

## CORRESPONDENCE



## Mild Traumatic Brain Injury in U.S. Soldiers Returning from Iraq

**TO THE EDITOR:** We wish to express a number of concerns about the methods used in the study of mild traumatic brain injury by Hoge et al. (Jan. 31 issue).<sup>1</sup> We learned through firsthand experience in the combat zone that immediately after a concussion, the soldier's reported account is most accurate during the initial 24 hours after the blast incident.<sup>2</sup> We therefore would be concerned about recall bias introduced 3 to 4 months after a return from deployment.

In addition, unlike perforation of the tympanic membrane, a transient neurologic event (e.g., a "split-second" loss of consciousness) after a blast incident is not a sentinel finding of direct-blast overpressure.<sup>2</sup> Rather, it is a combination of at least three biodynamic variables: bodily displacement, direct-blast overpressure (involving intrinsic neural-tissue strains), and cardiopulmonary insufficiency.<sup>3-5</sup>

The adverse effects of cardiopulmonary-induced transient neurologic events (e.g., vasodepressor presyncope) are neither necessarily permanent nor cumulative, as a result of biologic restorative processes.

Thus, we are concerned that the assessment methods used do not properly reflect the dimensions of mild traumatic brain injury. Furthermore, we believe that the diagnosis of mild traumatic brain injury can be made only over time.

Michael S. Xydakis, M.D., Lt. Col.

Uniformed Services University of the Health Sciences  
Bethesda, MD 20814  
michael.xydakis@usuhs.mil

Anthony S. Robbins, M.D., Ph.D.

David Grant USAF Medical Center  
Travis Air Force Base, CA 94535

Gerald A. Grant, M.D.

Duke University Medical Center  
Durham, NC 27710

The views expressed in this letter are those of the authors and do not reflect an official position of the Department of Defense.

1. Hoge CW, McGurk D, Thomas JL, Cox AL, Engle CC, Castro CA. Mild traumatic brain injury in U.S. soldiers returning from Iraq. *N Engl J Med* 2008;358:453-63.
2. Xydakis MS, Bebartha VS, Harrison CD, Conner JC, Grant GA, Robbins AS. Tympanic-membrane perforation as a marker of concussive brain injury in Iraq. *N Engl J Med* 2007;357:830-1.
3. Vander Vorst M, Ono K, Chan P, Stuhmiller J. Correlates to traumatic brain injury in nonhuman primates. *J Trauma* 2007;62:199-206.
4. Dodd KT, Mundie TG, Lagutchik MS, Morris JR. Cardiopulmonary effects of high-impulse noise exposure. *J Trauma* 1997;43:656-66.
5. Young AJ, Jaeger JJ, Phillips YY, Fletcher ER, Richmond DR. Intrathoracic pressure in humans exposed to short duration airblast. *Mil Med* 1985;150:483-6.

**TO THE EDITOR:** Hoge and colleagues report that traumatic brain injury is strongly associated with psychiatric symptoms (e.g., depression and post-traumatic stress disorder [PTSD]) that appear to mediate other physical health issues. The study,

### THIS WEEK'S LETTERS

- 2177 Mild Traumatic Brain Injury in U.S. Soldiers Returning from Iraq
- 2179 Outcomes 18 Months after the First Human Partial Face Transplantation
- 2180 Selective Publication of Antidepressant Trials
- 2182 Physicians and Execution
- 2183 Perspective Roundtable: Lethal Injection
- 2184 Letting the Genome Out of the Bottle
- 2185 Serotonin Syndrome and Triptan Monotherapy

however, has at least two major limitations. First, subjects were recruited and examined at a minimum of several months to 1 year after traumatic brain injury, making it somewhat difficult to establish a temporal relationship between traumatic brain injury and psychiatric symptoms.<sup>1</sup> Second and more important, the authors do not provide information on the soldiers' psychiatric history predating the traumatic brain injury. Previous studies have shown that significantly large numbers of subjects with depression after traumatic brain injury had preexisting depression.<sup>2</sup> Alcohol and substance abuse are also risk factors for psychiatric issues after traumatic brain injury<sup>1,3</sup>; data regarding these issues are also not included in the article by Hoge et al.

Rohit R. Das, M.B., B.S., M.P.H.

