Researchers find promising new biomarkers for concussion

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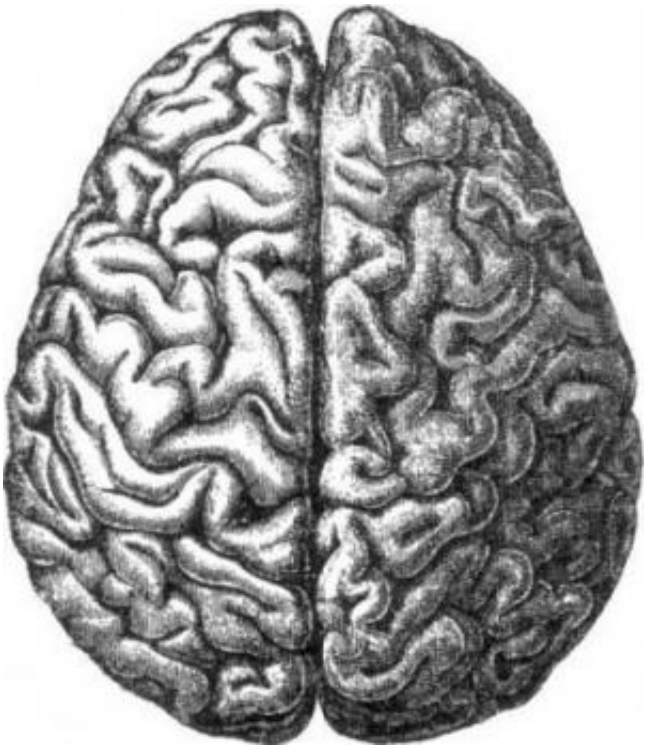

The body produces many proteins in response to injury. Four of them in the bloodstream may signal that a concussion has occurred, as distinguished from a broken bone or other injury. The finding may be useful for both diagnosis and treatment.

By looking at the molecular aftermath of concussion in an unusual way, a team of researchers at Brown University and the Lifespan health system has developed a candidate panel of blood biomarkers that can

accurately signal mild traumatic brain injury within hours using standard, widely available lab arrays. The results appear in a new study in the *Journal of Neurotrauma*.

Many researchers have reported recent progress in identifying possible blood biomarkers for concussion—an advance sought because diagnosis is currently limited to cognitive measures that can be subjective. Most groups have focused on detecting proteins released from dying brain cells, but those proteins are not always abundant after injury and often require exotic or proprietary antibodies to measure, said study corresponding author Adam Chodobski, associate professor (research) of emergency medicine in the Alpert Medical School of Brown University.

"Our approach was very different," said Chodobski, also a Lifespan researcher who directs the Neurotrauma and Brain Barriers Research Laboratory. "We wanted to look at proteins that are produced in response to injury and then appear in the circulation."

With that approach, informed by prior research in animals, the research team ultimately identified four proteins (copeptin, galectin 3, matrix metalloproteinase 9 and occludin) that changed dramatically in the bloodstream of patients shortly after they had a concussion. The correlation of two of them—galectin 3 and occludin—distinguished patients who had concussion from subjects who suffered an orthopedic injury, such as a bone break.

Concussions and controls

Chodobski's team, including lead author and former Brown student Rongzi Shan and researcher Joanna Szmydynger-Chodobska, structured the study to ensure that any biomarkers they found would be sensitive and specific for diagnosing concussion. Donor Diane Weiss and the

Department of Emergency Medicine at Brown funded the effort.

The team recruited three groups of patients, one experimental group and two controls. The experimental group comprised 55 emergency room patients who had concussions diagnosed by other means. One control group included 44 people who were uninjured, while the other control group contained 17 patients who had long-bone fractures. In all of the patients they measured 18 proinflammatory proteins.

An analysis of the results identified four of the proteins as potential biomarkers. Specifically, within eight hours of injury, they found around a four-fold increase in the concentration of galectin 3, matrix metalloproteinase 9, and occluding, and a three-times lower concentration of copeptin in concussed patients compared to the uninjured controls.

While uninjured individuals might have had a high level of one or the other of these proteins, none had high levels of two or more at a time, but 90 percent of the patients with concussion had significantly altered concentrations of two or more. When the researchers looked at a combination of three proteins in patients with concussion—copeptin, galectin 3, and matrix metalloproteinase 9—they found significant changes in the levels that provided a high degree of sensitivity and specificity for injury compared to the controls.

While each of those three proteins was also significantly altered in patients with bone breaks, as was occludin, the researchers found that only in the concussed patients did elevated occludin correlate with elevated galectin 3. Thus the four proteins considered together not only can indicate concussions in people for whom a brain injury is the only suspected problem, but also they can distinguish the possibility of a concussion from that of an injury elsewhere in the body.

Szmydynger-Chodobska noted that the four proteins' significance in indicating concussion endured regardless of patient age, gender, body-mass index or other medical characteristics.

"This was a broad spectrum of the population with different genders, different ethnicities, different age, and different physical conditions, and on this background these four biomarkers were not influenced," she said.

Rapid test and maybe treatment

The study indicated that the proteins are readily measurable with standard assays, but the team hopes to develop a microfluidic chip that can derive reliable readings within just two hours (well within the duration of many emergency room visits). They said they have already filed for a patent of the idea.

"Our plan is to commercialize this," Chodobski said.

Szmydynger-Chodobska said the team is also interested in looking at the proteins as therapeutic targets. Although there is some debate, research suggests that some of these inflammatory proteins may affect the integrity of the blood-brain barrier. That might mean patients who suffer traumatic brain injury not only suffer from the physical damage of the blow to the head but also from the resulting inflammatory response, especially within the first 24 hours.

"If you have a patient who has very high levels of MMP9, we can think about a treatment that blocks MMP9," she said. "It degrades the tight junction proteins at the blood-brain barrier. If you open the blood brain barrier, unwanted things from the blood get to the brain and that just makes the situation worse and increases the inflammation."

The panel may therefore eventually help not only with diagnosis, the

researchers said, but may also aid treatment during a critical window of time.

Provided by Brown University