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# The relationship between psychological distress and neurotrophins in patients with alopecia areata: A cross-sectional study

## *Alopesi areata hastalarında psikolojik distres ve nörotrofinler arasındaki ilişki: Kesitsel bir çalışma*

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### Abstract

**Background and Design:** Alopecia areata (AA) is a common, chronic, autoimmune disease that causes psychological effects on patients. Distress and psychological factors play roles in the onset and flares of the disease. We aimed to evaluate the relationship between neurotrophins (NT) and psychological distress in AA patients.
**Materials and Methods:** The study included 50 AA patients and 50 healthy volunteers as a control group. The Distress Tolerance Scale (DTS) and the Depression Anxiety Stress Scale-21 (DASS-21) were used in the evaluation of psychological distress. Serum levels of NTs [brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4)] were measured.
**Results:** Scores of DASS-21 were found to be higher, and scores of DTS were found to be lower in AA patients. Serum BDNF and NT-3 levels did not differ significantly between groups. While the serum NGF level was significantly higher, the NT-4 level was significantly lower in the AA group than in the control group. In the AA group, a similar significant relationship was found between BDNF and stress subscale scores; in the control group, no significant correlation was found between serum NT levels and DASS-21 and DTS scores.
**Conclusion:** Our study supports the relationship between AA, psychological factors, and NTs. More studies are needed to investigate the relationship between AA and stress neuroimmunology to understand better the common pathophysiology of AA, stress, and various psychiatric diseases.
**Keywords:** Alopecia areata, neurotrophin, psychological stress

### Öz

**Amaç:** Alopesi areata (AA), hastalar üzerinde psikolojik etkileri olan, sık görülen, kronik, otoimmün bir hastalıktır. Hastalığın ortaya çıkmasında ve alevlenmesinde sıkıntı ve psikolojik faktörler rol oynamaktadır. Çalışmamızda AA hastalarında nörotrofinler (NT) ile psikolojik distres arasındaki ilişkiyi değerlendirmeyi amaçladık.
**Gereç ve Yöntem:** Çalışmaya 50 AA hastası ve kontrol grubu olarak 50 sağlıklı gönüllü dahil edildi. Psikolojik distresin değerlendirilmesinde Sıkıntıya Dayanma Ölçeği (SDÖ) ve Depresyon Anksiyete Stres Ölçeği-21 (DASS-21) kullanıldı. Serum NT düzeyleri [beyin kaynaklı nörotrofik faktör (BDNF), sinir büyüme faktörü (NGF), nörotrofin-3 (NT-3) ve nörotrofin-4 (NT-4)] ölçüldü.
**Bulgular:** AA hastalarında DASS-21 puanları daha yüksek, DTS puanları ise daha düşük bulundu. Serum BDNF ve NT-3 düzeyleri gruplar arasında anlamlı farklılık göstermedi. AA grubunda kontrol grubuna göre, serum NGF düzeyi anlamlı olarak yüksek bulunurken, NT-4 düzeyi anlamlı olarak düşük bulundu. AA grubunda BDNF ile stres alt ölçeği puanları arasında da aynı yönde anlamlı ilişki bulundu; kontrol grubunda ise serum NT düzeyleri ile DASS-21 ve SDÖ skorları arasında anlamlı bir korelasyon saptanmadı.
**Sonuç:** Çalışmamız AA ile psikolojik faktörler ve NT'ler arasındaki ilişkiyi desteklemektedir. AA, stres ve çeşitli psikiyatrik hastalıkların ortak patofizyolojisini daha iyi anlamak için AA ile stres nöroimmünolojisi arasındaki ilişkiyi araştıran daha fazla çalışmaya ihtiyaç vardır.
**Anahtar Kelimeler:** Alopesi areata, nörotrofin, psikolojik stres

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## Introduction

Alopecia areata (AA) is a common and organ-specific autoimmune disease resulting in non-scarring alopecia. While the exact pathogenesis is unknown, genetic, autoimmune, neural, hormonal, and psychological factors may be involved. Immunologic destruction of the privilege of the hair follicle is the most accepted theory[1,2].

