Cortisol and Brain-Derived Neurotrophic Factor Levels Prior to Treatment in Children With Obsessive-Compulsive Disorder

Şeref Şimşek, MD[a,*]; Salih Gençoğlan, MD[b]; Tuğba Yüksel, MD[a]; İbrahim Kaplan, MD[c]; and Rümeysa Alaca, MD[a]

ABSTRACT

Objective: In this study, we investigated serum brain-derived neurotrophic factor (BDNF), adrenocorticotropic hormone (ACTH), and cortisol levels between children with obsessive-compulsive disorder (OCD) prior to treatment and healthy controls. In addition, the study aimed to assess any correlations between OCD symptom severity and BDNF, ACTH, and cortisol levels.

Methods: Twenty-nine children, aged from 7 to 17 years (male/female: 21/8) and diagnosed with OCD according to *DSM-IV* prior to treatment, were compared with 25 healthy control subjects (male/female: 16/9). The study was conducted between December 2012 and December 2013. The Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (K-SADS-PL), Children's Yale-Brown Obsessive Compulsive Scale, and Children's Depression Inventory (CDI) were administered to the children. BDNF, ACTH, and cortisol levels were detected using a prepared kit with the enzyme-linked immunosorbent assay method.

Results: BDNF, ACTH, and cortisol levels in the OCD group were significantly higher when compared with the control group ($P = .02$, $P = .03$, and $P = .046$, respectively). No association was detected between the severity and duration of OCD symptoms and BDNF, ACTH, and cortisol levels. CDI scores in both groups were similar. The mean (SD) duration of OCD symptoms was 17.9 (18.5) months.

Conclusions: Our findings suggest that BDNF levels adaptively increase as a result of the damaging effects of the hypothalamic-pituitary-adrenal (HPA) axis hyperactivity on brain tissue in the early stages of OCD. HPA axis abnormalities and BDNF may play a role in the pathogenesis of the disease.

J Clin Psychiatry 2016;77(7):e855–e859
dx.doi.org/10.4088/JCP.15m10146

[a]Dicle University, Medical School, Department of Child Psychiatry, Diyarbakır, Turkey
[b]Yüzüncü Yıl University, Medical School, Department of Child Psychiatry, Van, Turkey
[c]Dicle University, Medical School, Department of Biochemistry, Diyarbakır, Turkey
**Corresponding author:* Şeref Şimşek, MD, Dicle University, Medical School, Department of Child Psychiatry, Sur, Diyarbakır, Turkey 21280 (drserefsimsek@gmail.com).

Obsessive-compulsive disorder (OCD) is a neuropsychiatric disease characterized by repeating and undesirable urges and images as well as the ritualistic behaviors performed to avoid them.[1] Symptoms of OCD start in childhood and adolescence in approximately 80% of the cases,[2] with a prevalence in children of 1%–3%.[3] OCD has etiologies that are largely multifactorial, involving complex interactions between genetic and environmental factors.[4] Environmental factors such as stress and traumatic life events occur in 50% of the individuals with OCD.[5,6]

Brain-derived neurotrophic factor (BDNF) plays an important role in the proliferation, differentiation, and survival of neurons during the development process of the nervous system. It also plays a role in synaptic efficiency and the development of neuronal plasticity.[7] BDNF has been reported to modulate a series of neurotransmitter systems, including dopaminergic, serotonergic, and glutamatergic pathways.[8–10] In vivo and in vitro studies have shown that BDNF promoted survival, differentiation, and regeneration of serotonergic and glutamatergic neurons.[11,12] It has been suggested that BDNF plays a role in the development of OCD.[13] Hall et al[14] showed a significant association between childhood-onset OCD and BDNF gene polymorphism (Val66met); however, this finding was not confirmed by other investigators.[15,16] BDNF levels were significantly lower in patients with anxiety disorders as compared with healthy controls.[17] In many studies, the BDNF levels were significantly lower in adult OCD patients as compared with healthy controls; however, no significant correlation was found between BDNF level and age, age at OCD onset, symptom severity, and duration of OCD.[18–20]

