Traumatic Brain Injury: The Silent Menace

Kenneth Hensley, PhD
Associate Professor
Department of Pathology

Kris Brickman, MD
Professor and Chair
Department of Emergency Medicine

Despite its straightforward name, traumatic brain injury (TBI) can be a surprisingly subtle culprit in brain disease. An acute TBI is usually obvious: A patient suffers a sudden blow to the head, which may or may not damage cranial bones. Sometimes, blood vessels rupture inside the skull causing a condition called hematoma. The hematoma can be severe enough to compress the brain, requiring emergency response to drain the blood and reduce swelling. These types of TBI sometimes happen in a fall, or a vehicle accident. Treatment is fairly straightforward in the immediate or acute stage, and often the patient is able to rehabilitate. As such, obvious acute TBI afflicts some 200,000 Americans annually.

This obvious type of TBI obscures the public’s awareness of more subtle, subacute or chronic aspects of physical brain damage. There are two main subtle but important components to chronic TBI injury. The first component is that the actual TBI may not be appreciated at all, immediately, by patients or physicians. Repeated shock to the head can occur in athletes, for instance, even if they do not sustain a diagnosed concussion. Or, a car crash survivor may walk away from the accident apparently unharmed, not realizing that sudden lateral deceleration tore delicate connections between his nerve cells. Perhaps a soldier on patrol sees an improvised explosive device detonate, but is far enough away to sustain any obvious damage i.e., neurologic deficit. Days or weeks later the victims of these events may succumb to headaches, dizziness, lack of focus, inability to concentrate, or short-term memory loss. By this point there is little to be done but manage the patient’s symptoms. Unfortunately, the initial unrecognized TBI might have been worsened by repeated exposure to head trauma through athletic contact, subsequent work or combat-related stress. In the long term, these mild (and often repeated) TBI events may trigger inflammatory processes in the brain, leading to early onset of dementia, Alzheimer’s disease, Parkinson’s disease or motor neuron disease.

Physicians and scientists at The University of Toledo and their collaborators around the world have recently made substantial strides toward measuring and treating so-called mild or chronic TBI. Current evaluation and management of mild TBI has advanced little over the last several years, for both the sports world and the military. These head injuries diagnosed as concussions are essentially monitored symptomatically, typically
with some limited cognitive assessment to determine who can and cannot return to duty or sports activity, based largely on subjective findings of the patient or athlete. We at The University of Toledo Health Science Campus (UTHSC) Department of Pathology and Department of Emergency Medicine pooled our experience to develop so-called “biomarkers” of mild TBI to give us a more objective perspective in evaluating mild TBI/concussions. Meanwhile, we have partnered with scientists at the Veteran’s Affairs of Greater Los Angeles Health System (VAGLAHS) and University of California at Los Angeles (UCLA) to test promising drugs being developed by UTHSC scientists that slow neural degeneration after TBI.

Dr. Kris Brickman, Director of the Emergency Department at The University of Toledo Medical Center and Team Physician for St. John’s Jesuit High School and I have engaged local high school athletes to utilize this unique methodology and a creative approach to measuring total brain injury in these athletes. In particular, athletes on the St. John’s High School football and hockey teams partnered with us to move this science forward. These athletes provided saliva samples at the beginning of their 2015 football and hockey seasons. Any player who sustained a potentially significant head injury i.e., concussion during a game or practice would then have subsequent saliva swabs taken within 24 hours and measured against their baseline. The saliva samples were probed for proteins released from damaged nerve cells identified in laboratory mice after experimental TBI. We found that one particular protein called CRMP2 (collapsin response mediator protein-2) that helps nerve cells maintain their structure, was chopped into small pieces that collect in blood and saliva. This is exciting work that we hope will eventually lead to a “TBI-meter” or “dipstick” approach to monitoring mild TBI. We see two ways this could help athletes and military personnel. First, persons who may have been exposed to potential brain trauma could be identified and diagnosed much more quickly and appropriately monitored for recovery before sustaining any further head trauma. Second, these individuals could be pre-tested at regular intervals to ascertain appropriate recovery from their TBI before reentering athletic or risky military activity where additional brain trauma could be sustained. This could have special importance to military personnel who have to be alert and clear-headed during combat operations. In this case, a soldier who is at risk for cognitive deficits because of an unappreciated TBI might be down-checked for recovery, thus avoiding operational errors.