AA has a cosmetic impact, and it is generally considered a medically benign disorder. Nevertheless, it has a negative effect on the quality of life of patients and causes stress and various psychiatric disorders. On the other hand, distress and psychological factors may also play a role in the onset and exacerbation of AA. Accordingly, it can be concluded that there is a bi-directional relationship between AA and distress and various psychiatric disorders. Stress-neuroendocrine immunology may be a bridge between AA, distress, and psychiatric disorders[1,3,4].

Neurotrophins are growth factors that control neurons' development, maintenance, and apoptosis. The neurotrophin family consists of four proteins: brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4). They exert cellular effects using two cell surface receptors, Trk and p75NTR. They have many non-neurotrophic functions in the skin, such as control of hair follicle development and turnover, epidermal proliferation and apoptosis regulation, and melanogenesis. Neurotrophins also play an important role in the pathogenesis of autoimmune diseases like AA. In AA-affected skin, neurotrophins were found to be involved in the regulation of immune cell functions[5-8]. Changes in neurotrophin levels have also been associated with psychiatric disorders, including anxiety and depression[9]. The stress response has been associated with an increase in serum levels of neurotrophins, which may be the cause of the stress-induced aggravation of skin diseases[8]. Although both stress and neurotrophins have been shown to be related to AA, no study shows the relationship between them.

In this study, we aimed to evaluate the relationship between neurotrophins and psychological distress in AA patients.

## Materials and Methods

### Sample

This research was cross-sectional (evaluating the relationship between levels of neurotrophins and stress) and a case-control study (AA patients and controls) conducted between June 2019 and June 2020. Consecutive fifty patients with AA and 50 healthy volunteers were included in the study. The study's exclusion criteria were determined as being cognitively incapable of completing the questionnaires alone, pregnant or breastfeeding, having any other systemic or dermatological diseases, and having any systemic treatment within the last month for both groups. In the control group, those with psychiatric diseases and those who had AA at any point in their lives were also excluded from the study. Healthy controls were recruited from hospital staff using the snowball method.

### Data collection tools

#### 1. Sociodemographic Data Form

Patients filled out a form with sociodemographic data, medical background, and family history. Socioeconomic and clinical features such as subtype of AA, age at onset, number of attacks, total duration of the disease, duration of the most recent AA attack in months, beard involvement, and disease severity were recorded. Disease severity was assessed using the severity of alopecia tool (SALT) score. In addition, accompanying nail involvement, nevus flammeus, and familial history of AA were also recorded.

#### 2. The Distress Tolerance Scale

Simons and Gaher developed the DTS to measure individual differences in the capacity to withstand distress[10]. Sargın et al.[11] have carried out the Turkish validity and reliability study. The factors were named by considering the original form of the scale and our culture's evaluations and attitudes about distress. Accordingly, the factor-1 "tolerance" subscale in which items 1, 2, 3, 4, 5, 10, 11, 12, and 15 are clustered; factor-2, on which items 8, 13, and 14 are loaded, is named "regulation" and factor-3, on which items 6, 7 and 9 are clustered, is named as "self-efficacy". Since factor-1 assesses the individual's distress and catastrophizing its consequences (such as distraction and dysfunction), it is called tolerance, factor-2 is regulation because it involves avoiding or coping with negative emotions, and factor-3 is self-efficacy because it evaluates the inadequacy of the individual's coping capacity[11].

#### 3. The Depression Anxiety Stress Scale-21

Lovibond created Depression Anxiety Stress Scale-21 (DASS-21) by selecting some elements of DASS-42[12]. The DASS-21 questionnaire measures three dimensions of mental health: Depression Anxiety Stress Scale-21-depression (DASS-21-D), Depression Anxiety Stress Scale-21-anxiety (DASS-21-A), and Depression Anxiety Stress Scale-21-stress (DASS-21-S). The primary function of DASS-21 is to assess the severity of the main symptoms of depression, anxiety, and stress. Each subgroup consists of 7 items[12]. The Turkish validity and reliability study was performed by Sarıçam[13].