Patients with OCD have been known to be sensitive to stress, with symptoms increasing during stressful conditions.[21] In addition, stressful life events have been observed in patients prior to the diagnosis of OCD.[6] The hypothalamic-pituitary-adrenal (HPA) axis is a major part of the neuroendocrine system that controls reactions and response to stress. The increase in HPA axis activity has been reported in patients with OCD.[22,23] The levels of nocturnal adrenocorticotropic hormone (ACTH) and cortisol have been shown to be significantly increased in patients with OCD as compared with healthy controls.[22] Similarly, cortisol levels in children and adolescents with OCD were higher than those in healthy controls.[23] BDNF synthesis and synaptogenesis increased in response to acute stress or acute glucocorticoid treatment.[24,25] A decrease in BDNF levels, dendritic structures, and synaptic intensity has been reported to occur in chronic stress and exposure to glucocorticoids.[24,25]

Most analyses of BDNF levels have been performed in adults with OCD. To the best of our knowledge, BDNF and cortisol levels have not been evaluated in child and adolescent patients with OCD prior to treatment. The current study aimed to investigate whether serum BDNF, cortisol, and ACTH levels differ between children and adolescents with

Clinical Points

- The hypothalamic-pituitary-adrenal (HPA) system and neurotrophic factors are closely linked and play an important role in the pathogenesis of many psychiatric disorders. There are separate studies related to both the HPA system and neurotrophic factors in adult patients with obsessive-compulsive disorder (OCD).
- The aim of this article was to assess the 2 systems simultaneously in child OCD patients. These patients will help us in understanding the pathophysiology of the disorder since these child patients have a developing brain, are in the early phases of the disorder, and received no psychotropic treatment prior to evaluation.

OCD and healthy controls. The current study also aimed to investigate whether there is an association between serum BDNF, ACTH, and cortisol levels and severity of OCD.

METHODS

Study Sample

The study was conducted in the Department of Child Psychiatry at Dicle University Training and Research Hospital between December 2012 and December 2013. A total of 44 OCD patients were admitted, with 39 agreeing to participate in the study. Ten patients were excluded from the study based on the exclusion criteria (see elsewhere in this paragraph). Thus the study included 29 children, aged 7 to 17 years (male/female: 21/8), with OCD prior to receiving treatment. The diagnosis of OCD was according to *DSM-IV*. Children who had mental retardation or history of head trauma, had received oral contraceptives or psychotropics, had previous or current cortisol therapy, were taking vitamins, had a body mass index ≥ 30 (kg/m^2), or had chronic systemic disorders or clinically active infection were excluded to prevent interference with biochemical parameters. Patients with simple tic disorders were included in the study. Simple motor tic disorder was present in 13.8% (n = 4) of the patients with OCD. Patients with other psychiatric disorders were excluded from the study. The control group consisted of age- and gender-matched children who were residing at geographic locations similar to those of the patient group and who did not have a history of medical problems. Two experienced psychiatric doctors evaluated the patients. Interrater agreement was 0.80. The Non-interventional Clinical Research Ethics Committee of the Dicle University Faculty of Medicine approved the study. The parents of the participants provided written volunteer informed consent.

Study Procedures

Sociodemographic features and clinical data of the participants were recorded by the psychiatrists. This recording was followed by structured psychiatric interviews (the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version [K-SADS-PL] and Children's Yale-Brown Obsessive Compulsive Scale [CY-BOCS]) and administration of the self-reported Children's Depression Inventory (CDI). Height and weight were measured, and body mass index was calculated. Venous blood sample (2 mL) was obtained for biochemical tests.

Forms and Scales

Sociodemographic data and clinical data form. This form included questions about age, gender, educational status, history of psychiatric disorders, height, weight, tic disorder symptoms, number of siblings of the patient; ages, educational status, and occupations of the parents; and consanguinity between parents.

K-SADS-PL. The K-SADS-PL was originally developed by Kaufman et al[26] and adapted to a Turkish version by Gökler et al in 2004.[27] The K-SADS-PL is administered during an interview with the parents and children. The final evaluation is performed using input from all data sources. The scale evaluates the presence of common psychopathologies, primarily OCD, in children and adolescents.

