How to Cite:
Basha, M. A., Elgarawany, M. M. E., & Ramadan, A. N. (2022). Correlation between serum brain-derived neurotrophic factor level and depression severity in alopecia areata patients. *International Journal of Health Sciences*, *6*(S4), 3116–3123.
https://doi.org/10.53730/ijhs.v6nS4.9899

Correlation between serum brain-derived neurotrophic factor level and depression severity in alopecia areata patients

Mohammed A. Basha
MD, Dermatology Andrology and STDs Department, Faculty of Medicine, Menoufia University, Menoufia Egypt
Email: mohammedbasha@yahoo.com

Marwa M. E Elgarawany
M.B.B.Ch, Dermatology Andrology and STDs Department, Faculty of Medicine, Menoufia University, Menoufia Egypt
Corresponding author email: elgaramarwa@gmail.com

Ahmed Nabil Ramadan
MD, Psychiatry Department, Faculty of Medicine, Menoufia University, Menoufia Egypt

***Abstract*---**Background: Alopecia areata (AA) is a type of non-scarring hair loss affecting anagen stage hair follicles with a multifactorial autoimmune pathogenesis and an unknown etiology. It affects about 2-3% of new patients attending Dermatology Clinics, presenting a wide range of clinical heterogeneity. Objectives: To investigate the correlation between serum BDNF level and depression severity in alopecia areata patients. Methods: The present study had been carried out on 50patients suffering from Alopecia Areata. A written informed consent was obtained from all subjects and approval of the Ethics committee will be sought. Results: Obtained data were presented as mean ± SD, ranges, numbers and percentages as appropriate. Nominal variables were analyzed using Chi-squared (x2) test. Continuous variables were analyzed using unpaired Student's t-test or Univariate two-group repeated measures "mixed-design" analysis of variance (ANOVA) with post hoc Dunnett's test as appropriate. Nominal and non-normally distributed variables were analyzed using Mann-Whitney U test. Statistical calculations were performed using Microsoft® Office Excel 2016 and SPSS (Version 20, 2011). P value < 0.05 was considered statistically significant. Conclusion: This analytical cross-sectional study revealed that the lower serum BDNF level, the higher the severity of depression and Alopecia Areata will be.

***Keywords*---**alopecia areata, brain-derived neurotrophic factor, depression severity, hair follicle, hair shaft.

Introduction

Alopecia areata (AA) is a type of non-scarring hair loss affecting anagen stage hair follicles with a multifactorial autoimmune pathogenesis and an unknown etiology. It affects about 2-3% of new patients attending Dermatology Clinics, presenting a wide range of clinical heterogeneity. [1] AA involves the scalp and any hair-bearing body surface, with possible nail localization in 10% of patients. A wide spectrum of clinical presentation can occur from single or multiple patches of hair loss to a complete hair loss on the scalp (alopecia totalis) or the entire body (alopecia universalis); the affected skin appears normal or slightly erythematous and edematous. [2]

Most cases of alopecia areata resolve spontaneously within 1 year, but up to 25% develop into severe forms such as alopecia totalis and alopecia universalis. Medications for AA are still being developed and researched, and hopefully will provide a suitable treatment for alopecia in the future. [2] AA can present with other autoimmune diseases such as thyroiditis and atopy.Multiple lines of evidence also suggest there is shared genetic risk factors between AA and other autoimmune diseases such as rheumatoid arthritis and type I diabetes. AA has also been found to have a considerable impact in a health-related quality of life (HRQoL). AA can usually be easily diagnosed. However, if the diagnosis is unclear, a scalp biopsy may be beneficial and demonstrate classic histopathologic features of AA. [1] Brain-derived neurotrophic factor (BDNF), is a protein which is a member of the neurotrophin family of growth factors that induce the survival, development, and function of neurons. It is found originally in the brain, but also found in the periphery. In the brain, it is active in the hippocampus, cortex, cerebellum, and basal forebrain ; areas vital to learning, memory, and higher thinking. BDNF is the second neurotrophic factor to be characterized, after NGF and before neurotrophin-3. BDNF produced in the CNS is transported through the blood–brain barrier and contributes to 70-80% of circulating BDNF. [3]

