Decreased serum BDNF levels in patients with epileptic and psychogenic nonepileptic seizures

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ABSTRACT

Objective: Neurotrophins promote neurogenesis and help regulate synaptic reorganization. Their dysregulation has been implicated in a number of neurologic and psychiatric disorders. Previous studies have shown decreased levels of brain-derived neurotrophic factor (BDNF) in the serum of patients with psychiatric disorders such as major depressive disorder (MDD) and conversion disorder (CD). In human patients with temporal lobe epilepsy, there is an increase in both BDNF mRNA and protein levels in surgically resected hippocampi compared to controls. One study of children with epilepsy has found normal to increased serum BDNF levels compared to controls. Serum BDNF levels have not been investigated in adult patients with epileptic seizures (ES). We hypothesized that BDNF would differentiate between ES and psychogenic nonepileptic seizures (PNES).

Methods: We assessed serum BDNF immunoreactivity in 15 patients with ES, 12 patients with PNES, and 17 healthy volunteers. Serum BDNF levels were measured using an enzyme-linked immunoassay.

Results: Healthy controls showed higher BDNF levels ($4,289 \pm 1,810$ pg/mL) compared to patients with PNES ($1,033 \pm 435$ pg/mL) ($p < 0.001$). However, unexpectedly, healthy controls also showed higher levels of BDNF compared to patients with ES without comorbid MDD (977 ± 565 pg/mL) ($p < 0.001$).

Conclusions: Unlike children, adults with epilepsy appear to have decreased levels of serum BDNF. Reduced serum BDNF levels can be used to differentiate adult patients with ES or PNES from healthy controls. Further human studies are needed to better understand the pathophysiology explaining the decreased serum BDNF levels found in epilepsy and in PNES. *Neurology*® 2010;75:1285-1291

GLOSSARY

AED = antiepileptic drug; **BDI-II** = Beck Depression Inventory II; **BDNF** = brain-derived neurotrophic factor; **CD** = conversion disorder; **ECS** = electroconvulsive seizure; **ES** = epileptic seizure; **GTC** = generalized tonic-clonic seizure; **HC** = healthy control; **MDD** = major depressive disorder; **PNES** = psychogenic nonepileptic seizure; **PRL** = prolactin; **RIH** = Rhode Island Hospital.

Along with video-EEG, serum prolactin (PRL) is used to assist in differentiating epileptic seizures (ES) and psychogenic nonepileptic seizures (PNES). PRL use, however, is limited in that it must be drawn within 30–60 minutes of the ictus, and the sensitivity and specificity are high only for generalized tonic-clonic seizures (GTCs).¹ A biomarker that is independent of recent seizure activity or semiology would be of diagnostic value.

Brain-derived neurotrophic factor (BDNF) dysregulation has been implicated in a number of neurologic and psychiatric illnesses. Serum BDNF was elevated in children with ES.² There is a paucity of literature on BDNF in patients with PNES. A recent study found decreased serum BDNF levels in patients with conversion disorder (some with PNES) without comorbid major depressive disorder.³ The low BDNF in conversion disorder is contrasted to the elevated

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BDNF in epilepsy. Data from separate studies on ES and on PNES raised the possibility that BDNF may be a serum biomarker that could aid in differentiating ES from PNES.

Serum BDNF levels in adults with ES have not been previously published. Comparisons of BDNF serum concentrations in adult patients with ES and with PNES are also lacking. The aim of the present study was to compare serum BDNF levels among patients with ES, patients with PNES, and healthy controls (HCs) to assess their utility as a diagnostic tool. We hypothesized that serum BDNF would differentiate ES from PNES, with higher levels of BDNF in patients with ES and lower levels of BDNF in patients with PNES than HCs.

METHODS **Standard protocol approvals, registrations, and patient consents.** This study was approved by the institutional review board of Rhode Island Hospital. Written informed consent was obtained from all participants.

Subjects. Outpatients and inpatients were recruited from Rhode Island Hospital (RIH) from February 2008 to December 2008. Patients were between the ages of 19 and 76 years and were seen at RIH Neuropsychiatry/Behavioral Neurology Clinic and RIH Epilepsy Clinic. Patients were diagnosed with either PNES ($n = 12$) or ES ($n = 15$) by history, examination, and video EEG/long-term monitoring. Extensive diagnostic assessments were administered to confirm diagnosis and to rule out exclusionary criteria.

