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Retrospective evaluation of clinical profile and comorbidities in patients with alopecia areata

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ABSTRACT

OBJECTIVE: The aim of the study was to determine the clinical profile of the patients with alopecia areata (AA) and whether or not any differences between the AA patients with and without comorbidity.

METHODS: A total of 218 patients diagnosed with AA between January 1, 2016, and August 31, 2020, in our outpatient clinic were analyzed retrospectively.

RESULTS: The mean age was 27.8±12.3. 61.5% of the patients were male (M/F=1.59). There were AA in 96.3%, alopecia universalis in 3.2%, and alopecia totalis in 0.5% of the patients. Most of them showed unifocal involvement (85.8%) and multifocal involvement to a smaller extent (10.5%). Number of patches was 1 in 75.2%, 2 in 16.7% and 3 or more in 8.1% of AA patients. Average disease duration was 18.1 months. Comorbid diseases were accompanying to 51.8% of the patients. Dermatological diseases were among the most common accompanying diseases (17.9%). However, hypothyroidism (12.8%) was the most frequent comorbid disease. There were thyroidal diseases in 15.1%, allergic disorders in 7.7%, psychiatric disorders in 7.3%, anemia in 5.9%, rheumatic diseases in 2.2%, other endocrine diseases in 1.8%, malignancy in 1.3%, and morbid obesity in 1.3% of the patients. Down syndrome accompanied in 0.9%. Vitamin-D deficiency (38.9%), low ferritin (13.8%), and B12 deficiency (9.6%) were also detected. Female gender (46.9 to 29.5%, p=0.008), extensive disease (p=0.085), Vitamin B12 deficiency (13.3 to 5.7%, p=0.059), and low ferritin level (20.4 to 6.7%, p=0.003) were observed more in patients with comorbidity than those without one.

CONCLUSION: AA accompanies various systemic, autoimmune, and psychiatric diseases. Dermatologists need to recognize potential comorbid diseases, evaluate and manage these patients with a multidisciplinary approach to achieve a better outcome.

Keywords: Alopecia areata; B12; comorbidity; ferritin; hypothyroidism; vitamin D.

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Alopecia areata (AA) is characterized by nonscarring inflammatory hair loss which is seen on the scalp, face and/or whole body, in a focal, multifocal, or generalized distribution. AA is seen in 1–2% of the population [1]. Lifetime incidence of AA ranges from 1.7% to 2.1% [2]. The age- and sex-adjusted incidences are reported as 20.9/100,000 person-years [3].

There is a slightly female predominance [4]. However, female/male (F/M) ratio may change according to the population. The majority of patients with AA in India and Turkiye is composed of men [1].

AA is mostly seen in younger (21–40 years of age) patients [2]. Recent studies report that 21–24% of patients with AA are younger than 16 years of age [1].

Its etiopathogenesis is still unclear, although there is evidence suggesting that environmental, genetic factors and tissue-specific autoimmunity could generate the disease [5].

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Early-onset in life, severe and long-lasting course, extensive disease, and nail dystrophy indicate poor a prognosis of AA [6, 7].

AA is highly associated with other autoimmune diseases. Autoimmune thyroiditis is the most common accompanying autoimmune disease in AA [8]. Many other autoimmune and systemic diseases can also accompany to AA. As comorbid diseases in AA increase, AA might progress clinically and its treatment also becomes more complicated.

Vitamins and minerals play a major role in the development of hair follicle and in immune function [9]. For this reason, these vitamins and minerals are added to treatment of AA in case of their deficiencies.

In this study, we aimed to determine the clinical profile, comorbid diseases in AA patients, and whether or not any differences between the AA patients with and without comorbidity.

Highlight key points

- Many autoimmune, inflammatory, dermatologic, endocrinologic, allergic, rheumatic, and psychiatric diseases may accompany to AA.
- The rate of comorbid diseases in AA is at about 1:2.
- The most common comorbid disease accompanying to AA is hypothyroidism.
- Female gender, low level of ferritin and Vitamin B12 deficiency increase the risk of accompanying comorbidities in patients with AA.
- A multidisciplinary approach is needed for the patients with AA to achieve good results in treatment.

MATERIALS AND METHODS

Patients Population

A total of 218 patients diagnosed with AA between January 1, 2016, and August 31, 2020, were included in this study.

