The Relationship Between Trichotillomania and Serum Brain-Derived Neurotrophic Factor Levels in Children and Adolescents: A Case-Control Study

İsmail Akaltun, MD

Objective: Trichotillomania (TTM) is a clinical psychiatric manifestation involving significant hair loss in association with recurrent hair-pulling behavior, the etiology of which is still unknown. Insufficiency or disorder in the synthesis of brain-derived neurotrophic factor (BDNF) is reported to be potentially associated with neurological, neurodegenerative, and psychiatric diseases in humans and animals. This study examines the relationship between serum BDNF levels and TTM.

Methods: Ninety-four children and adolescents, 47 patients with TTM and a 47-member control group, were included in the study. Participants were administered the Schedule for Affective Disorders and Schizophrenia for School-Aged Children (6–18 Years) Present and Lifetime Version, and the members of the case group completed the Clinical Global Impression scale. Serum BDNF levels were determined from blood specimens collected from the study and control groups, and the results were subjected to statistical analysis.

Results: Serum BDNF levels were 11.06 ± 1.9 ng/mL in the TTM group and 13.78 ± 2.2 ng/mL in the control group. Serum BDNF was significantly lower in the case group than in the control group. Moderate negative correlation was also determined between Clinical Global Impression scores and serum BDNF levels in the case group.

Conclusions: Low serum BDNF was associated with TTM and the severity thereof. Furthermore, more extensive studies are needed to elucidate this association.

Key Words: trichotillomania, BDNF, child and adolescent

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For the diagnosis of trichotillomania (TTM), the person must pull their hair repeatedly to cause hair loss, there must be repeated attempts to reduce or stop the hair pulling, and the hair pulling must cause clinically significant distress or impairment in at least one area of functionality.[1] Several studies have reported that the onset of TTM occurs in childhood or adolescence. Hair pulling is most commonly observed in TTM, together with, less frequently, pulling out hairs from other parts of the body, such as the eyebrows, eyelashes, beard-mustache, armpits, and groin.[2,3] Although there is no consensus concerning the cause of TTM, the disorder is thought to probably involve a complex interaction between more than one pathway and genetic, psychological, and social factors. Studies have shown that neurotransmitters, such as serotonin, dopamine, and γ-aminobutyric acid, are associated with TTM in addition to alterations in reward processing and impulse control.[4,5]

Department of Psychology, Faculty of Socıal Sciences, Hasan Kalyoncu University, Gaziantep, Turkey.

Address correspondence and reprint requests to İsmail Akaltun, MD, Department of Psychology, Faculty of Social Sciences, Hasan Kalyoncu University, Gaziantep, Turkey; E-mail: drmahirx@hotmail.com

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Brain-derived neurotrophic factor (BDNF) is a neurotrophic factor that affects synaptic and neuronal life, growth, and functions in the central and peripheral nervous systems, that provides the stabilization and plasticity of synapses, and that regulates axon and dendrite branching. Brain-derived neurotrophic factor essentially assists the growth and renewal of neurons in the central nervous system and contributes to the structural health and maintenance of important nerve pathways.[6,7] It is involved in neurogenesis of critical importance to synaptic formation in cognitive processes and dopaminergic, glutamatergic, and serotonergic neuronal transmission. Its principal reported effect is on region-specific synaptic function and neuronal morphology.[8] It is responsible for short-term memory and long-term potential and is involved in recall, cognition, emotional state, spatial orientation, and learning.[9] Insufficiency or disorder in the synthesis of BDNF is reported to be potentially associated with neurological, neurodegenerative, and psychiatric diseases in humans and animals. Brain-derived neurotrophic factor has therefore become a neurotrophin frequently researched in recent years in the context of neuropsychiatric diseases, such as mood disorders, schizophrenia, anxiety disorders, neurodevelopmental disorders, dependence, and eating disorders.[8] The aim of the present study was to examine the relationship between serum BDNF levels and TTM and the severity thereof and to evaluate this through comparison with a control group.

MATERIAL AND METHODS

This study was planned after obtaining approval from the ethics committee as a prospective case-controlled study evaluating serum BDNF levels. Forty-seven patients presenting to the Gaziantep Dr Ersin Arslan Education and Research Hospital Child and Adolescent Psychiatry Clinic, Turkey, with symptoms of TTM and 47 children and adolescents with no psychiatric diagnoses presenting to the biochemistry laboratory from other clinics for blood tests and consenting to take part were included in the study. We planned to compare patients diagnosed with TTM and healthy children and adolescents in terms of serum BDNF levels.

