Imaging Sheds Light on Lasting Effects of TBI

VITALS

Major Finding: Various functional and structural imaging techniques can provide a prognosis for TBI patients and objective evidence to insurers to cover rehabilitative services.

Data Source: A review of recent imaging studies of traumatic brain injury.

Disclosures: None

BY MICHELE SULLIVAN

BANGKOK, THAILAND – New imaging techniques may help to explain the disabling symptoms that can plague patients with traumatic brain injury long after their acute problems have resolved, and eventually guide the best choice for medical therapy.

Survivors of traumatic brain injury who complain of depression, irritability, and memory or cognitive problems are often written off as psychiatric cases or malingerers, Dr. Ramon Diaz-Arrastia said at the World Congress of Neurology. "This is the frustrating thing about TBI. The patients might look OK—they don't have paralysis; they are walking around. But their cognitive and behavioral problems are real."

Imaging techniques that are now well established in other areas of neurology—such as diffusion-weighted and susceptibility-weighted magnetic resonance imaging—are now being used to show that brain injuries leave permanent, life-altering marks behind after the contusions and hematomas have healed.

These findings may have both immediate and long-range benefits, said Dr. Diaz-Arrastia, a professor of neurology at the University of Texas Southwestern Medical Center, Dallas. "Right now, imaging these patients has the primary value of providing a prognosis and perhaps helping them obtain the care that they need. In terms of reimbursement, it's useful to have an objective documentation of the injury when trying to convince insurers to cover rehabilitative service."

In the future, imaging the post-TBI brain may help guide medical treatment choices and monitor drugs' effectiveness.

So far, nearly 30 drugs have provided effective neuroprotection in animal models of TBI, he said. However, none that has undergone testing in well-designed phase III trials has proven beneficial to humans.

Part of the problem may be the heterogeneity of human brain injury, Dr. Diaz-Arrastia said. There are many subtypes of TBI, yet "from the point of view of the clinical trials, all patients who present in a coma [after a brain injury] are treated the same way, even though the injuries can be very different, with very different prognoses."

Susceptibility-weighted imaging (SWI) is one technique being studied in TBI patients. It measures the paramagnetic shift of intravascular deoxyhemoglobin and methemoglobin, amplifying the appearance of microhemorrhages and making them much easier to identify. "SWI picks up 640% more lesions and 200% more lesion volume than does gradient-recall echo," Dr. Diaz-Arrastia said, referring to work by Dr. Karen Tong from Loma Linda (California) University.

SWI is very good at identifying diffuse microvascular injury, a marker for diffuse axonal injury that is usually invisible on computed axial tomography. "The only problem is that SWI may be overly sensitive," he said. "One patient with a lot of microhemorrhages might be complaining only of headache and dizziness, whereas another with a similar volume might have a lot more problems."

Diffusion-weighted imaging (DWI), which is well established in the stroke world, is understudied in TBI, probably because it's a challenge to perform magnetic resonance imaging on these acutely ill patients. But this technique provides detailed information about the makeup of lesions, showing vasogenic and cytotoxic edema, as well as location in the superficial or deep structures in both gray and white matter.

Dr. Diaz-Arrastia and his colleagues performed DWI on 99 patients with TBI. Of these, the study identified corpus callosum lesions in 84%. It was able to

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NEUROSCIENCE TODAY, NEUROLOGY TOMORROW

Branched Chain Amino Acids Enhanced Post-TBI Recovery

Mice with concussive brain injury to their hippocampus can reverse cognitive impairment associated with the injury by ingesting a solution of branched chain amino acids, according to a report by Jeffrey T. Cole, Ph.D., of the division of neurology at Children's Hospital of Philadelphia, and his associates.

The branched chain amino acids corrected an imbalance in the metabolism of the neurotransmitters glutamate and gamma-aminobutyric acid (GABA) that had developed in hippocampal neurons of the mice after the injury. The brain uses branched chain amino acids as raw material for the production of glutamate and GABA.

Previous clinical studies have shown that intravenous administration of branched chain amino acids to severely brain-injured patients is associated with mild cognitive benefits, based on assessments with the Glasgow Coma Scale and the Disability Rating Scale. However, the investigators of those studies did not try to give the patients any specific cognitive testing or account for the mechanisms of action of branched chain amino acids.

Dr. Cole and his colleagues wrote that although their results "show tremendous promise for clinical applications, further study needs to be conducted to determine the relative permanence of the changes mediated by BCAA application. In addition, it will be important to determine the effect of chronic BCAA treatment on improving delayed effects of TBI, which can take months or years to manifest themselves" (Proc. Natl. Acad. Sci. U.S.A. 2009 Dec. 7 [doi:10.1073/pnas.0910280107]).

'Supplying specific branched chain amino acids ... [is] a logical avenue to pursue to improve not only survival after traumatic brain injury, but also functional recovery.'

At the end of a 7-day period, mice that had received a lateral fluid percussion injury (which reliably damages the limbic hippocampus) showed significant declines the levels of 3 of 18 branched chain amino acids in the ipsilateral hippocampus, unlike mice that received sham injury. But after injured mice drank water with a mixture of these three branched chain amino acids—valine, isoleucine, and leucine—for 5 days, the concentrations of the three amino acids returned to levels similar to those observed in sham-injured mice.

Dr. Cole and his associates chose to study the mice after 7 days because it is within the clinically relevant "therapeutic time window" and it allowed the mice time to recover for 5 days after the typical 48 hours it takes for the acute transient alterations in brain function to subside.