CY-BOCS. The CY-BOCS is a semistructured tool to measure the severity of OCD signs within the past week.[28] There are 5 major sections: instructions, obsession screening list, items to determine the severity of obsessions, compulsion screening list, and items to determine the severity of compulsions. Information is gathered from the child and his or her parents. The validity and reliability study of the Turkish version of this scale was carried out by Erkal et al.[29]

CDI. The CDI, developed by Kovacs[30] based on the Beck Depression Inventory, was used in this study. However, questions specific to the childhood period such as school success and relationship with friends were added. The scale was adapted to the Turkish language by Öy, and the scale contains 27 items.[31] Each item is scored as 0, 1, or 2 points depending on the severity of the symptom. The highest possible score is 54 points. Higher scores indicate a higher level or greater severity of depression. The cutoff point for the scale is 19 points.

Measurement of BDNF, ACTH, and Cortisol

The blood samples were collected into gel tubes between 9:00 AM and noon and left at room temperature for 15 minutes to facilitate clotting. Blood samples were centrifuged at 5,000 rpm for 6 minutes. The serum was transferred to 1.5-mL polypropylene tubes and stored at −80°C for later analysis. Measurements of BDNF, ACTH, and cortisol were performed with the appropriate kits. The measurements were performed the same day. Serum BDNF, ACTH, and cortisol concentrations were determined by enzyme-linked immunosorbent assay (ELISA) test. These kits (Hangzhou Eastbiopharm Co, Ltd, China) use ELISA based on Biotin double antibody sandwich technology to assay human BDNF, ACTH, and cortisol levels in serum, blood plasma, saline, urine, and other related tissue liquid. Procedures were performed as follows: 50-µL standards were added in standard solution wells, and 40-µL serum samples and 10-µL BDNF, ACTH, or cortisol pro antibodies were added in sample wells. Then, 50-µL streptavidin-HRP was added to each well except for a blank well, and the plate was covered with seal plate membrane. The plate was shaken gently to

Table 1. Sociodemographic Data for Patients With OCD and Healthy Controls[a]

Variable	OCD (n = 29)	No OCD (n = 25)	*P* Value
Age, y	12.4 (2.7)	12.4 (2.3)	.98
Sex, male/female, n	21/8	16/9	.71
Education duration, y	6.6 (2.5)	6.6 (1.9)	.98
Mother's age, y	41.5 (8.1)	38.9 (5.8)	.20
Mother's education duration, y	5.7 (4.8)	6.1 (6.1)	.98
Father's age, y	45.7 (7.8)	44.4 (5.4)	.51
Father's education duration, y	9.9 (3.9)	10.1 (4.6)	.54
No. of siblings	4.7 (2.5)	4.7 (2.7)	.96
Length, cm	154.6 (18.3)	153.0 (12.2)	.56
Weight, kg	47.9 (17.3)	47.1 (13.4)	.86
BMI, kg/m^2	19.5 (4.2)	19.8 (3.6)	.59
Duration of OCD symptoms, mo	17.9 (18.5)	…	…

[a]Values shown as mean (SD) unless otherwise noted.
Abbreviations: BMI = body mass index, OCD = obsessive-compulsive disorder.
Symbol: … = not applicable.

Table 2. Rating Scale Scores for Patients With OCD and Healthy Controls[a]

Scale	OCD (n = 29)	No OCD (n = 25)	*P* Value
CDI			
Score	12.8 (6.6)	11.2 (4.9)	.34
Depression/no depression, n[b]	7/19	2/23	.14
CY-BOCS			
Obsession	12.3 (3.4)	…	…
Compulsion	11.3 (3.5)	…	…
Total	23.6 (6.6)	…	…

[a]Values shown as mean (SD) unless otherwise noted.
[b]The cutoff point for the scale is 19 points.
Abbreviations: CDI = Children's Depression Inventory, CY-BOCS = Children's Yale-Brown Obsessive Compulsive Scale, OCD = obsessive-compulsive disorder.
Symbol: … = not applicable.

mix and was incubated at 37°C for 60 minutes away from light. The plate was washed carefully 5 times and then was blotted. 50-µL chromogen reagent A was added to each well, and then 50-µL chromogen reagent B was add to each well; the plate was then incubated for 10 minutes at 37°C away from light for color development. Finally, 50-µL stop solution was added to each well. We measured the optical density of each well under 450 nm wavelength within 10 minutes after having added stop solution. According to standards concentrations and corresponding optical density values, we calculated the linear regression equation of the standard curve and determined BDNF, ACTH, and cortisol concentration of samples.

