifetime risk of alopecia areata in first-degree relatives of patients as well as the impact of stress.
Objectives: The primary aim of this study was to calculate the lifetime risk of alopecia areata in first-degree relatives of index patients. The secondary aim of this study was to assess the role of stressful events in the onset/recurrence of disease.
Patients and Methods: One hundred and twenty-one patients with alopecia areata and their first-degree relatives, which included 597 subjects in addition to 119 controls, were studied. We considered a gender and age-matched control for each patient. They were investigated for the occurrence of stressful events within the previous six months before the onset/recurrence of the disease.
Results: More than twenty-six percent of patients had a positive family history, while 6.4 percent of first-degree relatives were affected by alopecia areata. Lifetime risks were estimated at 7.6% for parents, 9.9% for siblings, and 6.4% for children. Eighty-eight patients (73.9%) experienced stressful events within six months prior to the onset or recurrences of alopecia areata, while 32 subjects (26.9%) of the control group reported such events in the last six months (P value = 0.000).
Conclusions: Calculated lifetime risks can be used in genetic counseling. It appears that stressful events can be considered to be contributing factors in the development of alopecia areata. Also, according to our results, the role of stress in the recurrence of alopecia areata is more prominent than the primary development of the disease.

Keywords: Alopecia Areata, Lifetime Risk, Stressful Event

1. Background

Alopecia areata (AA) is a common non-cicatricial alopecia. It presents with a sudden onset of hair loss from the scalp or other hair-bearing regions without scarring (1). Most patients are less than 40 years old and usually have no other symptoms. The hair loss ranges from a small round, patchy hair loss in mild cases to entire body hair loss in severe cases (2).

AA is more common in the military population than in civilians. While stress is apparently a triggering factor and the fundamental etiology of AA is still unknown, there is strong evidence that it has an autoimmune basis and that genetic factors may play a role (3). Familial aggregation of AA has been described previously (4-17); however, few studies have assessed family members of patients and calculated the lifetime risk of AA (14). In addition, there is no consensus regarding the role of stress in AA. Some studies have emphasized the role of stressful events (18-21), while others have provided controversial evidence for the role of stress (12, 22).

2. Objectives

In this study, we sought to assess the pattern of AA among patients and their family members as well as to estimate the lifetime risk and the possible role of stressful events in the onset or recurrence of AA.

3. Patients and Methods

The study was performed in the dermatology clinic of our university from 2009 to 2011. We studied 121 patients with AA and their first-degree relatives, which included 597 subjects. The institutional review board (IRB) of our university approved the study protocol, and informed consent was obtained from all participants. All patients had experienced a recent onset of the current episode. Index patients, first-degree relatives and their affected family members, were interviewed directly. Data of other family members were also obtained from the patients and their interviewed family members. The family members who had experienced at least one episode of the dis-

ease in their lifetime were considered to be affected relatives. A positive family history for a patient was defined as having at least one affected first-degree relative.

The patients' ages and sex, affected family members, disease severity, age of onset, disease severity in affected family members, age of onset in affected family members, positive history of stressful events within six months before the onset or recurrence, other concomitant autoimmune diseases (i.e. thyroid disease, pernicious anemia, Addison's disease, vitiligo, systemic lupus erythematosus, ulcerative colitis, diabetes mellitus, rheumatoid arthritis, Crohn's disease, celiac disease, and psoriasis), and nail involvement were recorded.

We considered a gender and age-matched control for each patient for assessing stress. The control group consisted of outpatients of the same dermatology clinic who had skin diseases with a clear etiology that was unrelated to stress (such as contact dermatitis, bacterial and viral infections, seborrheic keratosis, mycosis, and simple nevus). Two patients were five and ten years old and were excluded from the assessment of stress.

To assess the occurrence of stressful events, we used the Holmes and Rahe's social readjustment rating scale (23). This questionnaire has been previously validated and applied among the Iranian population (24). Stressful events that had occurred within six months before onset or recurrence of the disease were recorded. In addition, the patients filled out a simple questionnaire that assessed the psychological impacts of AA on their life. For this procedure, we used the questionnaire that was published in the study undertaken by Tan et al. This questionnaire comprises 13 items and thus is rated on a zero-to-thirteen scale for each patient (12).

