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Serum Cytokine Levels and Anxiety and Depression Rates in Patients with Alopecia Areata

Alopesi Areatalı Hastalarda Serum Sitokin Düzeyleri, Anksiyete ve Depresyon Oranları

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Abstract

Objective: Alopecia areata (AA) is a disease characterized by patchy hair loss. Although the etiopathogenesis of AA is still unclear, it has been hypothesized that immune system dysfunction and stress are involved. The aim of this study was to evaluate possible associations between AA and depression, anxiety and serum levels of cytokines interleukin (IL)-1β, IL-6, IL-8 and IL-10.

Materials and Methods: Forty-three patients who were diagnosed with AA were prospectively enrolled into the study. Thirty age- and sex-matched healthy individuals were included as the control group. The Hamilton Rating Scale for Depression and the Hamilton Rating Scale for Anxiety were used. For children between the ages of 7 and 16, the Children's Depression Inventories was completed. Serum levels of the cytokines IL-1 β, IL-6, IL-8, and IL-10 were analyzed by ELISA.

Results: No significant differences were observed between patients and controls with respect to serum cytokine levels ($p>0.05$). Depression rates were found to be 50% and 30% in AA patients and controls, respectively ($p<0.05$). Similarly, anxiety rates were found to be 63% and 23.3% in AA patients and controls, respectively ($p<0.05$).

Conclusion: Depression and anxiety were found more frequent in AA patients than healthy individuals. Therefore, when considering management therapy, an entire psychiatric evaluation should also be performed. However, no differences were found in serum cytokine levels of patients and controls.

Key Words: Alopecia areata, Depression, Anxiety, Cytokines

Özet

Amaç: AA yama şeklinde kıl kaybı ile karakterize bir hastalıktır. AA'nın etyopatogenezi hala açıklanamamakla birlikte immün sistem bozuklukları ve stres gibi bazı faktörler suçlanmaktadır. Bu çalışmanın amacı AA ile depresyon, anksiyete ve serum sitokinlerinden interlökin (IL) -1β, IL-6, IL-8, IL-10 arasındaki muhtemel ilişkileri değerlendirmektedir.

Gereç ve Yöntem: AA tanısı konmuş 43 hasta prospektif olarak çalışmaya alındı. Yaş ve cins uyumlu 30 gönüllü birey kontrol grubu olarak alındı. Hamilton Depresyon Skalası ve Hamilton Anxiete Skalası kullanıldı. 7-16 yaş arası çocuklar için Children's Depression Inventory anketleri doldurduldu. Serum sitokinlerinden IL-1β, IL-6, IL-8, IL-10 seviyeleri ELISA metoduyla analiz edildi.

Bulgular: Serum sitokinlerinden IL-1β, IL-6, IL-8, IL-10 için hasta ve kontrol grubu arasında anlamlı fark gözlenmedi ($p>0.05$). Depresyon oranları kontrol grubundaki %30 orana karşın hasta grubunda %50 olarak bulundu; benzer şekilde anksiyete oranları AA grubunda %63 iken kontrol grubunda %23.3'tü ($p<0.05$).

Sonuç: Depresyon ve anksiyete AA hastalarında sağlıklı bireylerden daha fazlaydı. Bu yüzden tedavi yönetiminde tam psikiyatrik değerlendirme yapılmalıdır. Fakat hastalarla kontrol grubu arasında serum sitokin seviyeleri açısından fark gözlenmedi.

Anahtar Kelimeler: Alopesi areata, Anksiyete, Depresyon, Sitokin

Introduction

Alopecia areata (AA) is a disease that causes marked cosmetic deformity and psychological morbidity, leading to hair loss on the scalp, face and body [1]. The worldwide incidence of AA is 0.1%, and it is seen in 1-2% of dermatology clinic out-patients. The distribution rate of its prevalence is equal among both sexes [1-4].

Etiopathogenesis of the disease remains unclear [2-4]. The suspected causes include immune system dysfunctions, hereditary factors and infectious and psychological factors [5].

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Various researchers have considered whether emotional stress plays a role in the etiology of AA; however, no primary criteria have been provided [1]. Studies related to immune cell dysfunction in AA patients are often contradictory among themselves [6].

In this study, we aimed to investigate the association between AA and depression, anxiety and cytokines, including interleukin (IL)-1β, IL-6, IL-8 and IL-10.

Materials and Methods

Forty-three patients who were clinically diagnosed with AA and 30 age- and sex-matched healthy controls were recruited for the study. The patient group included 31 men and 12 women. The mean age was 23.42±11.41 (range 5 to 47). The duration of the disease ranged from 1 month to 19 years (mean: 15.54±36.37 months). Demographic features of the patients and controls are presented in Table 1. No age or gender differences were taken into account when defining the subjects. No criteria related to the distribution of lesions or the type of alopecia was taken into account. Patients and controls were examined for AA, atopia, vitiligo, thyroid disease, diabetes mellitus and pernicious anemia, and they were questioned about their familial history of these diseases.