Brigham and Women's Hospital  
Boston, MA 02115  
rohitdas@yahoo.com

1. Deb S, Lyons I, Koutzoukis C, Ali I, McCarthy G. Rate of psychiatric illness 1 year after traumatic brain injury. *Am J Psychiatry* 1999;156:374-8.
2. Jorge RE, Robinson RG, Arndt SV, Forrester AW, Geisler F, Starkstein SE. Comparison between acute- and delayed-onset depression following traumatic brain injury. *J Neuropsychiatry Clin Neurosci* 1993;5:43-9.
3. Federoff JP, Jorge RE, Robinson RG. Depression in traumatic brain injury. In: Starkstein SE, Robinson RG, eds. *Depression in neurologic disease*. Baltimore: Johns Hopkins University Press, 1993:139-49.

**TO THE EDITOR:** As an endocrinologist with a special interest in pituitary dysfunction secondary to traumatic brain injury, I question the conclusions drawn in the article by Hoge et al. These authors report that soldiers with traumatic brain injuries have significantly higher rates of self-reported physical and mental health problems than soldiers with other injuries, and they imply that many of these symptoms could be related to PTSD. What the authors have overlooked, however, is the idea that these symptoms could also be related to hypopituitarism and growth hormone deficiency related to head trauma.

Pituitary deficiency occurs in 20 to 50% of patients with traumatic brain injury<sup>1-4</sup>; growth hormone deficiency is common and often occurs without other deficiencies.<sup>1-4</sup> The psychological and neurobehavioral complications after head injury, usually attributed to brain damage itself or currently to PTSD, may in some cases be related to growth hormone deficiency or other pituitary dysfunction, and treatment could improve the rehabilitation of these patients.<sup>2,4</sup> Good clinical

practice therefore suggests that these patients should at least be screened for pituitary disease.

Larry D. Stonesifer, M.D.

St. Francis Medical Center  
Federal Way, WA 98003  
ldstonesi@aol.com

1. Aimaretti G, Ambrosio MR, Di Somma C, et al. Residual pituitary function after brain injury-induced hypopituitarism: a prospective 12-month study. *J Clin Endocrinol Metab* 2005;90:6085-92.
2. Agha A, Rogers B, Sherlock M, et al. Anterior pituitary dysfunction in survivors of traumatic brain injury. *J Clin Endocrinol Metab* 2004;89:4929-36.
3. Agha A, Phillips J, O'Kelly P, Tormey W, Thompson CJ. The natural history of post-traumatic hypopituitarism: implications for assessment and treatment. *Am J Med* 2005;118:1416.
4. Kelly DF, Gonzalo IT, Cohan P, Berman N, Swerdloff R, Wang C. Hypopituitarism following traumatic brain injury and subarachnoid hemorrhage: a preliminary report. *J Neurosurg* 2000;93:743-52.

**TO THE EDITOR:** Hoge and colleagues and Bryant,<sup>1</sup> in an accompanying editorial, argue for caution in assigning a diagnosis of mild traumatic brain injury solely on the basis of reported history. The Department of Veterans Affairs (VA) appreciates the importance of appropriately diagnosing and treating traumatic brain injury and the mental health consequences of military service, including PTSD. Military personnel entering the VA system undergo a detailed, multistep screening for traumatic brain injury. The initial step is a questionnaire. Veterans identified by the initial screening undergo a second-level evaluation for traumatic brain injury. The evaluation team includes physicians and psychologists who are trained to detect traumatic brain injury and mental health issues, including PTSD and depression. We evaluate findings to determine whether they are best attributed to traumatic brain injury, mental health issues, or preexisting conditions. Consequently, although the initial part of the screening process for traumatic brain injury depends on self-report, the second-level assessment relies on physical examination, psychiatric assessment, neuroimaging, and neuropsychological test results. The care of veterans is directed at treating both physical and mental problems. The VA aims to return veterans as closely as possible to their precombat state.

Robert L. Ruff, M.D., Ph.D.