Exclusion criteria included patients with mixed ES and PNES, other active neurologic diseases, and alcohol/substance abuse within the 6 months preceding the study. Patients with ES who had comorbid psychiatric or neurologic illness were excluded. This was accomplished through systematic chart review, assessment, and symptom survey with the Beck Depression Inventory II (BDI-II). Patients with ES taking psychotropic medication 6 months prior to study consent were excluded.

Physicians at both clinics prescreened patients for eligibility criteria. If patients met diagnostic and exclusionary criteria, they were directed to a trained research assistant who introduced the study and obtained consent.

The HCs ($n = 17$) were recruited from Brown University staff and student volunteers. In order to exclude any neurologic or psychiatric lifetime diagnosis, all pertinent assessments were administered to HCs and interviews were carried out at RIH. Similar exclusionary criteria were applied to all subjects.

Measurement of serum BDNF. Ten milliliters of blood was drawn from the antecubital vein of participants and was centrifuged. The supernatant was removed to prevent the red cells from potentially hemolyzing when thawing and contaminating the samples. Serum samples were initially frozen at -20°C and later moved to -80°C for long-term storage. BDNF levels were assayed using the BDNF Emax Immunoassay System kit (Promega, Madison, WI) in accordance with the manufacturer's instructions. This assay system has been independently validated by the manufacturer. It has been shown to measure BDNF se-

rum levels accurately and with high reproducibility, and detects a minimum of 15.6 pg/mL of BDNF.⁴ The antibody also has less than 3% cross-reactivity with other related neurotrophins.⁴ A standard curve was established using the control samples provided by the manufacturer. For the assay, 96-well plates were coated with anti-BDNF monoclonal antibody and incubated at 4°C for 18 hours. The plates were incubated in a blocking buffer for 1 hour at room temperature. The samples and BDNF standards were maintained at room temperature under conditions of shaking for 2 hours, followed by washing with TBST washing buffer. The plates were incubated with antihuman BDNF polyclonal antibody at room temperature for 2 hours, washed, and incubated with anti-IgY antibody conjugated to horseradish peroxidase for 1 hour at room temperature. The plates were incubated in peroxidase substrate and tetramethylbenzidine solution to produce a color reaction. The reaction was stopped with 1 mol/L hydrochloric acid; the absorbance at 450 nm was measured with an Emax automated microplate reader.

Statistical analysis. Statistical analysis was done using SAS/STAT 9.2 (SAS Institute; 2009). One-way nonparametric analyses of variance (ANOVA) using the Kruskal-Wallis test statistic was used to compare the ES, PNES, and HC groups on continuous variables; pairwise differences were based on the Wilcoxon test statistic. Fisher exact test was used to compare the groups on categorical variables. Between-group comparisons in serum BDNF levels were adjusted for covariates showing differences at baseline using weighted least squares regression with a power-of-the-mean variance function. An a priori p value <0.05 was considered significant for overall group differences; a multiplicity-adjusted threshold of 0.05/3 was used for pairwise comparisons.

RESULTS **Population.** Thirty-eight patients with PNES were screened for the study, and of those, 13 patients consented. One patient's body mass index was in the obese range, and was excluded from analysis, given the influence of obesity on BDNF levels.⁵

Eighteen patients with ES were deemed eligible, and all 18 consented. Three were not included in the analysis because 1 patient's seizure diagnosis was equivocal, 1 patient died and the medical comorbidity was unclear, and 1 patient was found to have fibromyalgia.

Nineteen HCs were screened for the study and agreed and consented, however, 2 HCs were excluded from analysis because they did not meet eligibility criteria (1 with heavy alcohol and tobacco use, and 1 because of undiagnosed eating disorder that eluded screening).

Between-group differences in age ($p < 0.001$) appeared driven by the fact that both the ES group ($p < 0.001$) and the PNES group ($p = 0.004$) were older than the HCs; there were no differences in age between ES and PNES groups ($p = 0.751$). All but one of the HCs was between the ages of 20 and 23 years. Although a higher proportion of females enrolled in the PNES group than in the ES and HC groups, which is consistent with the literature, gender differences were not significant.