Psychiatric evaluations were performed using the Hamilton Rating Scale for Depression (HAM-D) [7] and the Hamilton Rating Scale for Anxiety (HAM-A) [8]. For children between the ages of 7 and 16, Children's Depression Inventories (CDIs) were completed [9]. Patients whose anxiety and/or depression scores were found to be high in these evaluations were referred to psychiatric examination and, if needed, to a psychiatry clinic for monitoring and treatment. Blood samples (6 cc) were drawn into K_3EDTA tubes for evaluating cytokine levels. Blood was stored in eppendorf tubes at -80^{0}C, and the plasma was separated by centrifuging for 5 minutes at 1,500 rpm. The measurement of cytokines was performed by ELISA using kits specific for human IL-1β, IL-6, IL-8 and IL-10 (Biosource).

The principles of the Helsinki Declaration were followed throughout the study, which was conducted with official permission of the Local Ethical Committee. Data analysis was performed using SPSS 10.0 for Windows software. Descriptive statistics were defined as median±standard deviation (S.D.) and %. For the comparison of parametric values, Student's t test was used, and for non-parametric values, chi square and Mann Whitney U tests were used. A probability of error of 0.05 was considered significant.

Results

A familial history of AA was present in 4 (9.3%) of the AA patients, and a history of recurrent AA was reported by 12 (27.9%). Disorders accompanying AA included atopia (6 patients; 13.9%), chronic urticaria (1 patient; 2.2%), lichen planus (1 patient; 2.2%), psoriasis (1 patient; 2.2%), and chronic renal failure (1 patient; 2.2%).

Of the patients with AA, 25 patients had lost only scalp hair, 9 had lost only beard hair, 1 had lost only eyebrows, 1 had lost only eyelashes and 1 had lost both scalp and beard hair. Full-body presentation existed in 7 patients. The distribution rates of patients related to body area are presented in Table 2.

Serum cytokine levels of patients with AA and healthy controls are indicated in Table 3. No statistical differences were found in terms of serum cytokine levels between the two groups (p values for IL-1β, IL-6, IL-8 and IL-10 were 0.626, 0.549, 0.918 and 0.127, respectively).

Depression and anxiety assessments of the patients with AA and controls are presented in Table 4. No depression was observed in 21 (70%) of the 30 healthy controls. In 9 individuals, mild depression was observed, according to the HAM-D. Of the 43 patients with AA, 27 patients over the age of 16 years were assessed using the HAM-D. Of these 27 patients, 11 (40.7%) showed no signs of depression, 9 (33.3%) showed mild depression, 5 (18.5%) showed moderate depression and

Table 1. Demographic features of patients and controls

		Controls	Alopecia areata	P
n:		30	43	
Age:		26.73±4.70	23.42±11.41	0.141
Gender	(Male)	63.3% (19)	72.1% (31)	0.453
	(Female)	36.7% (11)	27.9% (12)	

Table 2. Distribution of patients according to affected body areas

Area Involved	Number of patients	%
Widespread	7	16.3
Only scalp	25	58.1
Only beard	9	20.9
Only eyebrows	1	2.3
Only eyelashes	1	2.3

Table 3. Cytokine levels in patients and controls

	Controls	Alopecia areata	P
n:	30	43	
IL-1ß (pg/mL)	0.255±0.867	0.345±0.686	0.626
IL-6 (pg/mL)	1.438±0.563	1.358±0.389	0.549
IL-8 (pg/mL)	20.83±30.55	19.754±50.623	0.918
IL-10 (pg/mL)	6.322±0.849	5.936±1.167	0.127

Table 4. Depression and anxiety assessment in patients and controls

		Control	Alopecia areata	P	
n:		30	43		
Depression (+)			30%	50% (18/36)	<0.05
HAM-D (over 16 years of age)	None		70% (21)	40.7% (11)	
	Mild		30% (9)	33.3% (9)	
	Moderate		-	18.5% (5)	
	Major		-	7.4% (2)	
Anxiety (+)			23.3% (7)	63% (17/27)	<0.05

HAM-D: Hamilton Rating Scale for Depression

2 (7.4%) showed severe depression. In the 9 AA patients aged younger than 16 years, the CDI was used. In this group, 2 were diagnosed with depression. No test could be performed on 2 patients under the age of 7, and due to incomplete testing, 5 patients were excluded. Overall, some degree of depression was observed in 30% of the controls and 50% of the AA patients, which was statistically significant ($p<0.05$). Anxiety was found in 7 controls (23.3%) and 17 AA patients over the age of 16 years (63%), which was also statistically significant ($p<0.05$). Depression assessments of healthy controls and AA patients over the age of 16 years are presented in Figure 1.