Depression is a serious health problem that can affect people of all ages, including children and adolescents. It is generally defined as a persistent experience of a sad or irritable mood as well as anhedonia, a loss of the ability to experience pleasure in nearly all activities. It also includes a range of other symptoms such as change in appetite, disrupted sleep patterns, increased or diminished activity level, impaired attention and concentration, and markedly decreased feelings of self-worth. [4]

Bath et al. [5] showed that BDNF level in depressed patients is also low. Psychological stress will reduce BDNF level through activation of the hypothalamic-pituitary-adrenal axis and sympathetic-adrenal-medullary axis which will increase cortisol and neuroinflammation cytokines and reduce BDNF level. The aim of this study to investigate the correlation between serum BDNF level and depression severity in alopecia areata patients.

Methods

The present study had been carried out on 50 patients suffering from Alopecia Areata. A written informed consent was obtained from all subjects and approval of the Ethics committee will be sought. This was an analytical cross-sectional study, including 50 patients suffering from alopecia areata. This study was recruited from the outpatient clinic of the Dermatology and Venereology Department, Menoufia University Hospital. Inclusion criteria: All patients will be enrolled in the study will have: Clinically typical alopecia areata lesions with different clinical varieties of alopecia areata. Different degrees of severity of alopecia areata. Age 20-65 years old. Willing to take part in the study and sign an informed consent letter.

Exclusion criteria: Patients with alopecia areata on topical or systemic therapy. Patients with other autoimmune disorders ex: (Atopic dermatitis – vitiligo – psoriasis). Patients suffering from bipolar disorder, schizophrenia and used antidepressant drugs. Laboratory study: Measurement of BDNF serum level using human brain-derived neurotrophic factor kit and ELISA method. The Human BDNF ELISA (Enzyme-Linked Immunosorbent Assay) kit is an in vitro enzyme-linked immunosorbent assay for the quantitative measurement of human BDNF in serum, plasma, cell culture supernatants and urine. The brain derived neurotrophic factor (BDNF) gene is mapped to human chromosome 11p14.1.BDNF is a member of the neurotrophin family of growth factors. The gene encodes a precursor protein, proBDNF. Mature BDNF (mBDNF) is synthesized by post-translational cleavage of proBDNF. Both proBDNF and mBDNF play crucial roles in cellular signaling. Informed consent: A written informed consent was taken from every patient before participation in this study.

Statistical analysis

Data were statistically analyzed using Statistical Package for the Social Sciences (SPSS) version 23 (SPSS Inc. Released 2015. IBM SPSS statistics for windows, version 23.0, Armnok, NY: IBM Corp.). Data were expressed as number and percentage for qualitative variables and mean + standard deviation (SD) for quantitative one.

Results

Shows general demographic data of included subjects. Age ranged from 20 to 65 years, 54% of included subjects were males and 46% were females. Mean weight was 88.5 kg with SD of 15.64 kg. Mean height was 175cm with SD of 20 Cm. From the all included subjects 7 were between 20, 29 years old, 15 were between 30 and 39 years old, 15 were between 40 and 49 years old, 11 were between 50 and 59 years old and only 2 were between 60 and 65 years old (Table 1, Figure 1). Show that 76% of included subjects have limited patches of A.A. while 24% have Extensive patchy A.A. Shows that 29 subjects (58%) have mild A.A, 9 subjects (18%) have moderate A.A. and 12 subjects (24%) have severe A.A. Shows that in 33 subjects (66%) there was a spontaneous recovery while only 6 subjects (12%) showed development of Aloplecia Totalis/Universalis. In 11 subject (22%) there were no change, neither development of Aloplecia Totalis/Universalis nor recovery

(Table 2, Figure 2). This study found that the average serum BDNF level was 912.45 ± 180.94 pg/ml as in (Table 3).

Table (1) General demographic data of all included subjects

General Demographic Data	N = 50 (100%)
Age (years) Sex Weight (Kg) Height (Cm)	20 - 65 (n=27) 54% Males | Females 46% (n=23) 88.5 ± 15.64 175 ± 20
Age group: 20-29 30-39 40-49 50-59 60 - 65 Height	 (n=7) 14% (n=15) 30% (n=15) 30% (n=11) 22% (n=2) 4%

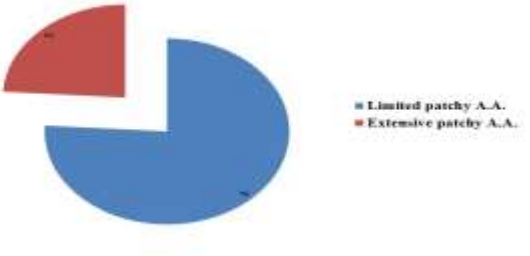

Figure (1): Percentage of subjects included in different age groups.