### Procedure

The Eskişehir Osmangazi University Local Ethics Committee approved the study protocol (approval number: 29, date: 11.04.2019). Fifty consecutive patients diagnosed with AA participated in the study. The study was introduced to the patients who had applied to the dermatology outpatient clinic, and they were invited to participate. Informed consent was obtained from those who agreed to participate in the study. Volunteers were included in the study. Data collection tools were presented to AA patients and healthy volunteers. Participants filled out these forms themselves. Afterwards, the patients were given an appointment for biochemical sampling.

### Analysis of serum samples

Serum levels of BDNF, NGF, NT-3, and NT-4 were measured for the study. After at least 8 hours of fasting, 15 mL peripheral venous blood samples were taken from the patient and control groups. The samples were centrifuged at 1500 g for 10 minutes, and their serum was separated and stored at -80 °C until the working day. Serum NT-3, NT-4, BDNF and NGF concentrations were measured using ELISA using MYBioSource (California, USA) brand commercial kits.

### Statistical Analysis

SPSS 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, version 21.0.Armonk, NY: IBM Corp.) software was used for data analysis. Continuous data are expressed as mean ± standard deviation for those with normal distribution and median Q1 (25th percentile) and

Q3 (75th percentile) for those without normal distribution. Categorical data are given as per cent (%). The Shapiro-Wilk test was used to observe whether the data showed normal distribution. In comparing groups that did not show normal distribution, the Mann-Whitney U test was used where the number of groups was two. The direction and magnitude of the relationship (correlation) between variables were calculated with Spearman's correlation coefficients for the variables that did not conform to the normal distribution. Pearson's exact chi-square test analyses were used to analyze the cross tables.

The results were evaluated within the 95% confidence interval and were considered statistically significant when the alpha error was less than 5% (p<0.05).

## Results

Fifty AA patients and 50 healthy volunteers were included in the study. The patient and control groups were similar in gender and age distribution (p=1,000, p=0.684, respectively). Sociodemographic features are summarized in Table 1.

Three (6%) patients had alopecia universalis, and 47 (94%) had patchy AA. The mean SALT score of AA patients was 15.79±24.88. The mean disease duration of the patients was 48.82±105.24 months, and the last attack duration was 14.06±33.61 months. The mean age at the onset of AA was 30.68±11.86 years. The mean total number of attacks of the patients was 1.54±1.33. Family history of AA was present in 26% (n=13) of the patients, nail involvement in 18% (n=9), and accompanying nevus flammeus in 26% (n=13). The pull test was positive in 36% (n=18) of the patients. Beard involvement was present in 71% (n=22) of 31 male patients. The clinical features accompanying AA are given in Table 2.

In the AA group, the total DASS-21 score was 16.50 (10.25-24.75); in the control group, the total DASS-21 score was 9.50 (4.00-14.00). Subscale (depression, anxiety, stress) and total DASS-21 scores were found to be significantly higher in the AA group compared to the control group (p=0.002, p=0.001, p<0.001, p<0.001, respectively). The total DTS score in AA patients was 45.00 (38.00-52.25); in the control group, it was 57.00 (50.25-63.5). The scores obtained from the subscales (tolerance, regulation, and self-efficacy) and the total DTS score were found to be significantly lower in the AA group compared to the control group (p<0.001, p=0.011, p<0.001, p<0.001, respectively) (Table 3).