This concept is analogous to the well-established practice of radiation dose. When a radiologist or scientist working with radiation goes to work, he first pins a radiation badge to his clothes. When the radiation badge turns dark he knows he needs to stop for a period of time. We don’t have a dosimeter for chronic brain trauma, but arguably, we need one.

Of course, preventing TBI is more important than treating damage – if possible – but what can we do if a person has sustained a TBI, to lessen long-term damage? We and our colleague Dr. Marni Harris-White of the VAGLAHS have been working on that aspect of TBI research as well. We have created an orally available, brain-penetrating small molecule that binds the same CRMP2 protein used in his biomarker research. The drug candidate, called LKE (lanthionine ketamine-ester), alters the structure of CRMP2 to protect the protein and make it function better. LKE-exposed CRMP2 is resistant to phosphorylation by cyclin-dependent kinases, and may be resistant to proteolysis after neurotrauma. This resilient CRMP2 continues to stabilize neural axons and promotes the beneficial process of neural autophagy, which helps clean up the damage after neural exposure to TBI. When given to mice after an experimental TBI, LKE reduced learning deficits and decreased neuroinflammation. Furthermore, LKE protected the myelin “insulation” surrounding neurons and maintained the nerve cell structure in the face of the injury. This noteworthy research was published in the Journal of Neurotrauma in winter 2015. The small molecule drug candidate is under advanced preclinical development for neurodegenerative diseases, and traumatic brain injury is one possible future clinical target.

We're still early in the process of understanding the long-term, subtle consequences of mild repetitive TBI. Nonetheless this is an important topic and we are making progress.

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**Research Update from the Center for Pain Management**

Joseph Atallah, MD  
Professor and Chief, Division of Pain Medicine  
Department of Anesthesiology

Pain is a universal phenomenon that health professionals across all disciplines encounter in individuals at all ages, in all health care settings, and across all situations. It is a complicated, often debilitating medical problem that can have a major impact on the physical and mental well-being of a patient.

The University of Toledo Center for Pain Management provides some of the most
advanced treatment modalities in a supportive and compassionate environment. Our team cares for hundreds of patients on an inpatient and outpatient basis each year. It has helped patients return to independence and comfort, and has restored their quality of life. The Center sees hundreds of patients on a yearly basis with a staff of 7 RNs in the Interventional Pain area and 5 MAs and 1 RN in the Pain Clinic. There is a Nurse Manager for the combined areas.

Our center is an advocate for research and education in pain management. Patients who qualify have the opportunity to participate in clinical studies seeking better, more effective treatments for managing pain. The Center for Pain management has a one-year fellowship leading to board certification in Pain Medicine by the American Board of Anesthesiology. There have been 5 graduates and currently 2 fellows in the program. There are opportunities involving sponsored and investigator initiated research. Thefellows are expected to participate in new or ongoing clinical research that results in the publication of an abstract, presentation of the abstract either orally or in poster format at a major meeting and eventual conversion to a manuscript for publication in a peer reviewed journal.

Recently, our center has been ranked third in the US in enrolling patients for the RELIEF study that is a prospective, multi-center, global registry trial to evaluate long-term effectiveness of a Boston Scientific neurostimulation system for chronic pain control of the trunk and/or limbs, including unilateral or bilateral pain associated with the following: failed back surgery syndrome, intractable low back pain and leg pain. In this study, we follow patients through the spinal cord stimulation (SCS) trial, with permanent implant and follow up out to 36 months. The international study started in May 2013 with an estimated enrollment of 4800 projected by April 2020. The Pain Center enrolled the first patient in November 2013 and recently enrolled our 51st subject. Enrollment continues and we hope to enroll up to 75 subjects. In another ongoing randomized controlled study called WHISPER, also sponsored by Boston Scientific, our center is enrolling patients with chronic back pain who have been previously implanted with the Precision SCS system and prefer no paresthesia, to evaluate the effectiveness of the system at a sub-perception amplitude. The study started in December 2014 with an estimated enrollment of 146 by December 2017. We are currently enrolling and hope to enroll 14 subjects.

We are conducting a study in conjunction with Dr. Daniel Gaudin in the Department of Surgery, to evaluate the Percutaneous Spinal Cord Stimulation Trial using dermatomal somatosensory evoked potential collision testing. We are in the enrollment phase of this investigator initiated study.