Table Serum BDNF levels, epileptic seizures, psychogenic nonepileptic seizures, and healthy control groups

	ES (n = 15)	PNES (n = 12)	HC (n = 17)	p Value
Gender, n (%)				
Male	7 (47)	2 (17)	9 (53)	0.1261 ^a
Female	8 (53)	10 (83)	8 (43)	
Age, y, mean $\pm$ SD	43.60 $\pm$ 16.57	40.75 $\pm$ 16.10	22.53 $\pm$ 4.30	<0.0001 ^b
BDI-II score, mean $\pm$ SD	2.27 $\pm$ 4.13	12.33 $\pm$ 8.62	5.47 $\pm$ 5.99	0.0003 ^b
Duration of seizure disorder, mo, mean $\pm$ SD	241.50 $\pm$ 166.96	80 $\pm$ 113.57	N/A	0.009 ^c
Serum BDNF, pg/mL, mean $\pm$ SD	977.48 $\pm$ 564.54	1,033.45 $\pm$ 435.50	4,289.02 $\pm$ 1809.96	<0.0001 ^b
Serum BDNF, pg/mL, adjusted mean $\pm$ SE	1,011.35 $\pm$ 173.02	1,036.59 $\pm$ 209.68	4,272.85 $\pm$ 456.69	<0.0001 ^d

Abbreviations: BDI = Beck Depression Inventory; BDNF = brain-derived neurotrophic factor; ES = epileptic seizures; HC = healthy controls; PNES = psychogenic nonepileptic seizures.

^a Between-group differences calculated using Fisher exact test.

^b Between-group differences calculated using Kruskal-Wallis nonparametric 1-way analysis of variance.

^c Between-group differences calculated using Wilcoxon test.

^d Adjusted for age and BDI-II via weighted least squares regression using a power-of-the-mean variance function.

Mean depression scores (BDI-II) were in the minimally depressed range for all 3 groups, and were lower for both the HCs (5.47 $\pm$ 5.99) and the ES group (2.27 $\pm$ 4.13) compared to the PNES group (12.33 $\pm$ 8.62) (p = 0.011 for the HCs and PNES group comparison, and p < 0.001 for ES group and PNES group comparison). Seizures occurred at a rate of 0 to 35 per week in the PNES group, and 0 to 56 per week in the ES group (p = 0.601). The most recent seizure occurred 1 day to 17.9 years prior in the ES group, and 1 day to 3.5 years prior in the PNES group (p = 0.575). Patients reported onset of seizures 1 to 46 years prior in the ES group, and 1 month to 35 years prior in the PNES group (p = 0.009). In the epilepsy group, 7 patients were considered refractory, and 8 were controlled. Eight had an idiopathic etiology, 5 had symptomatic epilepsy, and in 2 the etiology was unknown. Twelve had focal and 3 had generalized seizures.

All but 1 of the patients in the ES group were taking antiepileptic drugs (AEDs) for their seizures, and 3 patients with PNES were taking AEDs for pain or headaches. Eight patients with PNES and none with ES were taking psychotropics. Polyserial correlation analyses showed a lack of association between BDNF levels and current psychotropic use (ρ = 0.007, p = 0.973).

There were large overall group differences in serum BDNF levels (p < 0.001). Patients with PNES had decreased levels of serum BDNF compared to HCs (1,033.45 $\pm$ 435.50 pg/mL compared to 4,289.02 $\pm$ 1,809.96 pg/mL; p < 0.001) (table; figure). Unexpectedly, however, patients with ES also had decreased levels of serum BDNF compared to HCs. Mean serum BDNF level was 977.48 $\pm$

564.54 pg/mL in the ES group compared to the 4,289.02 $\pm$ 1,809.96 pg/mL in HCs; p < 0.001 (see table and figure). There was no difference between the PNES group and the ES group (p = 0.868).

The log of age and square root of BDI linearized the relationship between these 2 covariates and serum BDNF levels. After adjusting for age and BDI-II score via weighted least squares regression, examination of pairwise contrasts indicated that the adjusted group means of the ES and PNES groups both differed from that of the HCs, but not from each other. PNES-adjusted group mean $\pm$ SE was 1,036.59 $\pm$ 209.68 pg/mL compared to 4,272.85 $\pm$ 456.69

Figure Serum brain-derived neurotrophic factor (BDNF) levels

Concentration of serum BDNF is decreased in patients with epilepsy and patients with psychogenic nonepileptic seizures (PNES) relative to healthy controls. ES = epileptic seizures.

pg/mL for the adjusted group mean $\pm$ SE of HCs ($p < 0.001$). ES group adjusted mean $\pm$ SE was $1,011.35 \pm 173.02$ pg/mL compared to $4,272.85 \pm 456.69$ pg/mL for HCs; $p < 0.001$ (see the table). There was no difference in the adjusted group means for the PNES group and the ES group ($p = 0.934$).