Children and adolescents aged 6 to 18 years and consenting to participate were enrolled in the study. Individuals diagnosed with pervasive developmental disorder or intellectual disability (IQ < 70), those not aged 6 to 18 years, and those unwilling to take part were excluded from the study. The study content was explained to the case and control groups and their families, and informed consent forms were obtained from those consenting to participate.

Sociodemographic data (age, sex, education, and premorbid characteristics) were obtained from parents before evaluation. Presenting parents were interviewed, and face-to-face interviews were also held with the children. Participants were administered the Turkish version of the Schedule for Affective Disorders and Schizophrenia for School-Aged Children (6–18 Years) Present and Lifetime Version (K-SADS-PL-T).[10] This is administered by means of interview with the parents and the child, a final evaluation being produced based on information elicited from all sources.

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TABLE 1. Case and Control Group Sociodemographic Data and Serum BDNF Levels

	Case	Control	*P*
n	47	47	
Sex, female	26 (55%)	24 (51%)	0.67*
Sex, male	21 (45%)	23 (49%)	0.67*
Age, y	12.7 ± 2.2	12.5 ± 2.1	0.97†
Length of education, y	4.6 ± 1.1	4.8 ± 1.2	0.49†
Maternal age, y	36.3 ± 3.6	37.1 ± 3.3	0.32†
Length of maternal education, y	8.8 ± 2.4	8.5 ± 2.4	0.36†
Paternal age, y	40.8 ± 3.9	40.5 ± 4	0.32†
Length of paternal education, y	9.2 ± 4	8.7 ± 3.2	0.38†
No. siblings	2.1 ± 1.1	1.9 ± 0.9	0.32†
Parents living together	38	44	0.063*
Parents separated	9 (19%)	3 (6%)	0.063*
Maternal history of any psychiatric treatment	13 (27%)	4 (8%)	<0.05*
Paternal history of any psychiatric treatment	7 (14%)	3 (6%)	0.18*

A history of psychiatric disease was also more common in mothers in the case group, and the distributions of these 2 parameters differed significantly (<0.05). No statistically significant difference between the groups was observed in terms of distributions of other parameters ($P > 0.05$).

*χ^2.

†Mann-Whitney *U*.

In case of preadolescents, the mother and father were interviewed first, while adolescents were interviewed first in case of adolescence. In case of discrepancy among data obtained from different sources, the interviewer used his own clinical judgment. K-SADS-PL was adapted from K-SADS-P by Kaufman et al[11] (1997), who described K-SADS-PL as a valid and reliable diagnostic scale.

The Clinical Global Impression (CGI) scale assesses severity of illness, the patient's response to treatment and the degree thereof, and adherence to treatment.[12] It consists of 3 sections including severity of illness, improvement, and adverse effect severity. The clinician assesses severity of illness, and degree of improvement in symptoms or adverse effects on a 7-point Likert-type scale (1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = extremely ill). High scores indicate functional impairment. Only the severity index section was used in this study. (The reason for using the CGI-S scale is that we could not find Turkish validity and reliability studies of the Yale Brown Obsessive-Compulsive Scale-Trichotillomania and other scales developed for TTM in our literature review).

Five cubic-centiliter fasting venous blood specimens collected from the patient and control groups between 08:00 and 09:00 A.M. for serum BDNF measurement were placed into biochemistry tubes and allowed to stand for 120 minutes. After clotting, the specimens were centrifuged for 20 minutes at 3000 rpm and then stored at −80°C until use. Serum BDNF levels were measured using the ELISA method and following the procedure specified by the manufacturer (Cloud-Clone Corp).

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah) and IBM SPSS V23 program were used for statistical analysis. While evaluating the research data, descriptive statistical methods (mean, SD, median, frequency, percentage, minimum, maximum) were used. The conformity of the quantitative data to the normal distribution was tested with the Shapiro-Wilk test and graphical examinations. Independent groups *t* test was used for comparisons between the 2 groups of normally distributed quantitative variables, and the Mann-Whitney *U* test was used for comparisons between 2 groups of nonnormally distributed quantitative variables. Pearson correlation analysis was used to evaluate the relationships between quantitative variables. IBM SPSS V23 program was used for linear regression analysis of independent variables affecting BDNF level in the case group. Statistical significance was accepted as a *P* value of less than 0.05.