Study Design and Ethical Approvals

This single-center retrospective observational study was approved by the Ethics Committee of the Pamukkale University NonInvasive Clinical Research (decision no: 60116787-020-100231). This study was conducted in accordance with the Principles of the Declaration of Helsinki.

Patients Characteristics and Classification of the Disease

Demographic data, clinical characteristics, and comorbid diseases of the patients with AA were recorded. Clinical type of the disease was classified as AA, alopecia totalis (AT), and alopecia universalis (AU). The site and number of the lesion were noted.

Diagnosis of Comorbid Diseases

The comorbid disease status of patients with AA was determined according to the International Classification of Diseases codes at the time of admission to dermatology and/or other clinics by examining the patient files retrospectively.

In addition, for the patients who were diagnosed with Vitamin D, B12 deficiency and/or anemia, relevant values were also noted by examining the biochemical test results.

Statistical Analysis

Statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL., USA). Continuous variables were expressed in mean±standard deviation, while categorical variables were expressed in number and frequency. Pearson Chi-square and Fisher's exact tests were used to compare categorical variables. Independent sample t-test was used to compare continuous variables. Logistic regression analysis was used to determine the factors increasing the probability of comorbid disease. A p value smaller than 0.05 was accepted as statistically significant.

RESULTS

The mean age of the patients was 27.8±12.3 years. The majority of the patients were male. M/F ratio was calculated as 1.59. The great majority of the patients were consisted of the patients with AA. AU and AT were seen much more less. Unifocal involvement was more frequent. Number of patch was 1 in most of the patients with AA. The average disease duration was 18.1 months. Detailed information about the demographic data and clinical characteristics of the patients is shown in Table 1.

There was comorbid disease in 51.8% of the patients. Dermatological diseases were the most common. However, hypothyroidism was the most frequent comorbid disease in AA patients. A detailed data about comorbid diseases are shown in Table 2.

Table 1. Demographic data and clinical characteristics of the patients with alopecia areata

Demographic data and clinical characteristics of patients	Number/mean / %/ratio/range	
Number of the patients (n=218)		
Mean age and age ranges	27.8±12.3 y	[2–68 y.]
Age interval		
<20	23.8	
[20–40]	65.6	
>40	10.6	
Gender		
Male	61.5	
Female	38.1	
Male/female ratio	134/84	1.59
Type of alopecia		
Alopecia universalis	3.2	
Alopecia totalis	0.5	
Alopecia areata	96.3	
Type of alopecia areata and localization of patch (n=210)		
Unifocal	89	
Hair (H)	72.3	
Beard (B)	15.2	
Eyebrow (E)	1.5	
Multifocal* (H plus B and/or E)	11	
Number of patch (n=210)		
1	75.2	
2	16.7	
3 or more	8.1	
Disease duration**	18.1 m.	[1–240 m.]

*: No combined involvement without hair involvement; **: Disease duration=Time to date since the first episode of disease was seen; y: year; m: months.

Table 2. Comorbid diseases to the patients with alopecia areata

	%
Comorbid diseases (n=218)	
(–) No	48.2
(+) Yes	51.8
Number of comorbid disease	
1	33
2	11.9
3 or more	6.9
Dermatological diseases (DDs)	17.9
Seborrheic dermatitis	5.5
Atopic dermatitis	3.2
Psoriasis	2.4
Contact dermatitis	2.3
Vitiligo	1.4
Nail dystrophy	1.4
LSC	0.9
Lichen planus	0.4
Palmoplantar pustulosis	0.4
DLE	0.4
Chronic urticaria	0.4
Nevus flammeus	0.4
Thyroid diseases	15.1
Hypothyroidism	12.8
Hyperthyroidism	2.3
Allergic disorders	7.7
Elevated IgE level	4.1
Asthma	2.7
Allergic rhinitis	0.9
Psychiatric disorders	7.3
Anemia	5.9
Rheumatic diseases	2.2
Juvenile arthritis	0.9
Ankylosing spondylitis	0.4
Iridocyclitis	0.4
Behçet's disease	0.4
Gastrointestinal disorders	2.2
Gastrit HP+, HP-	1.8
Colitis ulcerosa	0.4
Endocrin diseases	1.8
Type I and II DM	1.4
Addison's disease	0.4
Cardiovascular diseases	1.8
Malignancy	1.3
Chronic myeloid leukemia	0.4
Colon Ca	0.4
Malign neoplasm	
Morbid obesity	1.3
Down syndrome	0.9
Other diseases	3.7

LSC: Lichen simplex chronicus; DLE: Discoid lupus erythematosus; HP: Helicobacter pylori; DM: Diabetes mellitus.