Median serum BDNF values were 20.12 (12.38-36.58) ng/mL in AA patients and 22.96 (11.15-83.92) ng/mL in the control group; median serum NGF values were 9.08 (6.88-16.77) pg/mL in AA patients and 7.16 (4.10-12.92) pg/mL in the control group; median serum NT-3 values were 8.90 (4.71-30.47) pg/mL in AA patients and 6.93 (4.41-27.75) pg/mL in the control group; median serum NT-4 values were measured as 1.99 (0.71-4.69) ng/mL in AA patients and 3.09 (1.57-5.33) ng/mL in the control group. Although the median serum BDNF values were lower and the median NT-3 values were higher in AA patients compared to the control group, no statistically significant difference was found between the groups. Serum NGF levels were significantly higher, and NT-4 levels were significantly lower in AA patients compared to the control group (p=0.020, p=0.040, respectively) (Table 4).

When the relationship between serum neurotrophin levels in the AA group and DASS-21 and DTS scores were evaluated, a similar significant relationship was found between BDNF and stress subscale scores (p=0.031) (Table 5). No significant correlation was found between serum neurotrophin levels and DASS-21 and DTS scores in the control group.

**Table 1. Sociodemographic features of participants**

| | | n (%) | | p |
|---|---|---|---|---|
| | | AA | Control | |
| Sex | Female | 19 (38%) | 20 (40%) | 1.000* |
| | Male | 31 (62%) | 30 (60%) | |
| Age (year) | | Median (Q1-Q3) | | 0.684** |
| | | 33.00 (26.25-41.50) | 34.50 (27.00-42.00) | |
| | | n (%) | | |
| Marital status | Single | 26 (52%) | 24 (48%) | 0.532* |
| | Married | 24 (48%) | 26 (52%) | |
| Educational status | Primary school | 6 (12%) | 0 (0%) | **<0.001*** |
| | Secondary school | 4 (8%) | 3 (6%) | |
| | High school | 17 (34%) | 6 (12%) | |
| | University | 22 (44%) | 31 (62%) | |
| | Postgraduate | 1 (2%) | 10 (20%) | |
| Smoking | Yes | 31 (62%) | 17 (34%) | **0.009** |
| | No | 19 38(%) | 33 (66%) | |
| Alcohol consumption | Yes | 13 (26%) | 16 (32%) | 0.659 |
| | No | 37 (74%) | 34 (68%) | |

*Pearson's exact chi-square test, ** Mann-Whitney U test, AA: Alopecia areata

| Table 2. Clinical features of AA patients | | |
|---|---|---|
| | | **Median (Q1-Q3)** |
| SALT score | | 5.00 (5.00-15.00) |
| Disease duration (month) | | 12.00 (2.00-36.00) |
| Last attack duration (month) | | 3.00 (1.25-9.50) |
| Mean age at onset | | 33.00 (36.25-41.50) |
| Total number of attacks | | 1.00 (1.00-2.00) |
| | | **n (%)** |
| Clinical subtype | Alopecia universalis | 3 (6%) |
| | Patchy alopecia | 47 (94%) |
| Presence of a family history of AA | | 13 (26%) |
| Presence of nail involvement | | 9 (18%) |
| Presence of nevus flammeus | | 13 (26%) |
| Presence of pull test positivity | | 18 (36%) |
| Presence of beard involvement (in males) | | 22 (71%) |
| SALT score: Severity of alopecia tool score, AA: Alopecia areata | | |

| Table 3. DASS-21 and DTS scores of groups | | | |
|---|---|---|---|
| | **Median (Q1-Q3)** | | **p*** |
| | **AA** | **Control** | |
| DASS-21-D | 4.00 (2.00-9.50) | 2.00 (1.00-4.00) | 0.002 |
| DASS-21-A | 5.00 (2.25-7.00) | 2.00 (1.00-4.00) | 0.001 |
| DASS-21-S | 7.00 (5.00-10.00) | 4.00 (2.00-6.00) | <0.001 |
| DASS-21-total | 16.50 (10.25-24.75) | 9.50 (4.00-14.00) | <0.001 |
| DTS-tolerance | 27.00 (22.00-32.00) | 35.50 (30.00-40.00) | <0.001 |
| DTS-regulation | 7.00 (5.00-9.00) | 9.00 (6.00-12.00) | 0.011 |
| DTS-self-efficacy | 10.00 (8.00-11.00) | 12.00 (11.00-13.75) | <0.001 |
| DTS-total | 45.00 (38.00-52.25) | 57.00 (50.25-63.5) | <0.001 |
| *Mann-Whitney U test, AA: Alopecia areata, DTS: Distress Tolerance Scale, DASS-21: Depression Anxiety Stress Scale-21, DASS-21-D: Anxiety Stress Scale-21-depression, DASS-21-A: Depression Anxiety Stress Scale-21-anxiety, DASS-21-S: Depression Anxiety Stress Scale-21-stress | | | |