RESULTS

Girls represented 26 of the 47 cases (55.3%) of TTM included in the study, and boys 21 (44.6%), while girls represented 24 of the controls (51%) and boys 23 (49%). The mean ages were 12.7 ± 2.2 years in the case group and 12.5 ± 2.1 in the control group. There was no significant difference between the groups in terms of age or sex. There was also no significant difference between the case and control group parents in terms of age or education. The number of parents living separately was higher in the case group than in the control group, but the difference was not statistically significant. Histories of psychiatric treatment were present in 13 mothers (27.6%) and 7 fathers (14.8%) in the case group, and in 4 mothers (8.5%) and 3 fathers (6.3%) from the control group. History of psychiatric treatment was significantly more common in the case group mothers, but no significant difference was determined between the fathers in the 2 groups (Table 1).

Hair pulling was present in 32 of the TTM cases (68%), eyelash pulling in 5 (10.6%), eyebrow pulling in 3 (6.3%), hair and eyelash pulling in 3 (6.3%), hair and eyebrow pulling in two (4.2%), and hair and skin pulling in 2 (4.2%).

Serum BDNF levels were 11.06 ± 1.9 ng/mL in the TTM group and 13.78 ± 2.2 ng/mL in the control group. Serum BDNF levels were significantly lower in the case group ($P = 0.001$, $P < 0.01$; Table 2).

The mean CGI score of the TTM group was 4.9 ± 0.9. There was a moderately significant negative correlation between BDNF measurements and CGI measurements of the participants. (As BDNF measurement decreases, CGI scores increase; $r = -0.703$, $P = 0.001$, $P < 0.01$; Table 3).

TABLE 2. Comparison of Serum BDNF Levels Between Case and Control

		Total	Control (n = 47)	Case (n = 47)	*P*
BDNF	Avg ± SD	12.43 ± 2.55	13.79 ± 2.04	11.06 ± 2.27	***0.001**†
	Median (min–max)	12 (8–18)	14 (9–17)	11 (8–18)	

Serum BDNF levels were significantly lower in the case group ($P = 0.001$, $P < 0.01$).

*Student *t* test.

†$P < 0.01$.

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TABLE 3. The Relationship Between Serum BDNF Level and CGI Scores

		BDNF
CGI	*r*	−0.703
	P	***0.001****

Statistically significant, moderate, negative correlation was present between CGI scores and serum BDNF levels ($r = -0.703$, $P = 0.001$, $P < 0.01$).

r, Pearson correlation coefficient.

*Student *t* test.

In the case group, BDNF measurements did not show a statistically significant difference compared with anxiety, depression, attention-deficit/hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), substance use, conduct disorder (CD), and only TTM ($P > 0.05$; Table 4).

When linear regression analysis was performed within the case group, the regression model obtained was found to be significant ($P = 0.002$). The effect of BDNF on CGI scores was statistically significant in the presence of comorbid anxiety disorders, OCD, CD, and substance use and only in the TTM group ($P < 0.05$). As the CGI value increases by 1 U within the case group, the BDNF value decreases by 0.873 U ($\beta = -0.873$, $P < 0.05$; Table 5).

One or more additional psychiatric disease was present in 35 of the patients with TTM (74.4%). These included anxiety disorders in 28 (59.5%), depressive disorder in 21 (44.6%), ADHD in 12 (25.5%), OCD in 8 (17%), substance use disorder in 7 (14.8%), behavior disorder in 5 (10.6%), excretion disorders in 4 (8.5%), body dysmorphic disorder in 3 (6.3%), and eating disorder in 2 (4.2%).

DISCUSSION

Brain-derived neurotrophic factor, which is involved in synaptic plasticity, in addition to dendrite growth and branching, also increases the resistance of hippocampal and cortical neurons and peripheral neurons in particular, thus contributing to their survival.[13–15] It also plays a role in the regulation of neural circuit development, including embryonic neural stem cell differentiation, axonal growth and orientation, and synapse formation and maturation during brain development.[16] Brain-derived neurotrophic factor has been reported to increase presynaptic neurotransmitter release and to accelerate synaptic restructuring, to regulate TrkB-mediated dopamine release, and to affect changes in 5-HT signaling.[14,17,18] It also plays an important role in learning, memory, attention, and cognitive functions by affecting synaptic transmission and cellular excitability.[17,19,20] Several studies have shown that BDNF is involved in the pathophysiology of brain-related diseases, including psychiatric disorders. Brain-derived neurotrophic factor levels have been shown to play a role in the pathophysiology of mood disorders, with lower serum levels being reported in patients in the depressive and manic periods compared with healthy controls in a number of studies.[20–22] Studies have also reported that an association between BDNF levels and schizophrenia and anxiety disorders.[23] When studies related to OCD are examined, it has been stated that low BDNF level is generally associated with OCD.[24] In a study conducted in China, BDNF levels were found to be lower in both unmedicated and drug-treated OCD patients compared with