Statistical Analysis

Statistical analyses were performed using SPSS 18.0 (SPSS Inc, Chicago, Illinois). The χ^2 test was used to evaluate the presence of a difference between the groups in terms of gender, consanguinity between parents, and history of psychiatric disorders. The Student *t* test was used to compare normally distributed variables in independent groups, and the Mann-Whitney test was used otherwise. The changes in BDNF and cortisol levels in terms of groups and the effects of age, gender, and depression were adjusted using 2-way analysis of variance and analysis of covariance tests. The Pearson test was used to evaluate correlation coefficients and statistical significance of normally distributed variables, and the Spearman test was used to evaluate non-normally distributed variables. A *P* value below .05 was considered statistically significant.

RESULTS

There was no significant difference between the gender and age of the OCD group (male/female: 21/8; age (mean [SD] years): 12.4 [2.7]) and the control group (male/female: 16/9; age: 12.4 [2.3]). No differences were detected in the occupation of the parents and presence of consanguinity between the parents among the groups. The presence of psychiatric diseases in the family and close relatives was significantly higher in the OCD group ($P < .001$) as compared with the control group. The sociodemographic data are presented in Table 1.

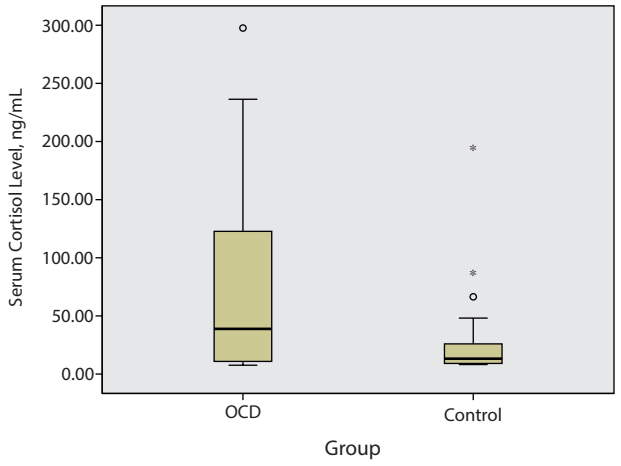
No significant difference was found in the scores for depression between the patient and control groups. The mean (SD) duration of OCD symptoms was 17.9 (18.5) months. Patients reported that their symptoms of OCD had increased to a level that impaired functioning for a mean of 3.6 (3.2) months. Data for the scales are given in Table 2. Serum cortisol (Figure 1), ACTH, and BDNF levels (Figure 2) were significantly higher in patients with OCD as compared with the control group ($P = .046$, $P = .03$, and $P = .02$, respectively). Depression and gender had no effect on BDNF levels ($F = 0.301$, $P = .57$ and $F = 3.520$, $P = .31$, respectively), while age had an effect on BDNF levels ($F = 6.743$, $P = .01$). Similarly, depression and gender did not have an effect on cortisol levels ($F = 0.594$, $P = .45$ and $F = 1.00$, $P = .32$, respectively), while age affected the cortisol level ($F = 6.637$, $P = .01$). Data from the biochemical analysis are presented in Table 3. The duration and severity of OCD symptoms were not significantly associated with cortisol, ACTH, and BDNF levels.

DISCUSSION

This study showed that serum BDNF, ACTH, and cortisol levels were significantly higher in pediatric patients with OCD prior to treatment as compared with healthy controls. The significance of the comparison continued when effects of age, gender, and depression scores were considered. To our knowledge, there is no similar study design in pediatric OCD patients.

