Brain Injury: Refinement and Restoration—The Light Is Coming On

Ross Zafonte, DO

The scope and extent of traumatic brain injury (TBI) as a regional, national, and international problem cannot be underestimated. The U.S. Centers for Disease Control and Prevention has estimated that 1.7 million people sustain TBI annually and that 75%-85% of these injuries are mild [1]. Sports and bicycle accidents account for 26% of mild TBI, with approximately 300,000 persons with sports-related TBIs presenting to the emergency department yearly. The vast majority of those were due to concussions. No other health issue has received more media recognition than sports-related concussion. Recent findings describe the high incidence of TBIs among service members returning from conflicts in Iraq and Afghanistan [2]. Yet, for sports- or military-related injuries, little in the way of compelling evidence is available to guide therapy. These numbers are additive to the large number of individuals who experience lifelong disability related to severe TBI each day. Although numerous clinical trials for neuroprotection have failed to show efficacy, a bright light exists in the refinement and neurorestorative arenas for the near future [3].

REFINEMENT

Critical to designing better therapies are pilot programs that assist in understanding the critical elements behind this heterogeneous disease, in other words, a refinement of the injury pattern and the person experiencing the injury. One such factor is an understanding of the biomarkers that may help us link to specific targeted therapies as well as serve as a proxy measure for plasticity treatment response and understanding of natural recovery. Wagner [4] and Kobeissy et al [5] have discussed the role of using rehabilomics as the measure of biologic effectiveness and understanding potential windows for which enhanced responsiveness may be possible. Neuroimaging may allow us to better define injury patterns and to classify them more accurately. Saatman et al [6] expressed concerns regarding the relatively desperate classification of those in the severe, moderate, and mild categories. Shenton et al [7] provide a recent review of more refined techniques within magnetic resonance and diffusion tensor imaging that would allow better characterization of injury patterns and potentially look at biomarkers of recovery among those with mild, moderate, and severe injury. They also discussed an important novel technique: namely, examining the role of inflammation that may allow improved characterization of injury patterns and the links between psychogenic and physiologic disease. Genetic-based issues can play an important role, and we are just starting to understand the contribution of genetics to variability and outcome as well as resiliency and behavioral homeostasis. McAllister et al [8] have described the critical polymorphism with brain-derived neurotrophic factor (BDNF). This factor plays an important role in cognition as well as neural survival and plasticity. These investigators found that polymorphisms in BDNF may influence cognitive performance shortly after mild TBI, thus raising the important issues regarding manipulation of BDNF. Additional genomic polymorphisms, such as DRD2, DAT, COMT, and Val158 Met, have been described as having a potential impact on the injury and recovery process.

Over the past several years, a transformational theory has been proposed that begins to link TBI not as a singular event but, rather, a disease process. Already acknowledged concerns regarding neurodegeneration in those patients with more severe injuries suggest that TBI is, in some ways, a lifelong process and one that can be uniquely managed by rehabilitation specialists [9]. This work is supported by findings that suggest chronic cortical changes in plasticity after mild injury [10] Goldstein showed that chronic traumatic

R.Z. Spaulding Rehabilitation Hospital, Harvard Medical School, 125 Nashua St, Boston, MA. Address correspondence to: R.Z.; e-mail: rzafonte@partners.org

Disclosure: 2A, Best Doctors, Oakstore; 4A, Demos Medical Publishing; 5A, U.S. Department of Justice; 8B, NIH, NIDRR, DOD; 9, board membership J Neurotrauma and J Neuroengineering and Rehabilitation

Disclosure Key can be found on the Table of Contents and at www.pmrjournal.org

encephalopathy may result from blast and/or chronic repetitive subconcussive types of injuries [11]. Thus, our understanding of the person and the refinement of disease assessment will be critical to our understanding and to developing treatments for both acute and chronic aspects of the disease. In many ways, a more elegant description of the endophenotype is needed that shows us what makes some persons more resilient than others.