Disease severity was classified according to guidelines published by Olsen et al. (25) It was classified into the following groups: S_1 (scalp hair loss less than 25%), S_2 (scalp hair loss 25% to 49%), S_3 (scalp hair loss 50% to 74%), S_4 (scalp hair loss 75% to 99%), S_5 (total scalp hair loss), S_5B_1 (total scalp and part of the body hair loss), and S_5B_2 (whole body hair loss). To calculate the lifetime risk, time was considered based on age of onset for affected relatives. In addition, time was specified as the age at the time of the interview and the age at death for non-affected alive and non-affected dead relatives, respectively. Lifetime risks for different groups of first-degree relatives were calculated using the Cox proportional hazard model.

Fisher's exact test was used to examine differences between the categorical variables, and an independent samples t-test was used to compare the means. A linear regression analysis was used to investigate the relation between age of onset in index patients and their affected first-degree relatives. The statistical analyses were performed using the software SPSS 13 (SPSS Inc. Chicago, IL, USA). The significance level of $P < 0.05$ was used.

4. Results

We studied 121 patients with AA. Seventy-four patients (61.2%) were male, and 47 patients (38.8%) were female. The age of patients ranged from 5 to 62 years old with a mean age of 26.6 years old. The age of onset ranged from 5 to 58 years old with a mean onset age of 23.4 years (SD ± 8.0 years). The mean age of onset was 23.3 years old (SD ± 8.6 years) for men and 23.7 years old (SD ± 7.0 years) for women (P value > 0.05). The first episode of the disease occurred in the first 20 years of life for 39.7% of patients and in the first four decades of life for 95.9% of patients. Fifty-one patients had experienced their first episodes of the disease, and 70 patients had experienced at least one attack previously (Table 1).

Seventy-six patients (62.8%) had hair loss of the scalp of less than 50% (S_1-S_2), 36 patients (29.8%) had 50% to 99% hair loss of the scalp (S_3-S_4), and nine (7.4%) patients had hair loss in the range of alopecia totalis to alopecia universalis (S_5-S_5B_2).

A total of 121 index patients had 597 first-degree relatives. Thirty-eight first-degree relatives (6.4%) had AA. Thirty-two index patients (26.4%) had at least one affected first-degree relative, and six patients (5%) had two first-degree relatives affected by AA. Table 2 shows the prevalence of AA in the first-degree relatives of index patients.

The disease severity and the age of onset between patients with and without a positive family history were not significantly different. A positive family history was higher in the patients with recurrent disease in comparison to the patients who experienced their first episode of AA (38.6% vs. 9.8%, P value = 0.000, OR: 5.8, 95% CI: 2.0 - 16.4). We also analyzed the relation between the onset age of index patients and positive family history, which was not significant. Table 3 shows the calculated lifetime risks for different groups of first-degree relatives.

One hundred and nineteen patients and 119 controls filled out the Holmes and Rahe's social readjustment rating scale. Eighty-eight patients (73.9%) experienced stressful events within six months prior to the onset or recurrences of the disease, while 32 subjects (26.9%) of the control group reported such events in the previous six months (P value = 0.000, OR: 7.7, 95% CI: 4.3 - 13.7). An occurrence of stressful events before onset or recurrence did not significantly differ between men and women (73.6% of men and 74.5% of women). The stressful events had occurred among 29 patients (59.2%) who experienced their first episode of the disease compared to the 13 subjects (26.5%) of the control group (P value = 0.002). Also, 59 patients (84.3%) with recurrent disease mentioned the occurrence of stress compared to 19 subjects (27.1%) of the control group (P value = 0.000) (Table 4). On the other hand, patients with recurrent disease reported more stressful events than the patients who experienced their first episode of AA (84.3% vs. 59.2%, P value = 0.003, OR: 3.7, 95% CI: 1.6 - 8.7).

One hundred and twelve patients filled out the brief questionnaire regarding the impact of AA on their lives. We sought to identify the patients' feelings about their body image and hair problems. Patients with severe disease obtained higher scores compared to patients with mild disease (Mean

± SE: 5.6 ± 0.4 vs. 2.7 ± 0.2 out of 13, P value = 0.000). In mild cases, female patients had higher scores than male patients and had a more negative body image and less adaptive functioning (3.6 ± 0.4 vs. 2.2 ± 0.3 out of 13, P value = 0.006), but in severe cases, there was no significant difference between the male and female patients (P value > 0.05).