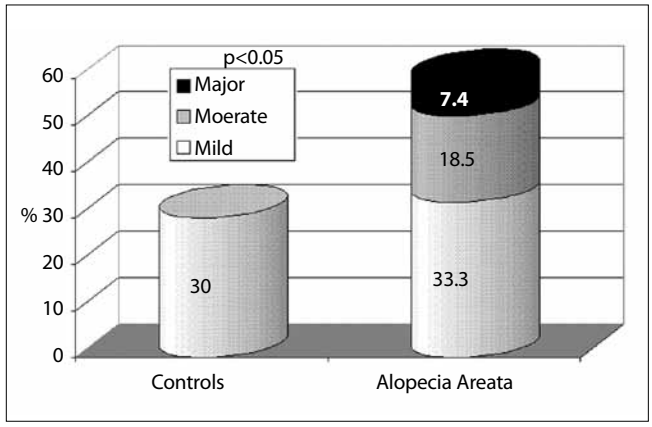

Figure 1. *Depression Assessment of Healthy Controls and AA Patients over the age of 16 years.*

Discussion

Many studies have been performed to examine the relationship between stress and AA. Ghanizadeh [10] suggested that there is a very high rate of psychiatric disorders in children and adolescents with AA, and Poot [11] determined that AA has an important psychiatric comorbidity, mostly presenting as anxiety and depression. Furthermore, Willemsen et al. [12] found aleximity rates to be high in AA patients.

However, other studies have suggested that stress is not a precipitating factor. Van Der Steen et al. [13] found no association between emotional triggers and any type of AA, and Gulec et al. [14] found no differences in the total number of stressful life events between AA patients and controls. Although the role stress plays in AA is controversial, the effect and existence of stress are undeniable factors in the disease. Contradictory results could stem from differences in the methods used obtain information. Self-report bias still remains a challenge because the patient and/or their family is generally the source of the information. In our study, both depression and anxiety rates were found to be high.

Although the cause of AA remains unknown, two key pathogenetic factors whose role in the etiopathogenesis of AA can be discriminated are cytokines and T cells. Histologically, the hair bulb is infiltrated and surrounded by mainly T-helper (Th) cells. A consistent feature was the presence of Th-1 cytokines (IFN-gamma, IL-2, and IL-1ß) [15]. Elevated levels of monocyte-derived inflammatory cytokines (TNF-alpha and IL-6), Th-1 cytokines (IL-12 and IFN-gamma) and Th-2 cytokines (IL-4 and IL-10) have been observed. Both Th-1 and Th-2 mechanisms are active in chronic murine AA [16].

Numerous studies have indicated the significance of cytokines in AA. In a control group composed of 50 AA patients and 64 healthy individuals, Galbraith et al. [17] investigated T1 and T2 phenotypes of serum TNF-α and determined a significant difference in the phenotypes of clinical forms of AA. While no difference was observed in the phenotypes between patchy-type AA and controls, they found a significant difference between alopecia universalis (AU)/alopecia totalis (AT) and control groups. In a study performed with 54 patients, Attia et al. [18] found the levels of serum immunoglobulin and IL-4 to be higher than in normal controls. In the present study, no difference was observed between the severity of the disease and IL-1ß, IL-6, IL-8 and IL-10 serum levels. Due to the fact that only 16.7% of the patients in the study had AA, it could be that no difference was detected.

Freyschmidt-Paul et al. have shown that IL-10$^{-/-}$ mice are less susceptible to AA induction, suggesting either a proinflammatory role of IL-10 in AA pathogenesis or a compensation for the IL-10-deficiency [19]. Arca et al. found that serum levels of IFN-gamma were significantly elevated in patients with AA and AT, AU, AT/AU, which indicates that Th-1 type cytokines may play a role in the pathogenesis of AA, especially in its most severe form [15].

Teraki et al. [20] investigated serum cytokines levels of 7 patchy-type of AA patients and 7 patients with AU/AT, and that found TNF-α and IL-6 levels were within normal limits in both patient groups. Similarly, in our study we found that serum IL-1ß, IL-6, IL-8 and IL-10 levels were not different between the patient and control groups. In the same study,

Teraki et al. found that serum levels of IL-1alpha and IL-4 were significantly elevated in patients with extensive forms. These results indicate that immune responses in the localized and extensive forms of AA are regulated by Th-2 and Th-1 cytokines, respectively. In this respect, we also investigated IL-1ß and IL-8 (Th-1 cytokines) and IL-6 and IL-10 (Th-2 cytokines).