Table (2): Types of Alopecia areata patches Shows A.A. severity Course of disease in included patients

Patches of Alopecia areata	Percentage
Limited patchy A.A. Extensive patchy A.A.	76% (n=38) 24% (n=12)
Mild Moderate Severe	58% (n=29) 18% (n=9) 24% (n=12)
Develop to Aloplecia Totalis/Universalis Spontaneous recovery No change	 12% (n=6) 66% (n=33) 22% (n=11)

Table (3): Correlation between serum brain-derived neurotrophic factor level and depression Severity in Aloplecia areata Patients and Aloplecia severity

Serum BDNF level (Mean ± SD) 912,45 ± 180,9	
p	r r^2

Serum BDNF level and depression severity	0,001	-0,667	0,445
Serum BDNF level and Aloplecia severity	0,0016	-0,595	0,354

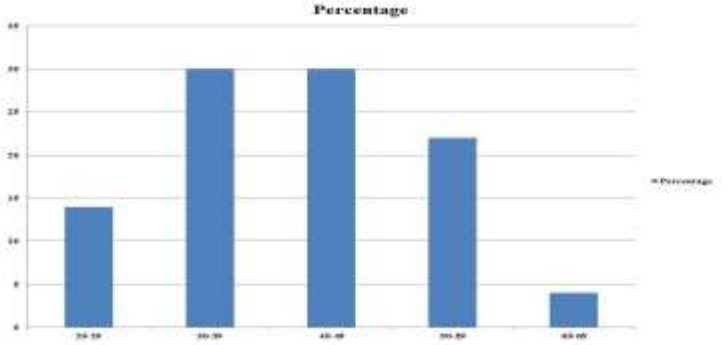

Figure (2): Pie chart shows types of Alopecia areata patches in included subjects.

Discussion

Alopecia areata is a common hair loss condition that is characterized by acute onset of non-scarring hair loss in usually sharply defined areas ranging from small patches to extensive or less frequently diffuse involvement. Depending on its acuity and extent, hair loss is an important cause of anxiety and disability. The current understanding is that the condition represents an organ-specific autoimmune disease of the hair follicle with a genetic background. [6]

Genome-wide association studies provide evidence for the involvement of both innate and acquired immunity in the pathogenesis, and mechanistic studies in mouse models of alopecia areata have specifically implicated an IFN-γ-driven immune response, including IFNγ, IFNγ-induced chemokines and cytotoxic CD8 T cells as the main drivers of disease pathogenesis. A meta-analysis of published trials on treatment of alopecia areata states that only few treatments have been well evaluated in randomized trials. Nevertheless, depending on patient age, affected surface area and disease duration, an empiric treatment algorithm can be designed with corticosteroids and topical immunotherapy remaining the mainstay of therapy. The obviously limited success of evidence-based therapies points to a more important complexity of hair loss. At the same time, the complexity of pathogenesis offers opportunities for the development of novel targeted therapies. [7]

New treatment opportunities based on the results of genome-wide association studies that implicate T cell and natural killer cell activation pathways are paving the way to new approaches in future clinical trials. Currently, there are ongoing studies with the CTLA4-Ig fusion protein abatacept, anti-IL15Rβ monoclonal antibodies and the Janus kinase inhibitors tofacitinib, ruxolitinib and baricitinib. [8]. Brain-derived neurotrophic factor (BDNF) is a protein which is a member of the neurotrophin family of growth factors that induce the survival, development, and function of neurons. It is found originally in the brain, but also found in the periphery. In the brain, it is active in the hippocampus, cortex, cerebellum, and

basal forebrain; areas vital to learning, memory, and higher thinking. BDNF is the second neurotrophic factor to be characterized, after NGF and before neurotrophin-3. BDNF produced in the CNS is transported through the blood–brain barrier and contributes to 70-80% of circulating BDNF. [9]

Depression is a serious health problem that can affect people of all ages, including children and adolescents. It is generally defined as a persistent experience of a sad or irritable mood as well as anhedonia, a loss of the ability to experience pleasure in nearly all activities. It also includes a range of other symptoms such as change in appetite, disrupted sleep patterns, increased or diminished activity level, impaired attention and concentration, and markedly decreased feelings of self-worth. [10] In this study we aim to investigate the correlation between serum BDNF level and depression severity in alopecia areata patients.