Table 1. Characteristics of Patients With Alopecia Areata in This Study[a]

Characteristics	Values
Age (mean ± SD), y	26.6 ± 9.1
Attack number	
1	51 (42.1)
2	30 (24.8)
3	20 (16.5)
4	13 (10.8)
> 4	6 (5.0)
Unsure	1 (0.8)
Onset age (mean ± SD), y	23.4 ± 8.0
Gender	
Male	74
Female	47
Mild/extensive (S_3 and above)	76/45
Positive family history (1^{st} degree)	32 (26.4)
Total	121

[a]Values are expressed as No. (%) unless otherwise indicated.

Table 2. Frequency of Alopecia Areata in the First-Degree Relatives of Index Patients

Relationship	Number of Subjects	Number of Patients	Prevalence Rate, %
Father	121	9	7.4
Mother	121	8	6.6
Brother	144	10	6.9
Sister	130	9	6.9
Son	38	1	2.6
Daughter	43	1	2.3

Table 3. Lifetime Risks in First-Degree Relatives of Patients With Alopecia Areata

Relation	Total Number	Number of Patients	Lifetime, % (95% CI)
Parents	242	17	7.6 (4.3 - 10.9)
Siblings	274	19	9.9 (5.8 - 14.0)
Children	81	2	6.4 (0.0 - 15.0)

Table 4. Comparison of Stressful Events Between Patients and the Control Group

Subjects who experienced stress	Number	Alopecia Areata Group[a]	Control Group[a]	P Value	Odds Ratio (95% CI)
In first episode group	49	29 (59.2)	13 (26.5)	0.002	4.0 (1.7 - 9.4)
In recurrent group	70	59 (84.3)	19 (27.1)	0.000	14.4 (6.3 - 33.1)
Total	119	88 (73.9)	32 (26.9)	0.000	7.7 (4.3 - 13.7)

[a]Values are expressed as No. (%).

5. Discussion

In this study, 26.4% of patients reported a positive family history. In addition, 6.4% of first-degree relatives of the index patients had AA. According to various studies, the rate of positive family history ranges from 5.7% to 21.8%, although the comparison between such rates is difficult due to differences in family sizes (14-17). The rate of first-degree relatives' being affected in this study is somewhat similar to the results of Blaumeiser et al. (14) (5.5%) but is higher than Yang et al. (13) reported (1.6%). The higher prevalence of AA among first-degree relatives of our patients in comparison to the study performed by Yang et al. could be explained by the diversity of genetic predisposing factors between subpopulations or more accurate data collection in our study.

Different studies have proposed contradicting results about the relation between positive family history and disease severity or age of onset (11, 13-16, 26). In our study, disease severity and age of onset were not significantly different between patients with and without affected family members. Contrary to our results, Blaumeiser et al. suggested that there is a positive correlation between the onset age of index patients and their family members (14). Moreover, in our study, the occurrence of stressful events before the onset and recurrence of AA was significantly higher than the control group. Although this is similar to the findings of Manolache and Benea (18), Picardi et al. did not observe any significant difference between patients and controls in this regard (22).

In general, there are numerous reports considering the role of stressful events in the incidence of AA. Manolache and Benea concluded that stress plays an important role in the development of AA (18). Moreover, Willemsen et al. documented a more prevalent positive history of childhood and lifetime traumatic events in patients with AA (20). Nonetheless, other studies have emphasized the role of trait-anxiety, stress perception, and vulnerability as major factors of AA development (27-29). Therefore, personality characteristics, such as alexithymia and poor social support, may be of more importance in the development of AA in comparison to the frequency of stressful events. Another explanation that should be considered regarding the controversy of reports is the relatively low numbers of patients, less than 100 patients, who have been assessed in most of such studies. Regardless, stressful and life traumatic events (i.e. death of spouse, divorce, fire at work, etc.) may act as triggers that increase the incidence of disease episodes when the predisposing circumstances are present (28, 29). Consistent with this explanation, patients in our study reported significantly more stressful events than the controls. This significant difference seems to emphasize the role of stress in the development of AA, and according to our results, it seems that the role of stress is more important in the recurrence of the disease than its primary development.

To date, little has been understood about the immune pathways that may be essential in the development of AA, and the extent to which genetic predisposition is determinant in this regard remains unidentified. In fact, most of the studies conducted to date have only assessed the familial aggregation patterns of AA, and thus the association between the occurrence/recurrence of AA and specific loci remain unclear. One way to determine the genetic predisposition in AA is by calculating the sibling risk ratio (14). Sibling risk ratio is defined as the ratio of sibling lifetime risk to lifetime population risk. According to a study performed by Safavi et al. (30) the lifetime population risk in the United States was 1.7%; therefore, in our study, the sibling risk ratio would be 5.8, which is somewhat higher than the sibling risk ratio calculated by Blaumeiser et al. (14) Nevertheless, this relatively high sibling risk ratio may be due to the underlying genetic predisposition of both mechanisms, including immune responses as well as similar personality characteristics of first-degree relatives. Thus, the extent to which genetic factors act independently from psychological determinants and personality traits (i.e. immune responses) should be evaluated in further studies.

