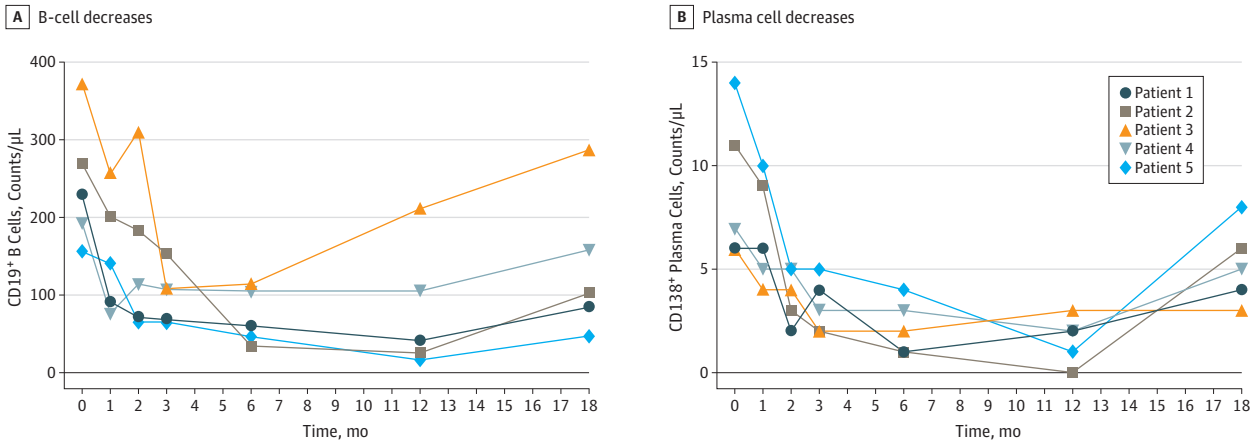
Figure. B-Cell and Plasma Cell Decreases



A, $CD19^+$ B-cell decreases. B, $CD138^+$ plasma cell decreases. To convert to $\times 10^9$ per liter, multiply by .001.

mechanisms of action. Relatively, patients with NMOSD exhibit a more progressive disease course and their relapses are harder to control. The rationale for initiating bortezomib, as stated in our article,[3] is that not all patients with NMOSD respond to rituximab therapy. To our knowledge, there is also no consensus or recommendation on which medication should be administered first for these patients. Apparently, such a decision can be made when a head-to-head randomized clinical trial of bortezomib and rituximab is conducted.

We suggest that it is too early to conclude that rituximab may be safer than bortezomib in NMOSD or other autoimmune diseases. Both bortezomib and rituximab would compromise humoral immunity, but rituximab would also affect antigen presentation by B cells. The dosage of 1 mg/m^2 that was adopted in our study produces less frequent adverse effects. When such adverse effects occur, it is mostly mild cytopenia with no significant neuropathy.[4] The reduction of adverse effects that was accompanied by similar levels of efficacy was observed on subcutaneous bortezomib administration.[5]

As with monotherapy or combination therapy, we believe that monitoring the dynamics or peripheral B cells and plasma cells is important to determine if more cycles of bortezomib treatment may be added for patients with NMOSD 1 year after the initial treatment. There is a need for more research to understand bortezomib in NMOSD, including its usefulness as an induction therapy, as proposed by Kim.

Taylor and Irani discuss the susceptibility of various antibody-secreting cells, including circulating plasmablasts and tissue-resident plasma cells, to bortezomib depletion. In addition, evidence from animal as well as human studies is raised that thymocytes, germinal center B cells, and regular B and T cells may also be susceptible to bortezomib depletion. This evidence is useful to interpret our observation that after bortezomib treatment for NMOSD cases, circulating antibody-secreting cells and $CD19^+$ B cells decreased to 71% and 82%, respectively.