Louis Stokes Veterans Affairs Medical Center  
Cleveland, OH 44106

1. Bryant RA. Disentangling mild traumatic brain injury and stress reactions. *N Engl J Med* 2008;358:525-7.

**THE AUTHORS REPLY:** We agree with Xydakis and colleagues that concussion (i.e., mild traumatic brain injury) can be accurately diagnosed only at the time of injury. We remain concerned that population screening for concussion and post-concussive symptoms months after injury will result in unintended iatrogenic effects from misdiagnosis, inconclusive neuropsychological or neuroimaging studies, costly referrals, or side effects of medication.<sup>1,2</sup> The letter by Xydakis and colleagues, however, is also an example of the circular arguments and speculation about injurious primary-blast effects that permeate the recent literature about mild traumatic brain injury.<sup>3</sup> The conclusion that “the diagnosis of mild traumatic brain injury can be made only over time” does not logically follow from the guidance regarding assessment within 24 hours after injury. Experimental blast models, such as air shock tubes, do not take into account vehicle and body armor, the high proportion of explosions that occur in open spaces, or the devastating effects of fragment dispersion and fire on persons close enough to be exposed to the primary overpressure wave.<sup>4</sup>

We agree with the comments by Das on the limitations of our study. However, our study focused on causal inferences at an important time when screening is becoming routine. If the suspected postconcussive symptoms 3 to 4 months after the return from deployment were caused by concussions, then we would expect this association both in soldiers with PTSD and in the larger group of soldiers without PTSD. This association was not observed in both groups; instead, the physical symptoms were clustered in the group with PTSD. The likely mechanism pertains to the very life-threatening context. PTSD is not known to be associated with sports-related concussions. Being knocked unconscious from a blast during combat is a life-threatening event that occurs in the context of other traumatic events. These experiences can precipitate stress responses and traumatic memory encoding that underlie the

development of acute stress disorder and PTSD, which, in turn, are strongly associated with generalized symptoms, including those in the “post-concussive” category, through autonomic nervous system and neuroendocrine dysregulation.<sup>5</sup>

We appreciate Stonesifer’s suggestion regarding pituitary dysfunction, but the literature to which he refers pertains almost exclusively to moderate or severe traumatic brain injury. We thank Ruff for detailing the multistep screening intervention in VA facilities. We only ask that Ruff consider the assumptions underlying each step and use scientific rigor to ensure that the expected risks and costs do not outweigh the hypothesized benefits. The value of screening would obviously be greater if effective treatments were available for concussions identified months after injury.

Charles W. Hoge, M.D.

Walter Reed Army Institute of Research  
Silver Spring, MD 20910  
charles.hoge@us.army.mil

Charles C. Engel, M.D., M.P.H.

Uniformed Services University of the Health Sciences  
Washington, DC 20910

Carl A. Castro, Ph.D.

U.S. Army Medical Research and Materiel Command  
Ft. Detrick, MD 21702

The views expressed in this reply are those of the authors and do not reflect an official position of the Department of Defense.

1. Iverson GL, Zasler ND, Lange RT. Post-concussive disorder. In: Zasler ND, Katz DI, Zafonte RD, eds. *Brain injury medicine: principles and practice*. New York: Demos Medical Publishing, 2007.
2. Wood RL. Understanding the ‘miserable minority’: a diathesis-stress paradigm for post-concussional syndrome. *Brain Inj* 2004;18:1135-53.
3. Bhattacharjee Y. Shell shock revisited: solving the puzzle of blast trauma. *Science* 2008;319:406-8.
4. Wade CE, Ritenour AE, Eastridge BJ, Young LA, Blackburne LH, Holcomb JB. Explosion injuries treated in combat support hospitals in the global war on terrorism. In: Elsayed NM, Atkins JL, eds. *Explosion and blast-related injuries*. Amsterdam: Academic Press (in press).
5. Boscarino JA. Posttraumatic stress disorder and physical illness: results from clinical and epidemiological studies. *Ann N Y Acad Sci* 2004;1032:141-53.

## Outcomes 18 Months after the First Human Partial Face Transplantation

**TO THE EDITOR:** The acceptance of a partial face allograft as a promising procedure for patients with facial disfigurement will depend on long-term functional results. An impressive recovery of sensory function was reported by Dubernard

et al. (Dec. 13 issue).<sup>1</sup> This recovery of sensory function is understandable, given that the maxillary and mandibular nerves were resutured in the recipient’s face. The recovery of motor function, however, remains a mystery, since only a single