This analytical cross-sectional study was carried out in the Dermatology and Venereology Department, Faculty of Medicine, Menoufia University Hospitals. Fifty patients suffering from alopecia areata have participated. Our results showed that Age ranged from 20 to 65 years, 54% of included subjects were males and 46% were females. Mean weight was 88.5 kg with SD of 15.64 kg. Mean height was 175cm with SD of 20 Cm. From all included subjects 7 were between 20, 29 years old, 15 were between 30 and 39 years old, 15 were between 40 and 49 years old, 11 were between 50 and 59 years old and only 2 were between 60 and 65 years old.

As regard Types of Alopecia areata patches, 76% of included subjects have limited patches of A.A. while 24% have Extensive patchy A.A. Regarding A.A. severity, 29 subjects (58%) have mild A.A, 9 subjects (18%) have moderate A.A. and 12 subjects (24%) have severe A.A. As for Course of disease in included patients, in 33 subjects (66%) there was a spontaneous recovery while only 6 subjects (12%) showed development of Aloplecia Totalis/Universalis. In 11 subject (22%) there were no change, neither development of Alopecia Totalis/Universalis nor recovery. Regarding Depression Severity and its percentage in the included subjects, 12 subjects (24%) showed no depression while only 1 subject (2%) showed severe depression. Prevalence of minimal, mild and moderate depression were 30%, 18% and 26% respectively.

This study found that the average serum BDNF level was 912.45 ± 180.94 pg/ml. There was a p value of 0.001 to the Serum BDNF level and depression severity and a p value of 0.0016 to the Serum BDNF level and Aloplecia severity. There is a strong correlation between serum brain-derived neurotrophic factor and depression severity and a weak correlation between serum brain-derived neurotrophic factor and Alopecia Areata severity. Sjahrir et al. [11] reported that Serum BDNF level and depression severity were analysed with Spearman correlation, the value of the correlation coefficient (r) was -0.667 with a significance value (p) of 0.001. There is a strong negative correlation between serum BDNF level with depression severity. The lower serum BDNF level, the higher the severity of depression will be. The coefficient of determination (r2) in this analysis was found 45%, which indicate that 45% factor that influence

severity of depression was serum BDNF level, and the remaining 55% are other factors.

Fathy et al. [12] reported that BDNF level was lower in both groups of psoriasis (without depression 25.2 ± 6.5; with depression 16.9 ± 2.5) compared to the healthy control group (26.5 ± 3.6). BDNF level was significantly lower in psoriasis vulgaris patients with depression compared to psoriasis patients who did not suffer from depression (mean difference 8.3; $p < 0.001$). BDNF level was also significantly lower in psoriasis vulgaris patients with depression and depressed patients without psoriasis compared to healthy controls ($p < 0.0001$ and $p < 0.001$). The mean BDNF level was significantly lower ($p < 0.01$) in the group of psoriasis patients with depression (16.9 ± 2.5) compared to depressed patients without psoriasis vulgaris (21.5 ± 5.8)

Duclot and Kabbaj, [13] reported that low BDNF level was known to play a role in depression pathophysiology, but can be increased by antidepressant. However, BDNF level in serum does not correlate with depression severity. Therefore, utilisation of BDNF as a biomarker of depression is still unclear. The role of BDNF in depression is proven by the presence of four things. First, depression causes a decrease in BDNF level in the hippocampus and the prefrontal cortex. Second, depression triggers atrophy of the nerve dendrites in the hippocampus and the prefrontal cortex. Third, there is evidence of increased BDNF level in the hippocampus and the prefrontal cortex after administration of antidepressant. Fourth, the BDNF level increased in the amygdala and neural accumbent area which facilitate symptoms of depression. Therefore, Yu et al. concluded that depressive symptoms depend on BDNF level in the affected anatomic location. [14]