Based on the reduction of aquaporin-4 antibodies and an annual relapsing rate during 1-year follow up among the patients with NMOSD who received bortezomib, a convenient hypothesis was made that removing long-lived plasma cells accounts for the attenuation of pathogenic humoral responses and clinical benefits for these patients. Apparently, this hypothesis needs reevaluation once we learn the precise effects of bortezomib on multiple immune cells in other autoimmune diseases, and particularly in NMOSD. We share the idea that is raised by Taylor and Irani that the ongoing anti-CD19 clinical trial, and perhaps bortezomib in the future, would offer an opportunity to understand the immunology that underlies NMOSD.

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Sensitivity to the Deficits Associated With Traumatic Brain Injury or Chronic Traumatic Encephalopathy

To the Editor The cognitive and depression outcomes observed between football players and nonplaying counter-

parts by Deshpande et al[1] are not surprising. Traumatic brain injury (TBI) has a predilection of the frontotemporal lobes and associated circuitry that are relatively "blind" to standard neuropsychological testing (NPT) and often neuropsychiatric assessments, including depression. Several influential neurological cases published during the last century have repeatedly alerted clinicians to the dramatic cognitive and behavioral dissociation after frontal lobe lesions. The Boston Crow Bar case and several frontal lobe patients emphasized the profound behavioral impairments in the context of otherwise normal NPT. Arnold Pick's frontotemporal (FT) dementia variant description noted primarily disinhibition and abulia, not cognitive impairment. Single TBI, repetitive TBI, and chronic traumatic encephalopathy, have been shown to directly cause FT dementia and TAR DNA binding protein 43 proteolysis.[2] The neuropathological data were discerning, with chronic traumatic encephalopathy diagnosed in 99% of National Football League players.[3]

Common screening tests, such as the Mini-Mental State Examination, Montreal Cognitive Assessment screening, and Frontal Assessment Battery screening are often normal and may miss the entry-triggering criteria for more in-depth NPT. Neuropsychological testing often yields normal or only mildly impaired results in patients with TBI. Various degrees of abulia, which is pervasive with concussions and mild TBI, may hinder adequate behavioral testing and NPT. The marked clinical cognitive-behavioral dissonance accounts for the enigmatic justifications that are given by some patients, such as "driving through a red light is wrong, but I may do so."

Of the tests used in their study, the only behaviorally relevant scale was the State-Trait Anger Expression Anxiety Inventory. An evaluation with the FT syndrome criteria of Rascovsky et al,[4] or the Daphne tool may serve as entry criteria for further evaluations. Thereafter, an interrogation for FT syndromes with behavioral neurological testing methods, such as the Frontal Behavioral Inventory, Frontal Systems Behavioral Examination, or Behavioral Rating Inventory of Executive Function, may be diagnostic.[5] Differing chronic traumatic encephalopathy subtypes are appreciated and diagnostic criteria for traumatic encephalopathy have been proposed, encompassing a more generic term for the various TBI syndromes.[6] Behavioral neurological tests that interrogate the inferior frontal lobes, anterior temporal lobes, and uncinate fasciculus are required for a more representative TBI evaluation. Pertinent syndromes may include partial or complete forms of Geschwind Gastaut and Klüver Bucy syndromes that are not captured by NPT. Traumatic brain injury is a progressive inflammatory, apoptotic, and microvascular disease that may progress for months to years. The nature and extent of a TBI diagnosis is important in view of emerging treatments, including computerized exercises (Cogmed), hypnosis, and pharmacotherapy (amantadine) that may help patients.

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In Reply Hoffmann contends that the clinical measures that were used in our study may not be sensitive to deficits associated with traumatic brain injury (TBI) or chronic traumatic encephalopathy (CTE), pointing to case studies that demonstrated a dissociation between cognitive and behavioral frontal lobe functions, the latter of which are difficult to capture with traditional neuropsychological tests (NPT). We agree that our study's measures represent an incomplete interrogation of frontal lobe functions and did not include tests of initiation, impulsivity, self-awareness, and apathy. While these functions may be impaired following moderate to severe TBI, there is less evidence that such deficits manifest with mild TBI and concussion.[1] However, decades of research have demonstrated the sensitivity of traditional NPT, particularly tests of verbal fluency and delayed word recall, to acute concussion, chronic TBI,[2] and dementias of various etiologies, including Alzheimer disease and frontotemporal dementia, both of which are associated with subtle deficits on NPT that may precede a formal clinical diagnosis.[3,4] As Hoffmann notes, in individual cases in which deficits are mild, NPT may be of little diagnostic use. Nevertheless, randomized clinical trials have consistently demonstrated group differences between cases and healthy individuals. This is particularly true in large samples such as ours (n = 3904).

