Blood test for brain injury may not be feasible

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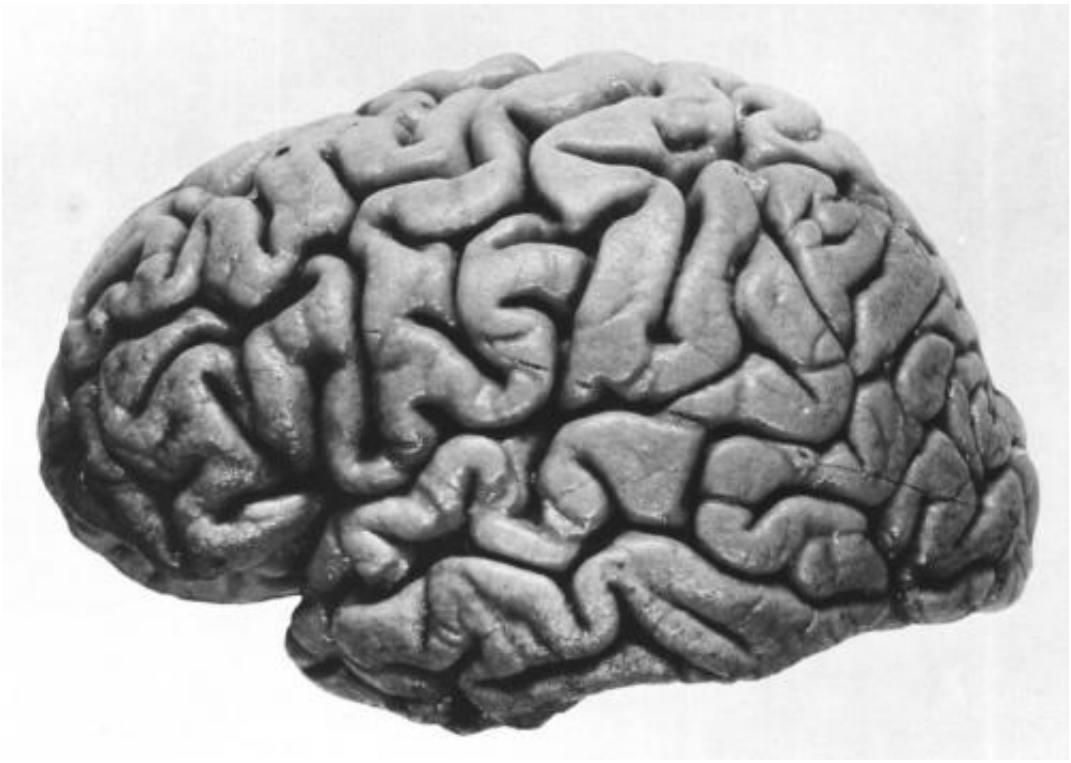

Left hemisphere of J. Piłsudski's brain, lateral view. Credit: public domain

Complications involving the brain's unique waste removal system - the existence of which has only recently been brought to light - may thwart efforts to identify biomarkers that detect traumatic brain injury (TBI). That is because proteins that are triggered by brain damage are prevented from reaching the blood system in levels necessary for a

precise diagnosis.

Tens of millions of dollars have been invested by the U.S. government and the private sector in recent years in an effort to develop a simple blood test that can help physicians quickly and accurately gage the extent of neurological damage after a blow to the head. However, a new study conducted in mice and published today in the *Journal of Neuroscience* appears to indicate that these efforts may be in vain.

"These findings show that a blood-based biomarker for TBI is unlikely to be effective for routine clinical use," said Maiken Nedergaard, M.D., D.M.Sc., co-director of the University of Rochester Medical Center (URMC) Center for Translational Neuromedicine and lead author of the study. "Both the injury itself and the clinical approach to TBI can impair the ability of the brain to remove waste, resulting in variable and - for the purpose of detection and diagnosis - unreliable protein levels in the blood."

More than 1.5 million Americans, both children and adults, suffer concussions every year. Furthermore, it is estimated that more than 300,000 U.S. military personal have been victims of TBI since 2000. Readily visible symptoms - such as headache, nausea, dizziness, and sleep problems - don't reflect the extent of the injury. Consequently, there is an urgent and compelling public health need to develop a method that can determine the severity of TBI and help predict which of these individuals may be at risk for long-term cognitive problems.

It is only within the last few years that researchers have begun to understand how the brain deals with waste. In 2012, scientists at the University of Rochester revealed that the brain possesses its own unique waste removal system, which has been dubbed the glymphatic system.

The glymphatic system consists of a plumbing network that piggybacks

on the brain's blood vessels and pumps cerebral spinal fluid through brain tissue to flush away waste. The waste flows out of the brain, into the lymph nodes, and eventually makes its way to the general blood circulation system and, ultimately, the liver.

It is known that during the shock of brain injury, certain proteins are shaken free from the brain's cells. This has led to the speculation that by measuring the levels of these proteins after they have made their way into the blood system, physicians may be able to ascertain the existence and severity of injury.

The Rochester team of researchers performed a series of experiments on mice with TBI and tested the animal's blood for three proteins (S100 beta, glial fibrillary acidic protein, and neuron specific enolase) that are considered strong candidates for a blood-based biomarker for TBI.

It turns out that the glymphatic system is very delicate and small alterations can disrupt function, impairing the ability to remove waste products, such as the proteins associated with TBI, from the brain. An earlier study showed that the blows to the head themselves can disrupt the function of the glymphatic system.

The current study shows that treatments for these conditions may also impair the brain's ability to remove waste. Just like a water pump, the glymphatic system requires pressure to function properly. Efforts to relieve the stress on the brain from swelling after an injury by using drugs like acetazolamide or employing a surgical procedure that drains CSF can "depressurize" the system and impair clearance of waste.

Furthermore, people under observation in hospitals for TBI are often subjected to frequent neurological evaluation by physicians, disrupting their sleep. In other instances, patients are given sedatives to induce sleep after TBI. Because the glymphatic system primarily functions

while we sleep, these variations in clinical care skew protein levels found in the blood.

During experiments that replicated these conditions in mice with TBI, the researchers were not able to detect reliable changes in protein levels in the blood.

"This study shows that even small changes can modulate the brain's ability to clear waste," said Benjamin Plog, an M.D./Ph.D. student in Nedergaard's lab and a co-author of the study. "Consequently, we need to recalibrate our efforts and begin to think about measuring brain damage in a manner that takes into account the level of impairment to the glymphatic system. "

Provided by University of Rochester Medical Center