The varying results in the literature may reflect inconsistencies between investigations. The methods of examining cytokines are not standardized, and studies have examined different cytokines. In addition, the fact that cytokine levels may differ in tissue and serum samples may be another contributing factor. McDonagh et al. [21] investigated IL-6 in tissue biopsies from the lesion area in a small group of 8 AA patients and determined a significant increase in IL-6 levels in the dermal papilla cells around the lesions. Most of the patients in this study exhibited patchy AA. The normal levels of cytokines may result from limiting injuries in patchy AA.

Depression and anxiety rates were significantly higher in AA patients than in controls. Therefore, psychiatric evaluations should be administered in conjunction with AA management. In our study, no significant difference was present in terms of IL-1ß, IL-6, IL-8 or IL-10 levels between patients and controls. Because immunological injury is localized in AA, we believe that cytokine levels surrounding the lesions should be investigated alongside serum cytokines, which could yield more significant findings.

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References

1. Ebling FJG, Dawber RPR, Wojnarowska FT. Disorders of hair. In: Rook A, Wilkinson D, Ebling FJG, Champion RH, Burton JL eds. Textbook of Dermatology, 6th Edn. Oxford, Blackwell Scientific pub, 1998; pp. 2869-973.
2. Olsen EA. Hair disorders. In: Fitzpatrick TB, Eisen AZ, Wolff K, Freedberg IM, Austen KF. Dermatology in General Medicine, 5th Edn. New York: McGraw-Hill, 1999; pp. 729-51.
3. In: Arnold HL, Odom BR, James WD. Andrew's Diseases of the skin. 9th Edn. Philadelphia: WB Saunders, 2000; pp. 943-90.
4. Diseases of the hair. In: Falco OB, Plewig G, Wolff HH, Burgdorf WHC. Dermatology. 4th Edn. Berlin: Springer Verlag, 2000; pp. 1099-140.
5. Garcia-Hernandez MJ, Ruiz-Doblado S, Rodriguez-Pichardo A, Camacho F. Alopecia areata, stress and psychiatric disorders: a review. J Dermatol 1999; 26: 625-32.
6. Ledesma GN, York KK. Supressor cell decrease in alopecia areata. Arch Dermatol Res 1982; 274: 1-8.
7. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiaty 1960; 23: 56-62.
8. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959; 32: 50-5.
9. Kovacs M. The Children's Depression, Inventory (CDI). Psychopharmacol Bull 1985; 21: 995-8.
10. Ghanizadeh A. Comorbidity of psychiatric disorders in children and adolescents with alopecia areata in a child and adolescent psychiatry clinical sample. Int J Dermatol 2008; 47: 1118-20.
11. Poot F. Psychological consequences of chronic hair diseases. Rev Med Brux 2004; 25: 286-8.
12. Willemsen R, Haentiens P, Roseeuw D, Vanderlinden J. Alexithymia in patients with alopecia areata: educational background much more important than traumatic events. J Eur Acad Dermatol Venereol 2009; 23: 1226.
13. Van der Steen P, Boezeman J, Duller P, Happle R. Can alopecia areata be triggered by emotional stress? An uncontrolled evaluation of 178 patients with extensive hair loss. Acta Derm Venereol 1992; 72: 279-80.
14. Güleç AT, Tanrıverdi N, Dürü 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: 352-6.
15. Arca E, Musabak U, Erbil AH, Tastan HB. Interferon-gamma in alopecia areata. Eur J Dermatol 2004; 14: 33-6.
16. McElwee KJ, Hoffmann R. Alopecia areata-animal models. Clin Exp Dermatol 2002; 27: 410-7.
17. Galbraith GL, Pandey JP. Tumor necrosis factor alpha (TNF- α) gene polymorphism in alopecia areata. Hum Genet 1995; 96: 433-6.
18. Attia EA, El Shennawy D, Sefin A. Serum interleukin-4 and total immunoglobulin E in nonatopic alopecia areata patients and HLA-DRB1 typing. Dermatol Res Pract 2010; 2010: 503-87.
19. Freyschmidt-Paul P, McElwee KJ, Happle R, Kissling S, Wenzel E, Sundberg JP, Zöller M, Hoffmann R. Interleukin-10-deficient mice are less susceptible to the induction of alopecia areata. J Invest Dermatol 2002; 119: 980-2.
20. Teraki Y, Imanishi K, Shiohara T. Cytokines in alopecia areata. Contrasting cytokine profiles in localized form and extensive form (alopecia universalis). Acta Derm Venereol 1996; 288: 153-6.
21. McDonagh AJG, Elliott KR, Messenger AG. Cytokines and dermal papilla function in alopecia areata. J Invest Dermatol 1995; 104: 9-10.