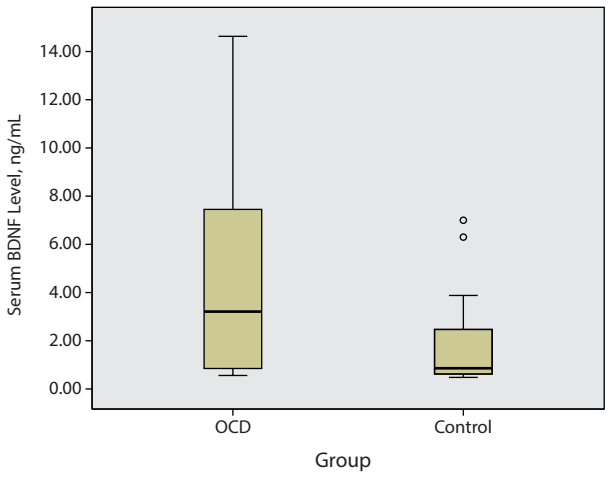
Low levels of BDNF have been reported to play a major role in the pathogenesis of OCD.[13] BDNF levels were consistently lower in adults with OCD prior to treatment as compared to control groups, with mean duration of the disease from 4.3 to 29.5 years.[18–20,32] In this study, the mean (SD) duration of the disease was 17.9 (18.5) months. The increased levels of BDNF at the early phase of the disease could be an adaptive response to preserve the neurons.

Figure 1. Serum Cortisol Levels in Patients With OCD and Healthy Controls[a]



[a]Cortisol levels were significantly higher in the patients with OCD than the control group ($P = .046$). Box = interquartile range, horizontal line in box = median, circle or asterisk = outlier.
Abbreviation: OCD = obsessive-compulsive disorder.

Figure 2. Serum BDNF Levels in Patients With OCD and Healthy Controls[a]



[a]BDNF levels were significantly higher in the patient group ($P = .02$). Box = interquartile range, horizontal line in box = median, circle = outlier.
Abbreviations: BDNF = brain-derived neurotrophic factor, OCD = obsessive-compulsive disorder.

The reason for HPA abnormalities in OCD patients has not yet been entirely elucidated. Children with OCD have been known to be sensitive to stress, and OCD symptoms increase during stressful conditions.[21] In addition, stressful life events have been observed to occur prior to the start of OCD.[6] In studies investigating basal HPA axis activity in adults with OCD, ACTH[22] and cortisol[33] secretions were increased. One other study has shown that basal cortisol levels at 8:30 AM were higher in youths with OCD compared to controls, while cortisol levels at 10:30 AM were similar.[23] OCD patients were known to be exposed to increased daily stressors.[34] Stress, in turn, increased the secretion of glucocorticoids through the activation of the HPA axis.[35] Exposure to excess

Table 3. Biochemical Parameters in Patients With OCD and Healthy Controls[a]

Serum Concentration	OCD (n = 29)	No OCD (n = 25)	*P* Value
Cortisol, ng/mL	77.3 (82.6)	30.3 (40.5)	.046
ACTH, ng/L	86.1 (57.3)	50.1 (37.9)	.03
ACTH/cortisol ratio	2.0 (1.0)	2.4 (0.8)	.10
BDNF, ng/mL	4.5 (4.5)	1.8 (1.8)	.02

[a]Values shown as mean (SD) unless otherwise noted.
Abbreviations: ACTH = adrenocorticotropic hormone, BDNF = brain-derived neurotrophic factor, OCD = obsessive-compulsive disorder.

glucocorticoids decreased dendritic structures and synaptic density.[36,37] BDNF synthesis and synaptogenesis increased in response to acute stress or acute glucocorticoid treatment, while decreased synthesis of BDNF and the elimination of dendritic structures were reported in response to exposure to chronic stress and/or glucocorticoids.[24,25]

Another important finding of this study was that there was not a significant relationship between the severity and duration of the disease and levels of BDNF, ACTH, and cortisol. Although no relationship was found between BDNF levels and severity and duration of the disease in most of the studies in the literature,[18,20,38] a significant relationship was found with religious/sexual symptoms in one study.[19] No relationship between disease severity and basal cortisol level has been found in adolescents with OCD.[23]

In the present study, the rates of the presence of psychiatric disease in the close relatives were significantly higher in the OCD group compared with the control group. In family studies, OCD and/or tic disorders have been reported to be at higher rates, and genetic load was also higher in first-degree relatives of children with childhood-onset OCD compared to late-start counterparts.[39]

There are research limitations in this study. The cross-sectional structure of the study is an important limitation. Only one interview was performed with the participants, and measurement of BDNF, ACTH, and cortisol levels was performed only once. History of trauma, which may affect the cortisol level of the participants, was not questioned. In addition, the subtypes of the symptoms of OCD were not evaluated. Also, the study sample size is small.