TABLE 4. Comparison of Serum BDNF Levels of Comorbid Diseases Among Themselves in the Case Group

		BDNF		
		Avg ± Ss	Median (Min–Max)	*P*
Anxiety + TTM	None (n = 19)	10.68 ± 1.45	11 (9–15)	***0.675**
	Yes (n = 28)	11.32 ± 2.68	11 (8–18)	
Depression + TTM	None (n = 26)	11.04 ± 2.13	11 (9–18)	***0.673**
	Yes (n = 21)	11.1 ± 2.49	11 (8–17)	
ADHD + TTM	None (n = 35)	10.83 ± 2.02	10 (8–17)	***†0.282**
	Yes (n = 12)	11.75 ± 2.86	11 (9–18)	
OCD + TTM	None (n = 39)	11.03 ± 2.37	11 (8–18)	***†0.451**
	Yes (n = 8)	11.25 ± 1.83	11 (9–15)	
substance use disorders + TTM	None (n = 40)	11.23 ± 2.36	11 (9–18)	***†0.374**
	Yes (n = 7)	10.14 ± 1.46	11 (8–12)	
CD + TTM	None (n = 42)	11.10 ± 2.38	10.5 (8–18)	***†0.671**
	Yes (n = 5)	10.80 ± 1.10	11 (9–12)	
Body dysmorphic disorders + TTM	None (n = 44)	11.09 ± 2.33	11 (8–18)	—
	Yes (n = 3)	10.67 ± 1.15	10 (10–12)	
Excretion disorders + TTM	None (n = 43)	10.91 ± 2.08	11 (8–17)	—
	Yes (n = 4)	12.75 ± 3.77	12 (9–18)	
Eating disorder + TTM	None (n = 45)	10.82 ± 1.97	11 (8–17)	—
	Yes (n = 2)	16.50 ± 2.12	16.5 (15–18)	
TTM only	None (n = 31)	11.35 ± 2.67	11 (8–18)	***0.855**
	Yes (n = 16)	10.50 ± 1.03	10.5 (9–12)	

In the case group, BDNF measurements did not show a statistically significant difference compared with anxiety, depression, ADHD, OCD, substance use, CD, and only TTM ($P > 0.05$).

*Student *t* test.

†Mann-Whitney *U*.

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TABLE 5. Regression Analysis Results for Arguments That Affect BDNF in the Case Group

	β* (95% CI)	IF	β †	*t*	*P*	Zero	Partial	The Part	VIF
Constant	15.358 (13.092 to 17.624)	1.116		13.759					
CGİ	−0.873 (−1.239 to −0.506)	0.180	−0.656	−4.835	**<0.05**	−0.605	−0.633	−0.557	1.388
Anksiyete + TTM	−2.001 (−3.476 to −0.319)	0.808	−0.543	−2.127	**0.023**	−0.275	−0.354	−0.248	3.586
Depression + TTM	−0.339 (−1.229 to 0.552)	0.439	−0.128	−0.772	0.445	−0.076	−0.129	−0.089	2.084
ADHD + TTM	−0.429 (−1.522 to 0.664)	0.539	−0.143	−0.797	0.431	−0.066	−0.133	−0.092	2.417
OCD + TTM	−2.039 (0.49 to 4.987)	0.989	0.473	2.472	**0.017**	−0.056	0.297	0.268	5.243
Substance use + TTM	−2.001 (−3.676 to −0.326)	0.825	−0.543	−2.425	**0.021**	−0.294	−0.379	−0.279	3.784
CD + TTM	2.739 (0.49 to 4.987)	1.108	0.644	2.472	**0.018**	−0.069	0.386	0.285	5.114
Body dysmorphic + TTM	−0.357 (−1.704 to 0.989)	0.663	−0.067	−0.538	0.594	−0.079	−0.091	−0.062	1.153
Excretion + TTM	0.021 (−1.256 to 1.298)	0.629	0.005	0.034	0.973	−0.015	0.006	0.004	1.351
Eating disorder + TTM	−0.577 (−2.422 to 1.268)	0.909	−0.089	−0.635	0.530	0.070	−0.107	−0.073	1.475
TTM only	2.739 (−3.87 to 0.486)	1.127	0.673	2.682	**0.019**	−0.071	0.384	0.296	4.944