| Table 4. Serum neurotrophin values of AA and control groups | | | |
|---|---|---|---|
| | **Median (Q1-Q3)** | | **p*** |
| | **(n)** | | |
| | **AA** | **Control** | |
| BDNF (ng/mL) | 20.13 (12.38-36.58) (n=50) | 22.96 (11.15-83.92) (n=49) | 0.452 |
| NGF (pg/mL) | **9.08** (6.88-16.77) (n=50) | 7.16 (4.10-12.92) (n=48) | **0.020** |
| NT-3 (pg/mL) | 8.90 (4.71-30.47) (n=47) | 6.93 (4.41-27.75) (n=45) | 0.693 |
| NT-4 (ng/mL) | 1.99 (0.71-4.69) (n=49) | **3.09** (1.57-5.33) (n=49) | **0.040** |
| *Mann-Whitney U test, AA: Alopecia areata, BDNF: Brain-derived neurotrophic factor, NGF: Nerve growth factor, NT-3: Neurotrophin-3, NT-4: Neurotrophin-4 | | | |

**Table 5. Relationship between serum neurotrophin levels and DASS-21 and DTS scores in AA group**

| | | BDNF (ng/mL) | NGF (pg/mL) | NT-3 (pg/mL) | NT-4 (ng/mL) |
|---|---|---|---|---|---|
| DASS-21-D | r | 0.218 | -0.241 | -0.217 | 0.000 |
| | p | 0.128 | 0.091 | 0.142 | 0.998 |
| DASS-21-A | r | 0.194 | -0.095 | 0.025 | -0.230 |
| | p | 0.177 | 0.514 | 0.866 | 0.112 |
| DASS-21-S | r | 0.305 | -0.109 | -0.062 | -0.037 |
| | p | **0.031** | 0.453 | 0.681 | 0.801 |
| DASS-21-total | r | 0.257 | -0.156 | -0.123 | -0.107 |
| | p | 0.071 | 0.278 | 0.411 | 0.463 |
| DTS-tolerance | r | -0.050 | -0.128 | -0.177 | -0.074 |
| | p | 0.729 | 0.375 | 0.234 | 0.614 |
| DTS-regulation | r | 0.045 | 0.124 | -0.038 | 0.188 |
| | p | 0.756 | 0.391 | 0.801 | 0.196 |
| DTS-self-efficacy | r | 0.087 | -0.052 | -0.099 | -0.077 |
| | p | 0.548 | 0.717 | 0.508 | 0.600 |
| DTS-total | r | 0.011 | -0.081 | -0.149 | -0.030 |
| | p | 0.940 | 0.578 | 0.319 | 0.839 |

r: Spearman Correlation Coefficient, DASS-21: Depression Anxiety Stress Scale-21, DTS: Distress Tolerance Scale, AA: Alopecia areata, BDNF: Brain-derived neurotrophic factor, NGF: Nerve growth factor, NT-3: Neurotrophin-3, NT-4: Neurotrophin-4, DASS-21-D: Anxiety Stress Scale-21-depression, DASS-21-A: Depression Anxiety Stress Scale-21-anxiety, DASS-21-S: Depression Anxiety Stress Scale-21-stress

## Discussion

AA is an autoimmune disease that has a multifactorial etiology. The role of stress and psychological factors in the course of AA is crucial. Although AA has little physical detrimental effect, it may cause psychological consequences[3,14,15]. It was shown that psychiatric disorders such as anxiety and depression are more common in AA patients[16-19]. Similarly, we found that depression and anxiety scores were significantly higher in the AA group than in the control group.