DISCUSSION We report on the differences between serum BDNF concentrations in healthy controls and in patients with PNES and ES. The results of this PNES-specific group study confirm prior reports of decreased serum BDNF levels in patients with a variety of conversion disorder manifestations.³ Eight of the patients with PNES were taking psychotropic medication, and half had current depression, scoring in the mildly depressed range on the BDI. This is of note given that studies have suggested that chronic antidepressant use increases serum BDNF levels in patients with depression.⁶ Thus, while BDNF level may play a similar role in the pathophysiology of depression and PNES, the differential response of serum BDNF to antidepressants could highlight an important difference between the 2 disorders. The fact that psychotropics did not increase serum BDNF levels in our study and that there were no BDNF differences between patients with PNES who were depressed and those who did not have depression would suggest that serum BDNF might represent a trait marker of PNES and this could potentially be useful in understanding the pathophysiology of conversion disorders. Other research on patients with somatoform disorders, including functional neuroimaging studies,^{7,8} implicate other neuropsychobiological processes,⁹ in what was once thought of solely as a psychological condition.

BDNF dysregulation has been implicated in a number of neurologic and psychiatric illnesses. Decreased serum BDNF levels in adult patients have been reported in depression,^{6,10} bipolar disorder,¹¹ Huntington disease,¹² late-stage Alzheimer disease,¹³ autism,¹⁴ and multiple sclerosis.¹⁵ Increased serum levels have been found in schizophrenia,¹⁶ fibromyalgia,¹⁷ and early-stage Alzheimer disease,¹³ and in children with ES.²

In our study evaluating serum BDNF levels in adult patients with ES, we found decreased levels of serum BDNF in patients with ES, compared to HCs. In fact, the serum BDNF levels between the 2 patient groups were strikingly similar ($1,033.45 \pm 435.50$ pg/mL for PNES compared to 977.48 ± 564.54 pg/mL for ES). This result is unexpected given the findings of elevated serum BDNF levels in children and the studies investigating BDNF concentration in brain tissue from adult patients with ES. Similar results have been found for serum BDNF levels in

adults and children with autism. Elevated levels of serum BDNF are reported in neonates with autism¹⁸ whereas adults with autism seem to have decreased levels of serum BDNF compared to HCs.¹⁴ maturational CNS differences in adults and children with neuropsychiatric disorders may explain some, but not all, BDNF differences.

We monitored for depression using patient interview, chart review, and BDI-II, to determine depression diagnosis and symptomatology. The HCs and the ES groups did not meet criteria for depression diagnoses. Only 1 patient with ES and 3 HCs endorsed symptoms of mild depression on the BDI-II. Since it has been shown that patients with depression have decreased serum BDNF levels,¹⁰ our findings support that the observed decreased serum levels in our ES group were not attributable to a diagnosis or symptoms of depression. Whether milder current comorbid psychological disturbance or previous significant comorbidity might explain the lack of difference between the ES and PNES group and may provide a clue to some explanatory mechanisms may be worth future study.

BDNF¹⁹ is the most abundant neurotrophin in the nervous system and binds specifically to the TrkB receptor.²⁰ TrkB receptors exist in either a full-length or truncated form.²¹ The full-length form contains a catalytic tyrosine kinase domain whereas the truncated form does not. Both receptor types bind BDNF with a similar affinity, but the truncated form can attenuate receptor signaling either by recruiting dominant negative inhibitors or by removing BDNF from the extracellular space via internalization.²²

In the CNS, both BDNF mRNA and Trkb receptor mRNA are located throughout the brain, but specifically high concentrations exist in areas such as the hippocampus and entorhinal cortex.²³ BDNF is anterogradely transported, stored in mossy fiber terminal boutons, and released acutely following depolarization.²⁴

Animal studies have demonstrated that BDNF crosses the blood–brain barrier^{25,26} and can be measured in both the CNS and in the periphery. BDNF also has been found in the plasma and serum. The strong correlation between serum and cortical BDNF concentrations in rats during development and maturation²⁷ indicates that central and peripheral BDNF changes occur in parallel. The studies imply that blood BDNF levels may be representative of brain levels; however, a study directly comparing CSF to serum BDNF has not been published to date.