Deficiency of Vitamin D and B12 and a low level of ferritin were observed in some patients, which have been shown as either rate and mean values in Table 3.

There was no control group in this retrospective study. Therefore, comorbid disease rates in patients with AA were compared with the population (Table 4).

AA patients with comorbid disease had a higher rate of mean age, female predominance, vitamin deficiencies (vitamin D and B12), and a low level of ferritin. Statistical differences between the AA patients with and without comorbid diseases are shown in Table 5.

The factors increasing the probability of comorbid disease are shown in Table 6.

Table 3. Vitamin D and B12 deficiency and low ferritin level in patients with alopecia areata

	Patients		Biochemical values
	n	%	Mean value*
Vitamin D deficiency	85	38.9	15.97±6.52 ng/ml
Low level of ferritin	30	13.8	11.26±7.62 ml/ng
Vitamin B12 deficiency	21	9.6	154.09±59.79 pg/ml

*: Average value in patients with deficiency.

Table 4. Comparative rates of comorbid diseases in patients with alopecia areata by the society

Comorbid disease	In normal society	In this study	Estimated rate of increase
	Incidence [Range]	Disease rate	
Hypotyroidism	0.2–5.3	12.5	↑↑↑
Seborrheic dermatitis	1–3	5.5	↑↑
Atopic dermatitis	2–10	3.2	–
Psoriasis	1.5–2	2.4	↑
Vitiligo	0.5–2	1.4	–
Vitamin D deficiency	52–77	38.9*	–
Low level of ferritin	8.3–8.8	13.8	↑↑
Vitamin B12 deficiency	3–5	9.6	↑↑

*: Lower and better result than reported according to the society.

DISCUSSION

AA frequently affects young adults, but it is also seen with high rate in young people under the age of 20 and children. However, it is less common in patients over the age of 40 [1]. In our study, the incidence of AA according to age groups was similar to the literature. Caldwell et al. [10] reported that pediatric AA patients consisted of 18.1% of all AA patients, showing the pediatric to adult ratio (P/A) of AA to be about 1:4. In our study, the number of pediatric patients was 44 (20.2%) and the number of adult patients was 174 (79.8%). The P/A ratio was approximately 1:4, similar to the literature.

AA generally affects male and female equally [1]. However, in our study, AA was seen as more common in male. Male / Female ratio was approximately 3:2.

Although AA can be seen as an isolated disease, mostly, it is seen concomitant with additional diseases. Furthermore, 51.8% of our patients also had comorbid diseases which were endocrinologic, dermatologic, psychiatric, allergic, hematologic, rheumatic, gastroenterologic, and cardiovascular diseases. Most of these diseases were autoimmune. In our study, the most common accompanying disease to AA was hypothyroidism. This result is consistent with previous studies [11]. The prevalence of hypothyroidism in the general population is ranging from 0.2% to 5.3% [12, 13]. In over 99% of cases, hypothyroidism is caused by primary hypothyroidism [12]. The most common cause of primary hypothyroidism is chronic autoimmune thyroiditis [13, 14]. Primary hypothyroidism is seen up to 8–9 times more common in female [13]. The most commonly associated abnormality in AA patients is autoimmune thyroiditis, and the incidence is between 8% and 28% [11]. In our study, the rate of hypothyroidism in AA patients was 12.8%. Female were 57.2% and male were 42.8% of AA patients with hypothyroidism. The F/M ratio was 4:3 (16 females vs. 12 males, F/M=1.33). The rate of patients with hypothyroidism by gender within the total of the patients was 19.04% for females and 8.9% for males, respectively. (F/M= 19.04%/8.9% = 2.13). Hypothyroidism in our patients with AA was showed female predominance. Female was approximately 2 times higher than male. While the F/M ratio for hypothyroidism is 8–9 in the normal population, this ratio has been dropped to 2 in our AA patients. Although hypothyroidism in patients with AA was more common still in females, there was an increase in hypothyroidism in males in our study.

AA affects relatively younger individuals, whereas autoimmune thyroiditis is associated with older age groups above 45–50 years [15]. The average age of our AA patients with hypothyroidism was greater compared to that of AA patients (32.89±14.07 vs. 27.8±12.3). However, this value appears to be still lower than the average age for autoimmune thyroiditis. We consider that AA prepares a suitable ground for the occurrence of hypothyroidism or its acceleration.