When linear regression analysis was performed within the case group, the regression model obtained was found to be significant ($P = 0.002$). The effect of BDNF on CGI scores was statistically significant in the presence of comorbid anxiety disorders, OCD, CD, substance use, and only in the TTM group ($P < 0.05$). As the CGI value increases by 1 U within the case group, the BDNF value decreases by 0.873 U ($\beta = -0.873$, $P < 0.05$).

$F(11.35) = 3.670$, $P = 0.002$, $R^2 = 39.0$, SE of estimate = 1.035.

*Unclassified coefficient.

†Standardized coefficient, Durbin-Watson = 2132.

CI, confidence interval; IF, Inflation Factor; VIF, Variance Inflation Factor.

normal controls. The same research group reported that plasma BDNF levels were lower in another group of OCD patients.[25] Again, in a study conducted in Italy, serum BDNF levels of 24 unmedicated OCD patients without psychological stressors and 24 healthy control groups were evaluated. In this study, it was shown that the serum BDNF level of OCD patients was lower than the control group.[26] In a study conducted by dos Santos and colleagues,[27] they compared the serum BDNF levels of 25 healthy control group and 25 unmedicated OCD patients. Again, similar to other studies, it was noted that the serum BDNF level of OCD patients was significantly lower compared with the control group.[27]

Although various studies have investigated the relationship between serum BDNF levels and adult and pediatric psychiatric diseases, our scan of the literature revealed no previous studies investigating the relationship between serum BDNF levels and TTM. This study therefore examined the relationship between serum BDNF levels and TTM and the severity thereof, by comparing these levels with those of a control group. The mean serum level in the TTM cases in this study was 11.06, compared with 13.78 in the control group. Serum BDNF levels were significantly lower in the case group compared with the control group. After TTM and comorbid patients were divided into groups in the case group, when serum BDNF levels were compared, no statistical difference was observed between them. It was also observed that there was a moderate inverse correlation between TTM severity and serum BDNF level. In the linear regression analysis performed within the case group, the effect of BDNF on CGI scores was statistically significant in anxiety disorders, substance use, OCD, CD, and only TTM groups. This suggests that TTM may be associated with serum BDNF level and severity, independent of comorbid conditions. However, to clarify this relationship, different studies are needed in which more cases and lower serum BDNF levels are associated and comorbid conditions are excluded.

Trichotillomania being classified under the OCD in the *Diagnostic and Statistical Manual of Mental Disorders*, *Fifth Edition*, under the most recent change shows the probability that both diseases share a common etiology. From that perspective, similarly to the present study, lower BDNF levels have been determined in OCD groups compared with healthy controls in all adult studies comparing the two.[24,28,29] In general terms, studies have reported that glutamate and neuroplastic changes may play a role in the etiology of TTM in addition to serotonin and dopamine neurotransmitter systems. Because BDNF plays a role in glutamate and neuroplastic changes in addition to the regulation of neurotransmitters such as serotonin and dopamine, it seems probable that a low BDNF level may be involved in the triggering, exacerbating, or etiology of TTM.

One of the principal limitations of this study is that it was performed with children and adolescents presenting for various reasons to a hospital in a specific region. Generalizing the study as a whole to society in general may therefore be problematic. Another limitation is that we looked at the serum BDNF level of the participants. This is because it is based on the assumption that peripheral BDNF levels reflect the amount of BDNF in the brain. This may be a limitation because there are other potential sources of BDNF. Our cases did have a relatively high comorbidity compared with published studies.[30,31] We postulate that in the region where we work, patients with TTM tend to apply for the treatment of comorbid conditions, either if it is very advanced or rather than TTM. We think that mild and moderate TTM patients generally do not apply to the hospital because they think that this situation is temporary, by cutting their hair very short if they are boys, or by finding ways to wear hats to children.

In conclusion, in this study, an association was found between low serum BDNF and TTM and TTM severity. To clarify this relationship, more large-scale studies are needed in which there are more cases with a lower level of serum BDNF, as well as comorbid diseases are excluded.

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