The relationship between AA and psychiatric disorders is bidirectional. Psychiatric disorders can trigger the onset and exacerbation of AA; on the other hand, AA causes psychological problems[4,20]. In our study, although AA patients had significantly higher depression and anxiety scores, it is not clear whether anxiety and depression are the cause or the result of the disease.

The relationship between AA and psychological stress is also bidirectional and complex. Hair follicles are both targets and sources of stress hormones[21]. Stress can trigger the onset of AA by altering immune responses associated with neuropeptides[22]. Stress is thought to cause follicle damage and AA by inhibiting the production of adrenocorticotropic hormone (ACTH), alpha-melanocyte-stimulating hormone, and the ACTH-releasing hormone[23]. Manolache and Benea[24] found that the mean number of stressful events was significantly higher in AA patients. Brajac et al.[25] found that the number of people who experienced four stressful events in the last 6 months was significantly higher in AA patients compared to the control group. In addition, anxiety and stress scores were significantly higher in both the first episodes of AA and the patient group with relapse compared to the healthy control group[25]. Arbabi et al.[26] also showed the relationship between hair loss and stress, stress intensity, and stressful events. In our study, consistent with the literature, the stress scores were significantly higher in AA patients than in healthy controls.

The higher incidence of depression, anxiety, and stress in AA patients indicates that a holistic approach to the disease is necessary. Vallerand et al.[27] showed that major depressive patients treated with antidepressants had a reduced risk of AA compared to patients who did not take antidepressants. They concluded that antidepressants had a protective effect on the development of AA[27]. It is crucial to detect psychiatric comorbidities in AA patients, and the course of AA may change with the psychiatric treatment.

Distress tolerance has been defined as the capacity to experience and withstand psychological stress[10]. Distress in AA patients appears to be primarily linked to changes in physical appearance[28]. In psoriasis, a psychodermatologic disease, distress tolerance was lower in patients than in the control group[29]. In our study, the DTS scores were lower in AA patients. Similarly, Gurok and Gocer Gurok[30] found that distress tolerance levels were low in AA patients. In the presence of high psychological distress and distress tolerance, AA patients should be referred to psychiatrists to increase coping strategies.

AA is an autoimmune hair follicle disease characterized by intra- and perifollicular inflammatory cell infiltrates composed of $CD4^+$ and $CD8^+$ T-lymphocytes, macrophages, and Langerhans cells. Abnormal expression of HLA class I and II in keratinocytes of hair follicles causes autoimmune attack by $CD8^+$ T-lymphocytes. Subsequently, it leads to inflammatory cell infiltration in and around the hair follicle[31]. Inflammation in AA may also play a role in the pathogenesis of psychiatric comorbidities. Based on the relationship between inflammation, AA and psychiatric diseases, we evaluated the relationship between neurotrophins and psychological stress in patients with AA.

Neurotrophins have various non-neurotrophic functions in the skin[6-8]. They also play roles in the pathogenesis of inflammatory dermatoses characterized by cell loss or hyperproliferation through neurogenic inflammatory processes or by causing an imbalance in cytokine

production and autoimmune responses[5]. A study on mouse dorsal skin showed that NGF and BDNF levels are increased in the outer and inner root sheath. In contrast, apoptotic receptor p75NTR is upregulated in the outer root sheath in the dermal papilla[31]. Neurotrophins and their receptors are expressed differently among immune cell groups in the skin affected by AA. Neurotrophins are strongly expressed in macrophages found in the inflammatory cell infiltrate around hair follicles. $CD8^+$ cells in the inflammatory infiltrate have been shown to express p75NTR[6]. In light of these findings, it can be said that neurotrophins can modulate AA development by targeting cutaneous nerves, immune cells, and hair follicle keratinocytes[31]. In our study, while serum BDNF and NT-3 levels did not differ between groups, serum NGF levels were higher, and serum NT-4 levels were lower in AA patients. Therefore, it can be thought that the increase in NGF and decrease in NT-4 levels may be related to the pathogenesis of AA. Considering the significant differences in the scores of DASS-21 and DTS scales, we can say that there may be a biological predisposition that may lead to neuropsychiatric disorders in AA patients.