The incidence of seborrheic dermatitis (SD) is 1–3% of the general adult population [16]. SD is most common between the ages of 20 and 40. Males are affected more than females (3.0% vs. 2.6%) in all age groups [16]. Given that SD is more common in immunocompromised patients, immunological defects may play a role in development of SD. SD frequently occurs on face and

Table 5. Clinical characteristics and the differences of alopecia areata patients with and without comorbid diseases

Parameters	Comorbid disease		
	(+)	(–)	p
	% / mean / range /ratio		
Number of the patients (%)	51.8	48.2	
Number of comorbid diseases	168	0	<**0.001***
Mean number of comorbid diseases	1.48	0	<**0.001***
Age			0.280
	28.6±14.1	26.8±9.9	
	[2–68 year]	[2–51 year]	
Gender (%)			**0.008***
Male	53.1	70.5	
Female	46.9	29.5	
Male/female ratio	1.13	2.38	
Type of alopecia (%)			0.217
Alopecia universalis	5.3	0.9	
Alopecia totalis	0.9	0	
Alopecia areata	93.8	99.1	
Number of patch in alopecia areata (%)			0.085**
1	71.7	78.8	
2	17.9	15.4	
3 or more	10.4	5.8	
Disease duration			0.557
	19.4 months	16.7 months	
Vitamin D deficiency (%)			0.273
	42.5	35.2	
	15.90±7.12	16.06±5.66	
Low Ferritin level (%)			**0.003***
	20.4	6.7	
	10.20±6.79	14.74±9.66	
Vitamin B12 deficiency (%)			0.059**
	13.3	5.7	
	153.83±45.25	157.58±30.08	

*: P value is significant; **: P value is very close to significant.

Table 6. The factors increasing probability of comorbid disease. Logistic regression analysis results

Parameters	p	Odds ratio
Age	0.234	1.01
Female gender	0.070*	1.58
Ferritin level	**0.021****	3.05
Vitamin D level	0.642	1.2
Vitamin B12 level	0.058*	2.32

*: Statistically not significant but close to 0.05; **: Statistically significant.

other visible areas, it has significant negative effects on patients' quality of life and self-esteem [17]. SD is also associated with psychiatric diseases [17]. In our study, SD was the most common disease accompanying to AA among dermatological diseases. SD was seen in 5.5% of AA patients. The high rate of SD in our patients may be explained by the fact that the majority of our AA patients were male, within the age range of SD and associated with psychiatric diseases.

Atopic dermatitis (AD) is a chronic and relapsing inflammatory skin disease with complex pathogenesis. Thomas and Kadyan reported that AD is seen 2 to

3 times more common in AA patients [18]. However, some previous studies revealed conflicting results about whether AD is associated with AA or not [19]. However, AD has been reported to be increased in patients with severe AA [19]. AD is an indicator of poor prognosis for AA [20]. In our study, AD was seen in 3.2% of AA patients. AD was observed more in our pediatric patients (P/A ratio=4:3). Moreover, in most of our AA patients, there was a limited involvement, unlike reported in the literature. New studies are still needed to clarify this issue because of these conflicting results. Furthermore, atopic disorders such as AD, elevation of Ig E, asthma, allergic rhinitis were seen higher (10.9%) in our patients. This result was consistent with literature [21].

Psoriasis is a chronic, recurrent inflammatory skin diseases affecting 1.5–1.89% of the population [22]. In our study, 2.4% of the patients had psoriasis concomitantly. There is an increased risk of psoriasis in AA patients [23]. This is considered to be secondary to common cytokine profile (produced by T helper type 1 cells) in both of the diseases [24, 25].

Several research groups have reported that AA has a strong association with autoimmune diseases such as vitiligo. The risk of developing AA is 4 times higher in vitiligo patients [26]. Surprisingly, there was no increase in terms of vitiligo in our study.

Nail changes were limited in our study. However, our patients with nail changes had an extensive AA involvement, similar to previous reports [27].

AA is frequently associated with psychiatric comorbidities, given their chronic, relapsing nature, and negative effect on the cosmetic appearance [21]. The estimated incidence of major depressive symptoms and anxiety disorders in patients with AA has been reported to be 39% [28]. AA can be seen as a result of some psychiatric disorders, but, it can lead to psychiatric problem and diseases, as well. It has been reported in the literature that stress and psychological disorders may play a role in both the development and exacerbation of AA [28]. In our study, we found that psychiatric diseases accompanied frequently to AA.