A study conducted by Botchkarev et al. [15] reported that there was no difference ($p = 0.59$) BDNF level in patients with mild psoriasis (3649 ± 3653 pg/ml) and severe psoriasis (3280 ± 2837 pg/ml). However, in Sjahrir et al. [11] psoriasis severity was not assessed with the PASI score, but was classified according to the presence of psoriatic arthritis and the used of systemic therapy such as methotrexate, cyclosporine, mycophenolate mofetil, biological agents and phototherapy. Raap et al. [16] reported that there was no correlation between BDNF level and PASI score. However, in their published article did not mention the mean of BDNF level in psoriasis patients, maybe because it was not the main purpose of their study

Conclusions

This analytical cross-sectional study revealed that the lower serum BDNF level, the higher the severity of depression and Alopecia Areata will be. Serum BDNF level might be considered as a biomarker of depression severity as well as a biomarker of Alopecia severity in patients with Alopecia Areata. BDNF might be the new Alopecia treatment target. However, further investigations with better design are still needed to prove this result.

No Funding
No conflict of interest

References

1. Hordinsky M and Junqueira AL. Alopecia areata update. Semin Cutan Med Surg. 2015; 34: 72-75.
2. Ganzetti G, Simonetti O, Campanati A, Giuliodori K, Scocco V, Brugia M, et al. Osteopontin: a new facilitating factor in alopecia areata pathogenesis?. Acta dermatovenerologica Croatica. 2015;23(1):19-20.
3. Rasmussen P, Brassard P, Adser H, Pedersen MV, Leick L, Hart E, et al. Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. Experimental physiology. 2009;94(10):1062-9.
4. Merrell KW. Helping children overcome depression and anxiety: A practical guide. New York: Guilford. 2001;1(1):21-22.
5. Bath KG, Schilit A, Lee FS. Stress effects on BDNF expression: effects of age, sex, and form of stress. Neuroscience. 2013; 239: 149-156.
6. FINNER AM. Alopecia areata: Clinical presentation, diagnosis, and unusual cases. Dermatologic Therapy. 2011;24(3), 348–354.
7. Kyriakis KP, Paltatzidou K, Kosma E, Sofouri E, Tadros A, Rachioti E. Alopecia areata prevalence by gender and age. Journal of the European Academy of Dermatology and Venereology: JEADV. 2008;23(5):572-3.
8. Trüeb RM, Dias MF. Alopecia areata: a comprehensive review of pathogenesis and management. Clinical reviews in allergy & immunology. 2018;54(1):68-87.
9. Bathina S, Das UN. Brain-derived neurotrophic factor and its clinical implications. Arch Med Sci. 2015;11(6):1164-78.
10. Kanter JW, Busch AM, Weeks CE, Landes SJ. The nature of clinical depression: Symptoms, syndromes, and behavior analysis. The Behavior Analyst. 2008;31(1):1-21.
11. Sjahrir M, Roesyanto-Mahadi ID, Effendy E. Correlation between serum brain-derived neurotrophic factor level and depression severity in psoriasis vulgaris patients. Open access Macedonian journal of medical sciences. 2019;7(4):583.
12. Fathy H, Tawfik AA, Madbouly N. Evaluation of serum brain-derived neurotrophic factor to assess the association between psoriasis and depression. Journal of the Egyptian Women's Dermatologic Society. 2015;12(3):186-90.
13. Duclot F, Kabbaj M. Epigenetic mechanisms underlying the role of brain-derived neurotrophic factor in depression and response to antidepressants. Journal of Experimental Biology. 2015;218(1):21-31.
14. Yu H, Chen Z. The role of BDNF in depression on the basis of its location in the neural circuitry. Acta Pharmacologica Sinica. 2011;32(1):3–11.
15. Botchkarev VA, Yaar M, Peters EM, Raychaudhuri SP, Botchkareva NV, Marconi A, et al. Neurotrophins in skin biology and pathology. Journal of investigative dermatology. 2006;126(8):1719-27.
16. Raap U, Werfel T, Goltz C, Deneka N, Langer K, Bruder M, et al. Circulating levels of brain-derived neurotrophic factor correlate with disease severity in the intrinsic type of atopic dermatitis. Allergy. 2006;61(12):1416-8.