The limitations of this study should be considered. We assessed the family history, disease severity, and number of attacks only once after the onset or recurrence of the disease; however, the clinical aspects of AA may change over time. In addition, we were unable to provide the possible routes by which genetic factors predispose patients to the development or recurrence of AA. Also, we could not define the role of genetic predisposition by means of similar personality characteristics in the observed familial aggregation. Hence, the study was performed via applying questionnaires regarding the nature and frequency of stressful events, so the collected data were prone to recall bias.

In conclusion, this study emphasizes the role of genetic factors in the development and recurrence of AA. We also found that stressful events may play a role in the development of AA, and future studies should be conducted to assess the role of various personality characteristics and to explain the exact role of stressful events in this regard. The estimated lifetime risks calculated in this study provide useful information for genetic counseling, considering the development and recurrence of AA among highly affected families.

Acknowledgments

We would like to thank Dr. Hossein Yavari for his help.

References

1. Alexis AF, Dudda-Subramanya R, Sinha AA. Alopecia areata: autoimmune basis of hair loss. *Eur J Dermatol.* 2004;**14**(6):364–70. [PubMed: 15564197]
2. McElwee KJ, Tobin DJ, Bystryn JC, King LJ, Sundberg JP. Alopecia areata: an autoimmune disease? *Exp Dermatol.* 1999;**8**(5):371–9. [PubMed: 10536963]
3. Green J, Sinclair RD. Genetics of alopecia areata. *Australas J Dermatol.* 2000;**41**(4):213–8. [PubMed: 11105363]
4. Anderson I. Alopecia areata: a clinical study. *Br Med J.* 1950;**2**(4691):1250–2. [PubMed: 14791998]

