Correspondence

DECREASED SERUM BDNF LEVELS IN PATIENTS WITH EPILEPTIC AND PSYCHOGENIC NONEPILEPTIC SEIZURES

Editor's Note: See erratum published in *Neurology*® 2011;76: 935, which notes: "For more accurate reporting and for any attempt to replicate the experiment, all references in the article to 'serum BDNF' should read: 'plasma BDNF.'" Please refer to the complete erratum for more information.

To the Editor: LaFrance et al.[1] reported lower plasma brain-derived neurotrophic factor (BDNF) levels in patients with epileptic seizures (ES) and psychogenic nonepileptic seizures (PNES) than healthy controls (HCs). Reduced BDNF in the plasma may be used to differentiate patients with ES and PNES from HCs, and probably from malingerers. However, the small sample size in this study is concerning.

Gender and age differences should be considered. Due to the small sample size, stratified analysis seems unlikely. Plasma levels of BDNF vary between different phases of the menstrual cycle.[2] It has also been shown that increasing age was associated with reduced levels of plasma BDNF.[3] The gender differences and Beck Depression Inventory II (BDI-II) score may partially explain the differences of plasma BDNF levels between patients with ES or PNES and HCs.

Although the authors stated that seizure frequency and temporal proximity did not influence the BDNF levels in either the PNES or ES group, the time point to obtain the blood samples was not consistent. Multiple studies have confirmed increased expression of BDNF after seizures.[4]

Confounders may have influenced the data interpretation. Determinants in the measurement of plasma BDNF include fasting/nonfasting state of blood draw, earlier/later measurement, and sample storage time.[5] Studies on these levels should correct for the time of blood withdrawal and storage.

In this study, the HCs were recruited from university staff and student volunteers. It is possible that the samples from the HCs were stored less time than the cohort, which may explain the higher levels of BDNF in the plasma of HCs compared to patients with ES or PNES.

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To the Editor: LaFrance et al.[1] reported decreased plasma BDNF levels in patients with epilepsy or with PNES. The authors concluded that adults with epilepsy appear to have decreased levels of plasma BDNF.[1] However, we think that some care should be taken when interpreting the results of this study.

The mean age for the controls was 22 years vs 43 years for epileptic patients and 40 years for patients with psychogenic nonepileptic seizures. Although the authors controlled for the effect of age using statistics, the control group may not have been adequate for this study. Even if plasma BDNF levels remain constant in 20- or 40-year-olds, some lifestyle aspects would differ between healthy 20-year-old subjects and patients with epilepsy or neuropsychiatric disease in their 40s.

In our view, lifestyle differences might potentially induce considerable systematic bias in studies like this. For example, some studies have shown that plasma BDNF levels might be influenced by daily life activities including watching television, eating fruit, or exercising.[6,7] It has also been shown that patients with epilepsy or other chronic conditions might have important lifestyle differences when compared to healthy individuals, including amount of physical activity, sleep disorders, and stress levels.[8,9] LaFrance et al.[1] did not control for potential biases induced by lifestyle differences. Perhaps the authors should have used their own group of patients with PNES.

The group with PNES was age-matched and had a chronic condition that would probably affect lifestyle. When the authors compared these 2 groups, they did not find any statistical differences regarding plasma BDNF levels. It may be premature to draw conclusions about the effects of epilepsy on plasma BDNF levels. Further studies with adequate controls are necessary to assess whether BNDF can be used as a biological marker of epilepsy in adults.

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Reply from the Authors: We appreciate the comments of Dr. Zhang and Dr. Bianchin et al. on our article.

Dr. Zhang cited the study by Cubeddu et al. on menstruation.[1] Studying BDNF levels in larger groups of patients with seizures and analyzing males and females separately could address the potential for menstrual-related levels. Dr. Zhang mentioned that the BDI-II score may partially explain the differences of plasma BDNF levels among patients. We specifically controlled for BDI-II score among all the participants and found no correlation between BDI-II score and decreased BDNF levels in the subjects with ES. Regarding the multiple studies confirming increased expression of BDNF after seizures, the prior studies did not examine plasma BDNF in adult patients with epilepsy. Moreover, we assessed for this potential influence by controlling for the time point between most recent seizure and blood draw. There was no association between most recent seizure or seizure frequency and BDNF level. Regarding the potential for effect of sample storage time, samples from HCs were gathered contemporaneously with samples from subjects.

In our article, we listed the limitations mentioned by Bianchin et al. regarding the ages of our sample groups. We acknowledged the limited ability of regression analysis to adequately control for confounding by variables whose distribution is largely nonoverlapping across groups.

Regarding the observation by Bianchin et al. on control and symptomatic group differences, the PNES group and the ES groups were alike in many ways, but differed in one significant aspect: psychiatric illness and comorbidities. The PNES group had more psychiatric comorbidities overall, higher BDI-II scores, and PNES itself is classified as a psychiatric illness. However, the ES group was carefully selected to exclude any subject with current or recent psychiatric illness confirmed through BDI-II, physician assessment, past histories, and subject reporting. Given the absence of psychiatric comorbidity in the epilepsy group and multiple reports of decreased plasma BDNF levels in other psychiatric illnesses, the similarly decreased levels of BDNF in a nonpsychiatric ES group is notable. Bianchin also commented on the potential effect of lifestyle differences on plasma BDNF levels. While we did not control for activity level, we acknowledged the literature showing that BDNF levels may be influenced by obesity. We excluded obese participants from the study, which could be an indirect control for some potential lifestyle effect.

Ultimately, the study was a novel finding in BDNF and seizures. In addition, it is a call for more data that could shed light on issues raised by the correspondents.

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Disclosure: See original article for full disclosure list.

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CORRECTION

Relationship of UV exposure to prevalence of multiple sclerosis in England

In the article "Relationship of UV exposure to prevalence of multiple sclerosis in England" by S.V. Ramagopalan et al. (*Neurology*® 2011;76:1410–1414), the following information was omitted: "For the study, researchers looked at all hospital admissions to National Health Service hospitals in England over 7 years. Specifically, they identified 56,681 cases of multiple sclerosis and 14,621 cases of infectious mononucleosis." The authors regret the omission.

Relationship of UV exposure to prevalence of multiple sclerosis in England

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