RESTORATION

The next step in the care of persons with TBI is to develop therapies that enhance restoration. A novel set of nonpharmacologic treatment regimens can carry a tremendous potential for limited adverse effects and potential clinical efficacy. Transcranial magnetic stimulation has been shown as a potential diagnostic tool for evaluating those patients with symptoms long after concussion as well as a potential modulator of depression and cognitive function. Modulation of motor performance and motor learning has occurred in both stroke and brain injury after transcranial direct current stimulation (tDCS). Recently, tDCS has been used to examine plasticity after injury and to enhance the potential for response to therapy. Hyperbaric oxygen is presently examined in a large clinical trial through the U.S. Department of Veterans Affairs. The role of hyperbaric oxygen in both acute and more chronic settings is being explored to understand its efficacy and mechanism [12].

Near-infrared transcranial laser therapy has been found to modulate various biologic processes acutely and, potentially, post-acutely after TBI. A recent study applied transcranial laser therapy to mice after TBI and noted long-term reduction in neurologic deficits, whereas Ando et al [13] looked at a continuous versus a pulse 810-nm laser, which showed evidence that the pulse waves were more effective for producing amelioration of injury. At present, a clinical study is ongoing that is evaluating the role of low-level laser as a chronic therapy for persistent postconcussive symptoms. Focused ultrasound was evaluated for targeted gene delivery in a murine model of central nervous system injury. This work showed that focused ultrasound can enhance blood–brain barrier penetration, thereby potentially allowing us to deliver viral, pharmacotherapy, or even nanotechnology-based therapy in this manner [14].

Patients with a disorder of consciousness have improved by delivery of intracortical modulation, specifically, central thalamic deep brain stimulation to enhance levels of arousal and clinical performance [15]. Several postacute clinical trials have represented an exciting frontier. Giacino et al [16] demonstrated an improved rate of recovery with amantadine administration for 6 weeks in persons with disorders of consciousness between 1 and 4 months after injury. Although the groups seemed to return to a parallel course of recovery after the medication was discontinued, this is the first large positive study that showed postacute interventional efficacy after TBI. This work suggests a wide window of opportunity to make an impact on recovery. Further work with potential refinement of dosing and duration of such interventions is warranted. The relatively pleiotropic mechanisms of amantadine suggest that further work could help to define the most effective and important pathways involved in efficacy. Other agents being evaluated for improving arousal or improved responses include methylphenidate, apomorphine cholinergic agents, acetylcholinesterase inhibitors, and noradrenergic reuptake inhibitors. Critical to this population and others with chronic neurologic deficits will be targeting outcome metrics as well as refining populations that may best benefit from proposed pharmacologic and nonpharmacologic interventions.

Few arenas in physiatric practice have as clear a need for clinical research as the treatment of concussion. Physiatrists can lend important insights into potential clinical studies of pharmacotherapy, vestibular interventions, nutraceuticals, cognitive rest, and exercise. In the area of concussion, both Leddy et al [17] and Gagnon et al [18] have suggested evidence that, in the postacute period of concussion, controlled exercise may be facilitatory in attempting to enhance recovery, improve focus, and ameliorate postconcussive symptoms. The benefit of cognitive rest is as yet unquantified and requires further investigation. Nutraceuticals carry great promise and potentially low risk; however, caution should be raised about the assumption of benefit and lack of harm [19]. The diffuse set of symptoms experienced after concussion have led to the ubiquitous use of psychopharmacology, yet specific studies regarding efficacy are lacking.

THE FUTURE FOR PHYSIATRY

Future training for physiatrists will require greater specificity in the pathophysiology of brain injury. An enhanced understanding of refined injury parameters and methods for restoration will also be needed. Physiatrists will need to play key roles in the care for those patients with a wide spectrum of brain injury, from disorders of consciousness to sports-related concussion. As brain injury medicine fellowships are developed and enhanced over the next decade, the need to focus on biologic and functional principles will grow. A significant obstacle for the future will be ensuring that adequate funding for clinical and research fellowships and postacute research remains a priority for interested advocacy groups and federal agencies.