Hoffmann does raise a critical point—to date, there is no strong evidence base to support the selection of measures that will be most sensitive to CTE. Though the clinical characterization of CTE remains in its infancy, current research suggests that CTE is associated with decreased attention, executive dysfunction, short-term memory loss, and neuropsychiatric symptoms, including depression and aggression.[5] This characterization has often been obtained postmortem via an interview with a relative or loved one of the deceased. By contrast, our study used a prospective assessment with psychometrically validated measures of depression, executive function, memory, and aggression. We

thus believe that our study was well-poised to detect these clinical manifestations of CTE, assuming that (1) CTE is associated with these particular symptoms and (2) CTE was present in a significant proportion of the football players in our study. However, if the head trauma experienced by these participants produced a different clinical profile that was perhaps characterized by disinhibition and abulia, as suggested by Hoffmann, we agree that the available measures would not be discriminating.

Hoffmann cites a recent study that suggests that "neuropathological data were discerning, with CTE diagnosed in 99% of National Football League Players."[6] This statement is misleading without mentioning this study's limitations. The high prevalence reported in this study is not based on a random sample of former National Football League players, but rather on a potentially biased sample of brains that were donated by families of former players, many of whom were symptomatic before death. Such studies cannot establish the base rate of neurodegeneration among the larger population of football players. To attribute cognitive and behavioral symptoms to CTE, future neuropathological studies should include rigorous control groups, such as individuals who experienced repetitive mild TBI without behavioral and cognitive symptoms. Ultimately, determining the true risks of participating in football will require a variety of approaches, including large-scale, retrospective "convenience cohorts" such as ours, as well as smaller, prospective studies with a more detailed phenotyping of exposed individuals.

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Further Actions Are Needed to Prevent Maternal Deaths From Epilepsy

To the Editor We read with interest the article by Razaz et al[1] that documented the increased risks of a range of pregnancy complications in women with epilepsy. Reassuringly, there was no additional increased risk associated with antiepileptic drug therapy. However, this large study did not have the power to examine the severest of maternal outcomes, maternal mortality.

The United Kingdom's confidential enquiry into maternal mortality showed that epilepsy was the leading cause of death due to neurological causes among pregnant and postpartum women from 2009 to 2012.[2] The maternal mortality rate due to epilepsy was the same as the mortality rate due to preeclampsia/eclampsia during 2009 to 2012 (0.4 per 100 000 women delivering) and notably, maternal mortality due to preeclampsia had subsequently decreased whereas mortality from epilepsy had not. The leading cause of death due to epilepsy during pregnancy was sudden unexpected death in epilepsy and there is concern that the rate of this is higher during pregnancy.[3,4]

We believe that deaths due to epilepsy during or after pregnancy are preventable. The confidential enquiry report[2] showed that most maternal deaths were among women with uncontrolled epilepsy. Therefore, we would like to further emphasize the importance of optimizing and continuing antiepileptic drug medication during pregnancy to help reduce the frequency of poor perinatal outcomes. Recent concerns regarding using sodium valproate[5] may lead to women stopping using antiepileptic drugs altogether, and this should be guarded against. It is important to reiterate, as Razaz et al[1] show, that epilepsy is a high-risk comorbidity in pregnancy and should be managed with this in mind. Women should be referred for appropriate specialist management throughout their pregnancies. In addition, preconception counselling for women with epilepsy is essential to ensure their antiepileptic drug regime is optimized for pregnancy. Only then can we begin to improve the outcomes for both mothers and babies.

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