5. Muller SA, Winkelmann RK. Alopecia Areata. An Evaluation of 736 Patients. *Arch Dermatol.* 1963;**88**:290–7. [PubMed: 14043621]
6. Valsecchi R, Vicari O, Frigeni A, Foiadelli L, Naldi L, Cainelli T. Familial alopecia areata--genetic susceptibility or coincidence? *Acta Derm Venereol.* 1985;**65**(2):175–7. [PubMed: 2408426]
7. Sharma VK, Kumar B, Surrinder K, Inderjeet K. Alopecia areata. A clinical study of 250 patients. *Ind j dermatol venereol leprol.* 1988;**54**(3):132–6.
8. Shellow WV, Edwards JE, Koo JY. Profile of alopecia areata: a questionnaire analysis of patient and family. *Int J Dermatol.* 1992;**31**(3):186–9. [PubMed: 1568816]
9. van der Steen P, Traupe H, Happle R, Boezeman J, Strater R, Hamm H. The genetic risk for alopecia areata in first degree relatives of severely affected patients. An estimate. *Acta Derm Venereol.* 1992;**72**(5):373–5. [PubMed: 1361288]
10. Ro BI. Alopecia areata in Korea (1982-1994). *J Dermatol.* 1995;**22**(11):858–64. [PubMed: 8557859]
11. Sharma VK, Dawn G, Kumar B. Profile of alopecia areata in Northern India. *Int J Dermatol.* 1996;**35**(1):22–7. [PubMed: 8838924]
12. Tan E, Tay YK, Goh CL, Chin Giam Y. The pattern and profile of alopecia areata in Singapore--a study of 219 Asians. *Int J Dermatol.* 2002;**41**(11):748–53. [PubMed: 12452996]
13. Yang S, Yang J, Liu JB, Wang HY, Yang Q, Gao M, et al. The genetic epidemiology of alopecia areata in China. *Br J Dermatol.* 2004;**151**(1):16–23. doi: 10.1111/j.1365-2133.2004.05915.x. [PubMed: 15270868]
14. Blaumeiser B, van der Goot I, Fimmers R, Hanneken S, Ritzmann S, Seymons K, et al. Familial aggregation of alopecia areata. *J Am Acad Dermatol.* 2006;**54**(4):627–32. doi: 10.1016/j.jaad.2005.12.007. [PubMed: 16546583]
15. Goh C, Finkel M, Christos PJ, Sinha AA. Profile of 513 patients with alopecia areata: associations of disease subtypes with atopy, autoimmune disease and positive family history. *J Eur Acad Dermatol Venereol.* 2006;**20**(9):1055–60. doi: 10.1111/j.1468-3083.2006.01676.x. [PubMed: 16987257]
16. Kavak A, Yesildal N, Parlak AH, Gokdemir G, Aydogan I, Anul H, et al. Alopecia areata in Turkey: demographic and clinical features. *J Eur Acad Dermatol Venereol.* 2008;**22**(8):977–81. doi: 10.1111/j.1468-3083.2008.02699.x. [PubMed: 18384559]
17. Al-Mutairi N, Eldin ON. Clinical profile and impact on quality of life: seven years experience with patients of alopecia areata. *Indian J Dermatol Venereol Leprol.* 2011;**77**(4):489–93. doi: 10.4103/0378-6323.82411. [PubMed: 21727697]
18. Manolache L, Benea V. Stress in patients with alopecia areata and vitiligo. *J Eur Acad Dermatol Venereol.* 2007;**21**(7):921–8. doi: 10.1111/j.1468-3083.2006.02106.x. [PubMed: 17659001]
19. Wygledowska-Kania M, Bogdanowski T. [Psychic factors in case histories of patients with alopecia areata--preliminary report]. *Psychiatr Pol.* 1996;**30**(4):669–76. [PubMed: 8975265]
20. Willemsen R, Vanderlinden J, Roseeuw D, Haentjens P. Increased history of childhood and lifetime traumatic events among adults with alopecia areata. *J Am Acad Dermatol.* 2009;**60**(3):388–93. doi: 10.1016/j.jaad.2008.09.049. [PubMed: 19026463]
21. Diaz-Atienza F, Gurpegui M. Environmental stress but not subjective distress in children or adolescents with alopecia areata. *J Psychosom Res.* 2011;**71**(2):102–7. doi: 10.1016/j.jpsychores.2011.01.007. [PubMed: 21767691]
22. Picardi A, Pasquini P, Cattaruzza MS, Gaetano P, Baliva G, Melchi CF, et al. Psychosomatic factors in first-onset alopecia areata. *Psychosomatics.* 2003;**44**(5):374–81. doi: 10.1176/appi.psy.44.5.374. [PubMed: 12954911]
23. Holmes TH, Rahe RH. The Social Readjustment Rating Scale. *J Psychosom Res.* 1967;**11**(2):213–8. [PubMed: 6059863]
24. Nia ME, Aliloo MM, Ansarin K. The role of stress and coping strategies in the emergence of asthma, and the moderating effects of gender in this illness. *Procedia - Social and Behavioral Sciences.* 2010;**5**:910–4.
25. Olsen EA, Hordinsky MK, Price VH, Roberts JL, Shapiro J, Canfield D, et al. Alopecia areata investigational assessment guidelines--Part II. National Alopecia Areata Foundation. *J Am Acad Dermatol.* 2004;**51**(3):440–7. doi: 10.1016/j.jaad.2003.09.032. [PubMed: 15337988]
26. Colombe BW, Price VH, Khoury EL, Garovoy MR, Lou CD. HLA class II antigen associations help to define two types of alopecia areata. *J Am Acad Dermatol.* 1995;**33**(5 Pt 1):757–64. [PubMed: 7593774]
27. Brajac I, Tkalcic M, Dragojevic DM, Gruber F. Roles of stress, stress perception and trait-anxiety in the onset and course of alopecia areata. *J Dermatol.* 2003;**30**(12):871–8. [PubMed: 14739513]
28. Gulec AT, Tanriverdi N, Duru C, Saray Y, Akcali C. The role of psychological factors in alopecia areata and the impact of the disease on the quality of life. *Int J Dermatol.* 2004;**43**(5):352–6. doi: 10.1111/j.1365-4632.2004.02028.x. [PubMed: 15117365]
29. Gupta MA, Gupta AK, Watteel GN. Stress and alopecia areata: a psychodermatologic study. *Acta Derm Venereol.* 1997;**77**(4):296–8. [PubMed: 9228223]
30. Safavi KH, Muller SA, Suman VJ, Moshell AN, Melton L3. Incidence of alopecia areata in Olmsted County, Minnesota, 1975 through 1989. *Mayo Clin Proc.* 1995;**70**(7):628–33. doi: 10.1016/S0025-6196(11)63913-X. [PubMed: 7791384]