BDNF has been studied in the CNS of patients with ES and in animal models of ES for over a decade. Multiple studies have demonstrated increased expression of BDNF after seizures, as follows. In kin-

dling models, both mRNA and protein levels of BDNF are elevated after seizures.²⁸ While the increase in BDNF mRNA is transient, it appears that protein levels remain elevated for longer. Recent studies demonstrate that BDNF protein levels are elevated in the hippocampus for up to 45 days postseizure in a kainic acid model of ES.²⁹ In human patients with temporal lobe epilepsy, there is an increase in both BDNF mRNA³⁰ and protein levels³¹ in tissue taken from the hippocampus and temporal lobe. One study has directly examined serum BDNF levels in children with ES.² Their data revealed that serum levels in children with ES are elevated compared to HCs ($p = 0.0249$) (mean sera BDNF = 30,000 pg/mL in the ES group, and 10,000 pg/mL in the HCs).

A model that may provide a unifying hypothesis on the decreased serum BDNF findings in ES and PNES may be related not to seizures, but to stress, which has been shown to lower BDNF.³² The stress of seizures may be a shared characteristic between the 2 groups and could be further investigated. We, however, were unable to find studies of animal models for BDNF and PNES, or for conversion disorders in general. A possible mechanism for epileptic seizures may come from recent animal studies examining electroconvulsive-induced seizures in mice. Epigenetic mechanisms have been implicated in experiments examining electroconvulsive seizures (ECS)-induced demethylation within the regulatory region IX of BDNF.³³ Furthermore, plasticity studies showed that *Gadd45b* is associated with ECS-dependent demethylation and that seizures may trigger demethylation in promoters of BDNF.³⁴ ECS and kindling-induced seizures have also been shown to increase full-length and truncated forms of Trkb mRNA expression in the brain.³⁵ In addition, lesions of the major afferent pathways to the hippocampus have been reported to increase truncated, but not full-length, Trkb mRNA.³⁶ Taken together, these studies set up a paradigm where repeated seizures and possible epileptogenic lesions could simultaneously increase central BDNF, and also increase signaling through the attenuating truncated Trkb pathway. This aberrant signaling could potentially lead to decreased serum levels of BDNF in seizure patients over time.

Seizure frequency and temporal proximity did not appear to influence the BDNF levels in either PNES or ES group. It has been suggested that AEDs could downregulate BDNF. One study found that phenobarbital, valproate, and phenytoin reduced BDNF mRNA levels in rat cingulate cortex, hippocampus, and thalamus³⁷; however, we found no study that has yet investigated the effects of AEDs on serum BDNF levels in adults. In the present study, all but one of

the patients in the ES group reported AED use during study. One of the patients with ES in our study was taking valproate, and 3 were taking phenytoin. The rest were taking other newer AEDs. Three patients were currently taking an AED for a reason other than for their seizures. Five had been prescribed AEDs at some point in the past, including 1 valproate, 1 phenytoin, 1 lamotrigine, 2 levetiracetam, and 2 oxcarbazepine (some in combination). The numbers of AEDs taken were too small to discern the potential impact of psychotropic (mood-stabilizing) properties of the AEDs in either group. Downregulation of BDNF by AEDs did not appear to be a mechanism in this study, as the majority of patients with PNES were not on AEDs. It is unknown if serum BDNF levels would be reduced in patients with ES not taking AEDs, thus, comparing patients with epilepsy taking AEDs and those off AEDs may be of great value in future studies.

Despite small sample sizes, our study was powered to show a difference between groups based on the large differences noted in the literature. A limitation is that our HCs were on average 19.8 years younger than our patients. So, although the differences between the HC and patient groups remained significant after regression adjustment for age and BDI-II (1,011.35 pg/mL for the ES group and 1,036.59 pg/mL for the PNES group, compared to 4,272.85 pg/mL for the HCs), this finding should ideally be replicated on a sample that includes elderly controls. A recent study, however, examined both whole blood and serum concentrations of BDNF and found that there were no significant age-related changes, even when controlling for gender.²

A strength of our study is that the ES group was without comorbid psychiatric or neurologic illness. There was also considerable variety among the patients with ES with regard to seizure frequency and most recent ictal event. Furthermore, in both PNES and ES patient groups, there was little variance among individual serum BDNF levels (table and figure). Additional studies incorporating children and adult patients with epilepsy not on AEDs are necessary to provide further insight into the physiology of BDNF in seizures.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. Papandonatos.

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DISCLOSURE

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