Many autoimmune and/or inflammatory diseases accompany to AA. Rheumatic diseases such as juvenile arthritis, ankylosing spondylitis, iridocyclitis, Behçet's disease, and inflammatory bowel diseases such as colitis ulserosa, other endocrine diseases as type I DM, Addison's disease, and morbid obesity were accompanied to AA in our study. Our results were consistent with the previous reports [6, 8, 15, 18, 19, 21, 23].

Although Vitamin D deficiency accompanies our AA patients at a high rate, Vitamin D deficiency is already seen at a high rate in society. The rate of Vitamin D deficiency in our study was not found significantly higher compared to the society. In addition, no significant difference was also found between AA patients with and without comorbid disease in terms of Vitamin D deficiency. Since Vitamin D plays an important role in the normal growth of hair follicle and immunomodulation, it is necessary to make up for the Vitamin D deficiency during the treatment of AA patients. Overall, the current literature has consistently shown that AA patients had lower levels of vitamin D [9]. Thompson et al. [29] reported that there was no significant association between Vitamin D and AA, similar to our study.

Low levels of ferritin and Vitamin B12 were frequently observed in our patients. However, there were only 13 patients who had been clinically diagnosed with anemia. Ten of them were females and 3 of them were males. F/M ratio was found to be approximately 3:1. However, when all male and female patients with AA were taken into account, 11.9% (10 out of 84 females) of female patients and 2.2% (3 out of 134 males) of male patients had anemia. The probability of anemia was approximately 5 times higher in females than in male patients (11.9 vs. 2.2%, F/M=5:1). This situation also increased the risk of comorbidity in female patients.

We found that approximately 1 out of 2 AA patients had a comorbid disease. The ratio of M/F in AA patients with comorbid disease was almost equal. M/F ratios were 1.13 versus 2.83, respectively, in AA patients with and without comorbid disease. A higher rate of comorbid diseases in females with AA can be explained by the higher prevalence of autoimmune diseases in females. It should be kept in mind that females have lower levels of ferritin and a higher incidence of anemia. Although low level of ferritin was an important factor increasing the risk of comorbidity in our study, this might also be explained by the higher rate of female patients in this group.

In our study, extensive disease involvement was seen higher in AA patients with comorbidity than those without any comorbidities despite no statistically significant differences. Since our study was retrospective, the extent of the disease could be evaluated only by the medical records. This issue can be clarified better with further prospective studies in which more objective methods such as Severity of Alopecia Tool (SALT) score is used [30].

Low level of ferritin and Vitamin B12 was significantly higher in AA patients with comorbid disease. However, the number of patients with Vitamin D deficiency was high, no significant difference was found between AA patients with and without comorbid disease in this regard.

As a result, in cases of female gender, extensive involvement, low levels of ferritin and Vitamin B12, the likelihood of comorbid diseases accompanying to AA increases. We think that these situations may lead to a more severe disease course and hence a poorer treatment outcome. To achieve better clinical results, treatment and follow-up with a multidisciplinary approach are mandatory in these patients.

Study Limitations

The greatest limitation of our study is the lack of a control group enabling us to compare the accompanying diseases. For this reason, the rates of accompanying diseases in AA patients have been compared with that of the general population. Furthermore, since patients with AA do not have completely similar characteristics to the general population (age, gender, etc.), the comparison made with the population may have played a limiting role in reaching accurate results.

Conclusion

Contrary to the literature, AA patients are mostly young men in our society. AA can be an isolated disease, but also it can be seen with many comorbid diseases. The most common disease accompanying to AA is hypothyroidism. However, many autoimmune, inflammatory, dermatologic, allergic, rheumatic, and psychiatric diseases may accompany to AA. The rate of comorbid diseases in AA is at about 1:2. In addition, AA development may be induced by certain vitamin and mineral deficiencies. For this reason, dermatologists should recognize possible comorbidities, vitamin and mineral deficiencies, and evaluate and manage them with a multidisciplinary approach to achieve good results in the treatment of AA.

Ethics Committee Approval: The Pamukkale University NonInvasive Clinical Research Ethics Committee granted approval for this study (date: 25.05.2021, number: 60116787-020-100231).

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