In conclusion, serum levels of BDNF, ACTH, and cortisol in children with OCD were higher than in healthy controls, and no association was found between symptom severity and duration of the disease and biochemical parameters. The increased levels of BDNF may be an adaptive response to the damaging effects of HPA axis hyperactivity on brain tissue in the early stages of OCD. Thus, HPA axis abnormality and BDNF may play a key role in the pathogenesis of the disease.

Submitted: June 4, 2015; accepted August 21, 2015.
Online first: June 7, 2016.
Potential conflicts of interest: The authors report no conflicts of interest.
Funding/support: None reported.
Disclaimer: The authors alone are responsible for the content and writing of the article.
Acknowledgments: We would like to thank our patients and their parents for taking part in this study.

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders*. Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.
2. Pauls DL, Alsobrook JP 2nd, Goodman W, et al. A family study of obsessive-compulsive disorder. *Am J Psychiatry*. 1995;152(1):76–84.
3. Heyman I, Fombonne E, Simmons H, et al. Prevalence of obsessive-compulsive disorder in the British nationwide survey of child mental health. *Br J Psychiatry*. 2001;179(4):324–329.
4. Pauls DL. The genetics of obsessive-compulsive disorder: a review. *Dialogues Clin Neurosci*. 2010;12(2):149–163.
5. Samuels JF. Recent advances in the genetics of obsessive-compulsive disorder. *Curr Psychiatry Rep*. 2009;11(4):277–282.
6. Gothelf D, Aharonovsky O, Horesh N, et al. Life events and personality factors in children and adolescents with obsessive-compulsive disorder and other anxiety disorders. *Compr Psychiatry*. 2004;45(3):192–198.
7. Numakawa T, Suzuki S, Kumamaru E, et al. BDNF function and intracellular signaling in neurons. *Histol Histopathol*. 2010;25(2):237–258.
8. Graham DL, Krishnan V, Larson EB, et al. Tropomyosin-related kinase B in the mesolimbic dopamine system: region-specific effects on cocaine reward. *Biol Psychiatry*. 2009;65(8):696–701.
9. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol*. 2006;27(1):24–31.
10. Lyons WE, Mamounas LA, Ricaurte GA, et al. Brain-derived neurotrophic factor-deficient mice develop aggressiveness and hyperphagia in conjunction with brain serotonergic abnormalities. *Proc Natl Acad Sci U S A*. 1999;96(26):15239–15244.
11. Mamounas LA, Altar CA, Blue ME, et al. BDNF promotes the regenerative sprouting, but not survival, of injured serotonergic axons in the adult rat brain. *J Neurosci*. 2000;20(2):771–782.
12. Martinowich K, Lu B. Interaction between BDNF and serotonin: role in mood disorders. *Neuropsychopharmacology*. 2008;33(1):73–83.
13. Stein DJ, Daniels WM, Savitz J, et al. Brain-derived neurotrophic factor: the neurotrophin hypothesis of psychopathology. *CNS Spectr*. 2008;13(11):945–949.
14. Hall D, Dhilla A, Charalambous A, et al. Sequence variants of the brain-derived neurotrophic factor (BDNF) gene are strongly associated with obsessive-compulsive disorder. *Am J Hum Genet*. 2003;73(2):370–376.
15. Dickel DE, Veenstra-VanderWeele J, Bivens NC, et al. Association studies of serotonin system candidate genes in early-onset obsessive-compulsive disorder. *Biol Psychiatry*. 2007;61(3):322–329.
16. Wendland JR, Kruse MR, Cromer KR, et al. A large case-control study of common functional SLC6A4 and BDNF variants in obsessive-compulsive disorder. *Neuropsychopharmacology*. 2007;32(12):2543–2551.
17. Suliman S, Hemmings SM, Seedat S. Brain-derived neurotrophic factor (BDNF) protein levels in anxiety disorders: systematic review and meta-regression analysis. *Front Integr Neurosci*. 2013:7:55.
18. Maina G, Rosso G, Zanardini R, et al. Serum levels of brain-derived neurotrophic factor in drug-naïve obsessive-compulsive patients: a case-control study. *J Affect Disord*. 2010;122(1–2):174–178.