CONCLUSION

The future opportunities for the care of those with TBI shine bright because of our ability to refine the injury pattern and individual variation. The biology of recovery is beginning to unfold. The intermingling of therapeutic technologies, neuromodulator and pharmacologic, will likely lead to a bright

future where quality of life can truly be enhanced for those with TBI. Although we are unlikely to quickly be able to ameliorate the entire impact of a diffuse brain trauma in the near future, it is likely that we will be able to have a substantial, life-changing impact on the extent of injury and the recovery of those with TBI. The light is truly coming on.

REFERENCES

1. CDC. Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Deaths. 2002-2006. 2010. Available at http://www.cdc.gov/traumaticbraininjury/tbi_ed.html. Accessed July 23, 2012.
2. Ling G, Bandak F, Armonda R, et al. Explosive blast neurotrauma. J Neurotrauma 2009;26;815-825.
3. McConeghy K, Hatton J, Hughes L, et al. A review of neuroprotection pharmacology and therapies in patients with acute traumatic brain injury. CNS Drugs 2012;26:613-636.
4. Wagner AK. TBI translational rehabilitation research in the 21st century: Exploring a rehabilomics research model. Eur J Phys Rehabil Med 2010;46:549-556.
5. Kobeissy FH, Guingab-Cagmat JD, Razafsha M, et al. Leveraging biomarker platforms and systems biology for rehabilomics and biologics effectiveness research [review]. PM R 2011;3(Suppl 1):S139-S147.
6. Saatman K, Duhaime A, Bullock R, et al. Classification of traumatic brain injury for targeted therapies. J Neurotrauma 2008;25;719-738.
7. Shenton ME, Hamoda HM, Schneiderman JS, et al. A review of magnetic resonance imaging and diffusion tensor imaging findings in mild traumatic brain injury. Brain Imaging Behav 2012;6:137-192.
8. McAllister TW, Tyler AL, Flashman LA, et al. Polymorphisms in the brain-derived neurotrophic factor gene influence memory and processing speed one month after brain injury. J Neurotrauma 2012;29:1111-1118.
9. Wishart HA, Roth RM, Saykin AJ, et al. COMT Val158Met genotype and individual differences in executive function in healthy adults. J Int Neuropsychol Soc 2011;17:174-180.
10. Baugh CM, Stamm JM, Riley DO, et al. Chronic traumatic encephalopathy: Neurodegeneration following repetitive concussive and subconcussive brain trauma. Brain Imaging Behav 2012;6:244-254.
11. Goldstein LE, Fisher AM, Tagge CA, et al. Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model. Sci Transl Med 2012;4:134ra60.
12. Sahni T, Jain M, Prasad R, et al. Use of hyperbaric oxygen in traumatic brain injury: Retrospective analysis of data of 20 patients treated at a tertiary care centre. Br J Neurosurg 2012;26:202-207.
13. Ando T, Xuan W, Xu T, et al. Comparison of therapeutic effects between pulsed and continuous wave 810-nm wavelength laser irradiation for traumatic brain injury in mice. PLoS One 2011;6:e26212.
14. Huang Q, Deng J, Wang F, et al. Targeted gene delivery to the mouse brain by MRI-guided focused ultrasound-induced blood-brain barrier disruption. Exp Neurol 2012;233:350-356.
15. Giacino J, Fins JJ, Machado A, et al. Central thalamic deep brain stimulation to promote recovery from chronic posttraumatic minimally conscious state: Challenges and opportunities. Neuromodulation 2012 May 24. Epub ahead of print.
16. Giacino J, Whyte J, Bagiella E, et al. Placebo controlled trial of amantadine for severe traumatic brain injury. N Engl J Med 2012:366:819-826.
17. Leddy JJ, Kozlowski K, Donnelly JP, et al. A preliminary study of subsymptom threshold exercise training for refractory post-concussion syndrome. Clin J Sport Med 2010;20:21-27.
18. Gagnon I, Galli C, Friedman D, et al. Active rehabilitation for children who are slow to recover following sport-related concussion. Brain Inj 2009;23:956-964.
19. Erdman J, Oria M, Pillsbury L, eds. Nutrition and Traumatic Brain Injury: Improving Acute and Subacute Health Outcomes in Military Personnel. Institute of Medicine, National Academies Press; 2011.