To test the effect of the branched chain amino acids on improving the cognitive impairment induced by the injury, the researchers tested the memory of the mice after they were exposed to a single fear conditioning trial either before or after being injured. Regardless of whether the investigators established a conditioned fear response in the mice either before or after injury, supplementation of branched chain amino acids for 5 days after injury eliminated any differences in cognitive performance that had existed between the injured and sham-injured mice. The improvement in cognition of the injured mice following the supplementation of branched chain amino acids always occurred with a simultaneous restoration of net synaptic efficacy in the CA1 and dentate gyrus areas of the hippocampus. The application of branched chain amino acids to hippocampal slices from these mice also reproduced this improvement in synaptic efficacy.

BY RICHARD S. ZIMMERMAN, M.D.

The restoration of net synaptic activity that was observed after administration of the branched chain amino acids to ex vivo brain slice preparations and after in vivo delivery of the branched chain amino acids to the mice suggested to the investigators "that BCAA supplementation may relieve a local metabolic stress in the hippocampus and improve synthesis, buffering, and maintenance of the synaptic glutamate and GABA pool."

The investigators found that concussive brain injury led to alterations in the expression of enzymes involved in transamination reactions with branched chain amino acids, glutamate, and GABA, which could account for low rates of de novo synthesis of glutamate and GABA in hippocampal slices, and consequently for the post-traumatic changes seen in net synaptic efficacy and cognition in the mice.

"We speculate that an increased demand for de novo glutamate synthesis toward maintaining the synaptic glutamate pool significantly alters the normal ratio (17:1) of BCAA transamination:BCAA oxidation and leads to a decline in hippocampal BCAA concentration after injury. This would cause irreversible catabolism of BCAAs as a byproduct of increasing demand for glutamate synthesis, thus accounting for their decreased concentration after injury," the researchers wrote.

Dr. Zimmerman's comment: Mortality from traumatic brain injury has been reduced approximately 30% over the last 3 decades. However, even though general supportive and intensive care measures have contributed to this improved outcome metric, the cognitive impairment and functional loss experienced by survivors continue to beg for specific therapies. The U.S. Census Bureau cites that more than 1.3 million Americans suffered TBI in 2000, with a cost of $206 billion. These TBI costs were dominated by quality of life losses and work losses ($129.5 billion and greater than $63 billion, respectively), with a minority of costs due to medical care (more than $13 billion). As strategies to improve the outcome from TBI are sought, solutions for cognitive restitution are paramount to quality of life for the individual survivor as well as the costs to society. This makes the work of Dr. Cole and his colleagues quite important.

Adequate and early general nutritional support has clearly gained acceptance as one of the critical pathways for treating TBI patients, with much of the attention directed at reacting to the hypermetabolism, extreme catabolic state, and secondary nitrogen loss observed with the injury. In addition, the interest in altered glutamate metabolism is not new in TBI research, and the massive release of glutamate immediately following cerebral injury is well established. This early reaction is suspected of causing excitotoxicity from glutamate overstimulation, and results in secondary injury mediated via calcium influx. The activation of calcium-dependent enzymes is suspected of triggering harmful intracellular cascades, including the production of free radicals. From this, one might note an interesting paradox with regard to the specific neurotransmitter, glutamate. In the early stages of brain injury, too much glutamate appears to mediate harm, which is perhaps one reason why Dr. Cole and his colleagues waited 48 hours before adding branched chain amino acids to their subjects' diet. However, in the subacute phase that follows, it is suggested that too little glutamate is also harmful, as it impedes recovery. The hypothesis that supplying specific branched chain amino acids as substrate to drive de novo glutamate synthesis to correct the depleted state is thus a logical avenue to pursue to improve not only survival after TBI, but also functional recovery. ■

Clinical perspective by DR. ZIMMERMAN, *associate professor of neurosurgery at the Mayo Clinic, Phoenix, Ariz.*

Research report by Jeff Evans, clinical news editor.

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differentiate between patients with primarily cytotoxic lesions (54%) and those with vasogenic lesions (46%). "We also found that the volume of these brain lesions, irrespective of location, explained about 28% of the variance in outcome among these patients," he said. "It's a relatively modest correlation with outcome, but it shows that what we are measuring is something that is functionally important and affects outcome."

Diffusion tensor imaging [DTI] shows how water tracks along the axons, giving a good view of white matter lesions. Follow-up scans on TBI patients have shown tantalizing clues to the possible causes of their long-term problems.

"When we scan patients within a day or two of injury, we may see subtle changes in the parameters. But if we come back 6 months later and rescan, we see much greater dropout of axons. Initially, the patient may be in a coma, and when they are scanned later they are usually much improved and walking around, albeit with problems with memory or executive function. So this tells us that something is happening weeks or months after the injury that results in white matter dropout."

Imaging provides objective documentation to help convince insurers to cover rehabilitative services.

DR. DIAZ-ARRASTIA

Another technique moving into trauma field is quantitative volumetric assessment of the cortical field. This technique measures the thickness and volume of different cortical and subcortical regions, Dr. Diaz-Arrastia said. "In our patients, we have found that the brain shrinks overall after a severe traumatic injury, but that not all structures shrink at the same rate. Some cortical regions shrink very little, while others, like the hippocampus, appear particularly sensitive to injury." This finding makes sense given the cognitive and mood issues that TBI patients can experience, he said.

On average, whole brain volume and both grey and white matter volumes decreased by 3%-10% in the first few months after severe TBI. In comparison, Dr. Diaz-Arrastia said, the rate of atrophy for patients with Alzheimer's disease is about 1%-2% a year.

Functional MRIs also provide some clues that the injured brain sustains long-term problems. In the resting state, the blood oxygen level dependent signal typically shows seemingly random fluctuations when the brain is at rest. But recent studies have shown that these fluctuations actually represent the communication between brain regions that work together.

"In our patients, we found a very high indication that the functional connectivity between the hippocampi was greatly reduced," compared with controls, he said. ■