19. Dos Santos IM, Ciulla L, Braga D, et al. Symptom dimensional approach and BDNF in unmedicated obsessive-compulsive patients: an exploratory study. *CNS Spectr*. 2011;16(9):179–189.
20. Wang Y, Mathews CA, Li Y, et al. Brain-derived neurotrophic factor (BDNF) plasma levels in drug-naïve OCD patients are lower than those in healthy people, but are not lower than those in drug-treated OCD patients. *J Affect Disord*. 2011;133(1–2):305–310.
21. Findley DB, Leckman JF, Katsovich L, et al. Development of the Yale Children's Global Stress Index (YCGSI) and its application in children and adolescents with Tourette's syndrome and obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry*. 2003;42(4):450–457.
22. Kluge M, Schüssler P, Künzel HE, et al. Increased nocturnal secretion of ACTH and cortisol in obsessive compulsive disorder. *J Psychiatr Res*. 2007;41(11):928–933.
23. Gustafsson PE, Gustafsson PA, Ivarsson T, et al. Diurnal cortisol levels and cortisol response in youths with obsessive-compulsive disorder. *Neuropsychobiology*. 2008;57(1–2):14–21.
24. Tapia-Arancibia L, Rage F, Givalois L, et al. Physiology of BDNF: focus on hypothalamic function. *Front Neuroendocrinol*. 2004;25(2):77–107.
25. Liston C, Gan W-B. Glucocorticoids are critical regulators of dendritic spine development and plasticity in vivo. *Proc Natl Acad Sci U S A*. 2011;108(38):16074–16079.
26. Kaufman J, Birmaher B, Brent D, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry*. 1997;36(7):980–988.
27. Gökler B, Ünal F, Pehlivantürk B, et al. Reliability and Validity of Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime Version-Turkish Version (K-SADS-PL-T). *Turk J Child Adolesc Ment Health*. 2004;11(3):109–116.
28. Scahill L, Riddle MA, McSwiggin-Hardin M, et al. Children's Yale-Brown Obsessive Compulsive Scale: reliability and validity. *J Am Acad Child Adolesc Psychiatry*. 1997;36(6):844–852.
29. Yucelen AG, Rodopman-Arman A, Topcuoglu V, et al. Interrater reliability and clinical efficacy of Children's Yale-Brown Obsessive-Compulsive Scale in an outpatient setting. *Compr Psychiatry*. 2006;47(1):48–53.
30. Kovacs M. The Children's Depression Inventory (CDI). *Psychopharmacol Bull*. 1985;21(4):995–998.
31. Oy B. The Children's Depression Inventory: validity and reliability study. *Turk J Psychiatry*. 1991;(2):132–136.
32. Fontenelle LF, Barbosa IG, Luna JV, et al. Neurotrophic factors in obsessive-compulsive disorder. *Psychiatry Res*. 2012;199(3):195–200.
33. Brambilla F, Perna G, Bussi R, et al. Dopamine function in obsessive compulsive disorder: cortisol response to acute apomorphine stimulation. *Psychoneuroendocrinology*. 2000;25(3):301–310.
34. Coles ME, Heimberg RG, Frost RO, et al. Not just right experiences and obsessive-compulsive features: experimental and self-monitoring perspectives. *Behav Res Ther*. 2005;43(2):153–167.
35. Holsboer F, Ising M. Stress hormone regulation: biological role and translation into therapy. *Annu Rev Psychol*. 2010;61(1):81–109, C1–C11.
36. Tata DA, Marciano VA, Anderson BJ. Synapse loss from chronically elevated glucocorticoids: relationship to neuropil volume and cell number in hippocampal area CA3. *J Comp Neurol*. 2006;498(3):363–374.
37. Wellman CL. Dendritic reorganization in pyramidal neurons in medial prefrontal cortex after chronic corticosterone administration. *J Neurobiol*. 2001;49(3):245–253.
38. Della FP, Abelaira HM, Réus GZ, et al. Tianeptine exerts neuroprotective effects in the brain tissue of rats exposed to the chronic stress model. *Pharmacol Biochem Behav*. 2012;103(2):395–402.
39. Leonard HL, Ale CM, Freeman JB, et al. Obsessive-compulsive disorder. *Child Adolesc Psychiatr Clin N Am*. 2005;14(4):727–743.

Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Karen D. Wagner, MD, PhD, at kwagner@psychiatrist.com.