We are also working on retrospective analysis of analgesic effectiveness with intrathecal pumps and chronic pancreatitis. To date, the accepted treatment for chronic pancreatitis induced abdominal pain consists of narcotic medical management. Although effective at modulating the patient’s symptoms, chronic narcotic use leaves the patient at risk for narcotic tolerance, dependence, and withdrawals. We examined and proposed an alternative interventional means for treating this symptom via an Intrathecal pain pump.

During the 2015 North American Neuromodulation Society annual meeting that is held December 10-13, in Las Vegas, we presented the results of one of our previous projects. The study was a randomized prospective analysis of three different techniques for anchoring the SCS leads to the skin during the 7-days trial period, to determine if a particular technique was superior in preventing migration. We found that inferior lead migration was demonstrated in all techniques used in our investigation. Most of the migrations occurred during the first three days of the trial among all techniques. The study manuscript is ready for journal submission.

Additionally, we reported few uncommon cases during our practice that we effectively managed in an exceptional, yet safe, way to help improve patient quality of life. From this experience, we published one paper in the Journal "Pain Physician" titled "Ultrasound-guided Phrenic Nerve Block for Intractable Hiccups following Placement of Esophageal Stent for Esophageal Squamous Cell Carcinoma: A Case Report".

Research in the Center for Pain Management is ongoing in the pursuit of providing the best treatment options for our patient population. We would like to send a special thanks to the Pain Center staff for their hard work, cooperation and providing an environment that fosters continuing research endeavors.

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**Clinical Research Snippets**

Editors: Anand Mutgi, MD & Sadik Khuder, PhD
Tumor-Treating Fields offers new ray of hope for patients with glioblastoma

Nauman Siddiqui, MD
Zarmina Khan, BDS
Jamal Saleh, MD

Glioblastoma multiforme is a very aggressive and lethal primary brain tumor. Most patients with this tumor die within 1 to 2 years of diagnosis. Many attempts have been made over the last 10 years to improve survival in patients with glioblastoma but most of them have failed to show any improvement when evaluated in randomized clinical trials. Standard therapy for glioblastoma consists of surgical resection followed by concurrent chemoradiation with temozolomide. This month we present a clinical trial of a new modality which consists of Tumor-Treating Fields (TTF) in the treatment of glioblastoma.

In this trial, 695 patients were randomized to receive TTF plus temozolomide (n=466) and temozolomide alone (n=229). After a median follow-up of 38 months, the median progression-free survival was 7.1 months in the TTF plus temozolomide group compared with 4.0 months in control group. This new intervention prolongs the median progression-free survival in this population by 3.1 months while overall survival was increased by 4.9 months over the temozolomide alone group.

TTF consists of low intensity alternating electrical fields to halt the cell division of tumor cells and does not affect the normal cells. In the interim analysis the current trial was successful in showing significant improvement in survival that resulted in early termination of the trial. Because of the high mortality for glioblastoma, 35 patients in the control group were switched to TTF treatment group to receive benefit from this new treatment.

TTF has improved survival in glioblastoma patients by almost 5 months which is a significant milestone and a ray of hope for patients suffering from this tumor type. TTF has a good safety profile without any significant increase in systemic toxicity. Most common adverse effects include mild to moderate local skin toxicity.

The findings of this trial showed the potential applicability of TTF as a novel therapeutic modality for glioblastoma. Before this trial, TTF was approved for use only in patients with tumor recurrence or progression despite standard treatment. Based on the findings of this trial, the FDA approved TTF for use as a first line therapy in combination with temozolomide for newly diagnosed patients.

TTF is an evolving and encouraging novel treatment concept. There are ongoing trials evaluating the efficacy of TTF in other malignancies including lung cancer, ovarian cancer and pancreatic cancers.

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New Clinical Trials

EVEREST: EVErolimus for Renal Cancer Ensuing Surgical Therapy
Dr. Samay Jain - Urology

Comparison of First Sense Breast Exam® to the University of Toledo Mammography and Biopsy Results.
Dr. Iman Mohamed - Medicine

A Prospective, Multi-Center Study Designed to Evaluate the Positive Predictive Value of WOUNDCHEK™ Protease Status on Venous Leg Ulcers (VLUs) and Diabetic Foot Ulcers (DFUs) by Testing Wound Fluid Swab Samples Collected from Two Types of Chronic Wounds
Dr. Munier Nazzal - Surgery

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IRB Corner
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**Contact Us**

Health Science Campus • Center for Creative Education Bldg.

2920 Transverse Drive, Floor 3 • Toledo, OH 43614

Phone: 419.383.6919 • ClinicalResearch@utoledo.edu