RESEARCH HIGHLIGHT

Altered Protein Profiling in Tears from Patients in a Traumatic Vegetative State

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Following severe traumatic brain injury (sTBI), patients may remain in a coma, vegetative state (VS), or minimally conscious state (MCS), all of which are also clinically termed disorders of consciousness. Patients in a coma show complete disability in the arousal system and fail to achieve awareness spontaneously; yet true coma represents a transient state and rarely lasts longer than a month [1]. The VS (also known as unresponsive wakefulness syndrome), characterized as a state with spontaneous or stimulus-induced eye-opening but the patient appears totally unaware of self and environment, may persist for months or years [2]. In contrast, the MCS is evidenced by preserved and reproducible signs of awareness as well as sleep-wake cycles, suggesting better recovery than coma and VS. Considering that no signs of consciousness are detectable, patients in a VS suffer from a high rate of misdiagnosis [3].

The molecular mechanisms involved in sTBI have been an intense area of investigation; however, no Food and Drug Administration-approved biomarkers are available for clinical use. In the field of proteomics technology, a growing number of studies have shown that potential biomarkers may be more sensitive and reliable in diagnosing and predicting recovery after sTBI. Emerging

proteomic studies have been conducted in the acute phase after trauma, but little is known about the protein biomarker profiles and pathophysiological conditions underlying the chronic stage. Since patients with disorders of consciousness can be acute and chronic, transient and permanent, reversible and irreversible, it is a great challenge for clinicians to recognize and identify biomarkers in the VS.

In this issue, Tang and colleagues [4] analyzed tear proteins differentially expressed in patients in a traumatic VS and healthy controls. Fifty-seven proteins were upregulated and 15 were downregulated in patients relative to controls. The differentially-expressed proteins were predominantly involved in the wound response and immune response signaling pathways. Similar to our previous study, sTBI patients showed a persistent immune response during the chronic stage [5]. Furthermore, the integrity of the blood-brain barrier, a mediator between the peripheral circulation and the central nervous system, is frequently damaged after severe brain injury, and this is accompanied by a secondary injury cascade [6]. Subsequently, seven promising tear proteins (CTSB, PRSS1, S100A7, GSTP1, CFH, KNG1 and ORM1) and ORM1 were further validated using ELISA kits. All seven proteins showed a strong ability to distinguish traumatic VS patients from healthy controls. These results may provide potential biomarkers for patients in a traumatic VS.

The diagnostic criteria of traumatic VS are currently based largely on the observable behavioral features, which provide an unreliable proxy for distinguishing patients with VS and MCS [7]. In fact, nearly 40% of VS patients retain some degree of consciousness. To date, diagnostic errors have been common and a ‘gold standard’ to precisely define and evaluate VS is lacking. Recent applications using functional neuroimaging such as fMRI and

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electrophysiological techniques such as EEG have been designed for detecting signs of residual conscious awareness, providing information for the prediction and prevention of VS. However, false negatives are difficult to avoid in view of the possibilities of deficiency in arousal, non-cooperation, auditory and visual inability, or incomprehension of the instructions during the scan [8]. In addition, both the clinical and neuroimaging findings are insensitive to small changes in disease progression.

It is well established that the early detection of biomarkers further facilitates the management of patients in a traumatic VS by providing a more accurate diagnosis and prognosis. Protein biomarkers, as economical and non-invasive measures, provide a novel option for assessing the outcome and guiding treatment in clinical trials. Nowadays, blood (serum and plasma), cerebrospinal fluid (CSF), and brain tissue are commonly-used samples for sTBI proteomics studies [9]. One of the body fluids, tears are complex with many proteins, and have been widely used for disease-related protein analysis [10]. Tang *et al.* were the first to analyze the tear proteome of patients with sTBI. This study revealed several strong candidate proteins for distinguishing sTBI patients and controls. Several limitations in this study should be noted, such as the limited number of samples and the lack of prognostic information for these markers. Moreover, the protein candidates were not independent of clinical measurements, so further validation in larger patient cohorts is necessary in future research.

The complex, heterogeneous properties of sTBI make it difficult to categorize and guide long-term treatment for non-responsive patients. Proteomics studies have described altered protein profiles related to specific pathophysiological conditions, which may propel molecular biology and develop therapeutic strategies. Therefore, we believe that,

in the near future, the identification of biomarkers in unconscious patients will yield important findings for clinical guidelines.

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