Clinical Biochemistry 47 (2014) 876–888

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Review

# Blood-based biomarkers for traumatic brain injury: Evaluation of research approaches, available methods and potential utility from the clinician and clinical laboratory perspectives

Frederick G. Strathmann [a,*], Stefanie Schulte [b], Kyle Goerl [c], David J. Petron [c]

[a] Department of Pathology, University of Utah School of Medicine, Salt Lake City, UT 84108, USA
[b] Department of Exercise and Sport Science, University of Utah School of Medicine, Salt Lake City, UT 84108, USA
[c] Department of Orthopaedics, University of Utah School of Medicine, Salt Lake City, UT 84108, USA

ARTICLE INFO

*Article history:*
Received 6 November 2013
Received in revised form 5 January 2014
Accepted 23 January 2014
Available online 31 January 2014

*Keywords:*
Traumatic brain injury
Biomarker
Mass spectrometry
Gender bias
Laboratory medicine
S100B
NSE
GFAP
MBP
UCH-L1

ABSTRACT

Blood-based biomarkers for traumatic brain injury (TBI) have been investigated and proposed for decades, yet the current clinical assessment of TBI is largely based on clinical symptoms that can vary widely amongst patients, and have significant overlap with unrelated disease states. A careful review of current treatment guidelines for TBI further highlights the potential utility of a blood-based TBI biomarker panel in augmenting clinical decision making. Numerous expert reviews on blood-based TBI biomarkers have been published but a close look at the methods used and the astonishing paucity of validation and quality control data has not been undertaken from the vantage point of the clinical laboratory. Further, the field of blood-based TBI biomarker research has failed to adequately examine sex and gender differences between men and women with respect to the clinical care settings, as well as differences in physiological outcomes of TBI biomarker studies. Discussions of tried-and-true laboratory techniques in addition to a few new ones already operating in the clinical laboratory are summarized with a consideration of their utility in TBI biomarker assessment. In the context of TBI biomarkers, the central concerns discussed in this review are the readiness of the clinical laboratory, the willingness of the research environment and the inherent ability of each to radically affect patient outcomes in TBI.



**Contents**



*Abbreviations:* TBI, traumatic brain injury; mTBI, mild traumatic brain injury; GCS, Glasgow Coma Score; NSE, neuron specific enolase; GFAP, glial fibrillary acidic protein; MBP, myelin basic protein; UCH-L1, ubiquitin c-terminal hydrolase-L1; CSF, cerebral spinal fluid; ELISA, Enzyme-Linked Immunosorbent Assay; IA, immunoassay; LDT, laboratory developed test.

* Corresponding author at: Department of Pathology, University of Utah, 500 Chipeta Way, Mail Code 115, Salt Lake City, UT 84108-1221, USA. Fax: +1 801 584 5207.
*E-mail address:* frederick.strathmann@path.utah.edu (F.G. Strathmann).

0009-9120/$ – see front matter 
http://dx.doi.org/10.1016/j.clinbiochem.2014.01.028

## Introduction

Blood-based biomarkers for traumatic brain injury (TBI) have been investigated and proposed for decades. In recent years, there has been increased focus on mild TBI and concussion with substantial media coverage surrounding concussion in sports [1] and the recognition of TBI as the defining injury for veterans of the Iraq and Afghanistan wars [2]. The current clinical assessment of TBI is largely based on clinical symptoms that can vary widely amongst patients and have significant overlap with unrelated disease states [1,3,4].

Findings generated in the basic research arena have been rapidly integrated into clinically-based studies very often using methods that would not be allowed to operate in the clinical laboratory. Further, many of the published studies provide limited information on assay validation or the use of fundamental laboratory techniques such as statistical quality control. Instead of adding to the accumulating number of expert reviews on TBI biomarkers, we focused on identifying methods used in the study of five of the most prominent biomarkers in the literature. We report on the limited amount of validation and quality control data provided. In fairness, it is possible that the authors of the reviewed publications completed a full, CLIA-approved validation for a high complexity test with the use of established quality control ranges to validate all published data. More likely, the publications selected for review illustrate a pervasive lack of appreciation for the rigorous quality standards required from clinical testing in an attempt to fulfill the promise of translational research expectations.

The clinical laboratory continues to grow in its ability to transform novel, highly complex research assays into routine clinical tests, while at the same time more advanced technology continues to find its way from research into the clinical laboratory. In addition, if sex and gender influences are not fully understood TBI research may fail to address important issues pertaining to the assessment and treatment of TBI. Due to a general ambiguity towards TBI in terms of definition, assessment, and treatment [3] and the fact that 77% of individuals with TBI are male [5], TBI research appears especially prone to gender bias. The subsequent focus of this review is on the clinical approach to TBI, methods used in TBI research, methods available in the modern clinical laboratory and sex and gender differences in TBI biomarker studies.

## Current clinical approach to TBI

TBI is a heterogeneous disease with numerous methods to classify patients, most often into mild, moderate or severe TBI, based on clinical severity, injury type and pathophysiology. The most commonly used tool for the assessment of TBI is the Glasgow Coma Score (GCS) [6] in addition to the inclusion of age, medical comorbidity and imaging studies [7,8]. Ideal in its simplicity, criticism of the GCS for TBI classification is based upon a number of confounding factors that may contribute to a skewed score [9].

### *Mild traumatic brain injury*

Mild traumatic brain injury (mTBI) is considerably more common than moderate and severe TBI; however, a risk of serious and long term complications can arise if adequate treatment is not provided. mTBI most often occurs as a result of contact and/or the physical and mechanical forces of acceleration and deceleration.

#### *Concussion in athletics*

A concussion is defined as a traumatically induced, transient disturbance of brain function. Concussion is correctly classified as an mTBI, with an important distinction in that not all mTBIs are concussions [1]. In 2012, a consensus statement provided by the 4th International Conference on Concussion in Sport held in Zurich identified common features useful in defining a concussion. These features include cause (direct blow to the head or elsewhere that is transmitted to the head), acute symptoms (short-lived impairment of neurologic function), neuropathological changes (due to functional and not structural changes often missed by imaging studies), a grouping of clinical symptoms which may or may not involve the loss of consciousness, and a step-wise resolution