Few studies in the literature investigated the relationship between AA and neurotrophins[32-34]. Erfan et al.[32] showed no difference in serum BDNF levels between the AA and control groups, similar to our study. Kang and Gao[33] found that NGF expression was significantly lower in AA patients compared to the control group. In the study of Meyronet et al.[34], no difference was found between the AA and control groups in terms of NGF and NGF receptor expression on the scalp. We did not measure neurotrophins in AA-affected skin, which can be considered a limitation of our study.

The stress response has been associated with an increase in serum levels of neurotrophins, which may be the cause of the stress-induced aggravation of skin diseases[8]. Experimentally induced stress can have strong effects on the expression of neurotrophins, especially BDNF in animals[35]. Peters et al.[36] showed that NGF expression in hair follicles increased with stress stimulation in mice. In an animal study by Joachim et al.[37], stress or exogenous NGF administration was found to increase neurogenic inflammation, and it was assumed that this inflammation might affect the hair follicle cycle and exacerbate AA. Our study found a significant correlation between stress and BDNF in the same way. Neurotrophin values could not be measured in the tissue; this may be why we did not find a relationship between other scales and neurotrophin levels.

Similar to our study design, Altunay et al.[38] evaluated levels of depression, anxiety, stress, and neurotrophins in lichen simplex chronicus patients. They showed that the scores of Stress Scale-10, Hospital Anxiety, and Depression Scale were statistically higher; serum levels of neurotrophins were significantly lower in patients compared to controls. They concluded that the low levels of neurotrophins might be directly related to the etiology of LSC or associated with the concomitant psychiatric disorders in that patient population[38].

### Study Limitations

Our study has several important implications. First, our results emphasize the relationship between AA and psychological distress. However, according to our results, it is not clear whether psychological distress is the cause or the result of the disease. In this context, more cohort studies are needed to determine the direction of the relationship between AA and psychiatric disorders. Second, to our knowledge, our study is the first to examine the relationship between neurotrophins and psychological distress in AA patients. While BDNF and NT-3 levels did not differ significantly between groups, NGF levels were higher, and NT-4 levels were lower in the AA group compared to the control group. Third, our findings are valuable in demonstrating the importance of a multidisciplinary approach to AA patients.

## Conclusion

Stress and neurotrophins play important roles in the pathogenesis of AA. Large-scale studies investigating serum and tissue neurotrophin levels in larger patient groups are needed to understand AA's pathogenesis better and identify future treatment targets. Considering the role of neurotrophins in hair growth control, selective neurotrophin receptor agonists and antagonists can be considered treatment targets in the future. Thus, better management of AA can be achieved.

### Ethics

**Ethics Committee Approval:** The Eskişehir Osmangazi University Local Ethics Committee approved the study protocol (approval number: 29, date: 11.04.2019).

**Informed Consent:** Informed consent was obtained from those who agreed to participate in the study.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: H.P.S., H.K.E., E.K., A.E.A., Concept: H.P.S., H.K.E., E.A., E.K., A.E.A., Z.N.S., M.B., Design: H.P.S., H.K.E., E.A., E.K., A.E.A., Z.N.S., M.B., Data Collection or Processing: H.P.S., H.K.E., E.A., E.K., A.E.A., M.B., Analysis or Interpretation: H.P.S., H.K.E., E.A., E.K., A.E.A., Z.N.S., M.B., Literature Search: H.P.S., H.K.E., Writing: H.P.S., H.K.E.

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