Brain injury may be autoimmune phenomenon, like multiple sclerosis, research finds

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Most scientists are starting to agree that repeat, sub-concussive hits to the head are dangerous and linked to neurological disorders later in life. A new collaborative study, though, attempted to find out why – and discovered that damage to the blood-brain barrier and the resulting autoimmune response might be the culprit.

Published in journal PLOS ONE by the University of Rochester Medical Center and the Cleveland Clinic, the research suggests a new way of thinking about concussions: That the brain degeneration observed among professional football players (including the much-publicized chronic traumatic encephalopathy) could result from an out-of-control immune response, similar to what multiple sclerosis patients experience. If so, this opens the door to investigating a vaccine or drug therapy to prevent head trauma.

Although he emphasized that the research is preliminary, co-author Jeffrey J. Bazarian, M.D., M.P.H., associate professor of Emergency Medicine at URMC, said it's exciting to discover a theory that appears to fit with the reality of what experts observe among athletes. Bazarian worked closely with lead investigator Damir Janigro, Ph.D., professor of Molecular Medicine at the Cleveland Clinic, and 67 college football players from northeast Ohio and Rochester, N.Y., who agreed to participate in the research.

"Although the awareness of sports-related concussions is much higher, we still know very little about the long-term consequences and what happens inside the brain," Bazarian said.

"Our theory is plausible as an explanation for how routine head hits that come with playing football can lead to severe neuro-degeneration later in life," said Bazarian, a national expert who has served on an Institute of Medicine committee for brain injury. "If others confirm this, it could present options with drugs that influence the immune response."

The blood-brain barrier is like a semi-permeable gate between the brain and bloodstream. No other organ has such a barrier. When the barrier is working properly, it holds in proteins and molecules that bathe the brain and protect it from foreign substances. With blows to the head, however, the barrier opens slightly and allows some proteins to leak into the bloodstream.

Researchers found that S100B, a well-accepted protein biomarker for traumatic brain injury, was present in varying degrees in the blood samples of the 67 football players after every game—even though none of them suffered a concussion. This demonstrates that even the most routine hits have some impact on the blood-brain barrier and possibly the brain itself, Bazarian said.

For the purposes of this project, however, the team wanted to explore what happens after S100B surges from the brain and enters the bloodstream. Again, they made an important finding – that the body views S100B as an enemy and begins to form antibodies against it as if it were a virus.

Researchers hypothesized that a buildup of antibodies would result in a more vigorous attack on S100B in the bloodstream. But in the process, they learned, some antibodies sneak back through the damaged blood-

brain barrier to the brain and begin to harm the healthy brain cells that produced the S100B protein in the first place. This is analogous to a missile searching for a target, Bazarian said, with some unintended targets eventually falling under attack.

Researchers also showed that S100B accumulates in dendric cells, which regulate auto-immune responses. Therefore, as the blood-brain barrier repeatedly opens during the football season it might set the stage for a continuous autoimmune-type attack on the brain, they reasoned.

In multiple sclerosis a similar breakdown occurs, when the body's own immune system damages myelin sheaths around the brain. Other health conditions that harm the blood-brain barrier include sepsis (overwhelming infection), burns, critical illness, or seizures.

The methods used to test the hypothesis involved each player giving blood samples before and after games. Researchers then analyzed the samples for S100B levels and auto-immune antibody levels. They also monitored the number of hits each player sustained by viewing game films and conducting post-game interviews, and gave each player standard cognitive and functional tests, pre-season and post-season.

In addition, a subset of 10 players from the University of Rochester received special brain scans with diffusion tensor imaging, a more sensitive MRI that can detect subtle axonal injury.

Results showed that players with the most head hits also had the highest S100B levels and elevated levels of autoimmune antibodies. Players who often remained on the sidelines had significantly lower S100B levels. In addition, the blood samples predicted abnormalities seen in the imaging tests, and correlated with observed cognitive changes.

Although many scientists are actively investigating concussions in the

United States right now, it's been difficult to study the link between brain injury, blood-brain barrier damage, and the long-term risk of neuro-degeneration because of a lack of simple, non-invasive tools, Bazarian said. But demonstrating that S100B can be used in this way adds a new dimension to the scientific literature. Other investigators have also used the S100B protein to study Alzheimer's patients, the study noted.

Bazarian hopes that eventually S100B will be a tool for emergency rooms and other clinical settings to screen for concussions. Doctors can accurately measure it with a simple finger prick; many European countries already use S100B to decide which patients need a CT scan when a concussion is suspected.

Provided by University of Rochester Medical Center