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Profiling biomarkers of traumatic axonal injury: From mouse to man

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ABSTRACT

Traumatic brain injury (TBI) poses a major public health problem on a global scale. Its burden results from high mortality and significant morbidity in survivors. This stems, in part, from an ongoing inadequacy in diagnostic and prognostic indicators despite significant technological advances. Traumatic axonal injury (TAI) is a key driver of the ongoing pathological process following TBI, causing chronic neurological deficits and disability. The science underpinning biomarkers of TAI has been a subject of many reviews in recent literature. However, in this review we provide a comprehensive account of biomarkers from animal models to clinical studies, bridging the gap between experimental science and clinical medicine. We have discussed pathogenesis, temporal kinetics, relationships to neuro-imaging, and, most importantly, clinical applicability in order to provide a holistic perspective of how this could improve TBI diagnosis and predict clinical outcome in a real-life setting. We conclude that early and reliable identification of axonal injury post-TBI with the help of body fluid biomarkers could enhance current care of TBI patients by (i) increasing speed and accuracy of diagnosis, (ii) providing invaluable prognostic information, (iii) allow efficient allocation of rehabilitation services, and (iv) provide potential therapeutic targets. The optimal model for assessing TAI is likely to involve multiple components, including several blood biomarkers and neuro-imaging modalities, at different time points.

1. Introduction

Traumatic brain injury (TBI) is a global public health problem. It is amongst the leading causes of mortality in young people in developed countries [1], and many survivors of TBI suffer from chronic, persistent disabilities. In the United States (US) alone, 1.7 million individuals sustain a TBI every year, causing 52,000 deaths, and contributing to approximately 30% of all injury-related deaths [2]. In Europe, the annual incidence of TBI is estimated to be around 235 cases per 100,000 across 23 different European countries, with an average mortality of 15 per 100,000 [3]. Furthermore, the incidence of TBI continues to rise globally, and is predicted by the World Health Organisation (WHO) to become one of the leading causes of death and disability by 2020. Approximately 5.3 million victims of TBI in the US [4], and 7.7 million in the European Union [3], live with disabilities resulting from the initial traumatic injury. Indeed, TBI consists of both an acute insult and delayed changes resulting in chronic disability. The clinical consequences of the continuing pathological process is reflected by a range of neurological, cognitive, and neuropsychiatric deficits [5,6], with a devastating impact on the patient's quality of life and considerable cost to the healthcare system as a result of its chronic and heterogeneous nature. Cognitive and neuropsychiatric dysfunction post TBI is diverse, including attentional deficits [7], memory impairment [8], executive dysfunction [9], defective emotional recognition [10], agitation [11], depression [12], and language difficulties [13].

Amongst the key components of TBI pathophysiology is traumatic axonal injury (TAI), sometimes referred to as diffuse axonal injury (DAI) [14]. TAI is thought to contribute to the long-term manifestations of TBI and its understanding could be vital for predicting outcomes. TAI can affect large white matter tracts of the brain, which play a key role in

Abbreviations: Aβ, amyloid beta protein; AD, Alzheimer's disease; APP, amyloid precursor protein; cmTBI, complicated mild traumatic brain injury; CSF, cerebrospinal fluid; CT, computed tomography; C-tau, C-terminal tau fragment; CTE, chronic traumatic encephalopathy; DAI, diffuse axonal injury; DTI, diffusion tensor imaging; DTT, diffusion tensor tractography; FA, fractional anisotropy; GCS, Glasgow coma scale; GFAP, glial fibrillary acidic protein; GOS, Glasgow outcome scale; GOSE, extended Glasgow outcome scale; HARDI, high angular resolution diffusion imaging; ICP, intracranial pressure; MAP, microtubule associated protein; MBP, myelin basic protein; MRI, magnetic resonance imaging; NF-H, heavy neurofilament chain; NF-L, light neurofilament chain; pNF-H, phosphorylated heavy neurofilament chain; P-tau, hyperphosphorylated tau; PTSD, post-traumatic stress disorder; RPCQ, rivermead post concussion symptoms questionnaire; SBDP, spectrin breakdown products; SNTF, spectrin N-terminal fragment; SWI, susceptibility weighted imaging; TAI, traumatic axonal injury; TBI, traumatic brain injury; T-tau, total tau; VABS, vineland adaptive behaviour scales; WHO, World Health Organisation

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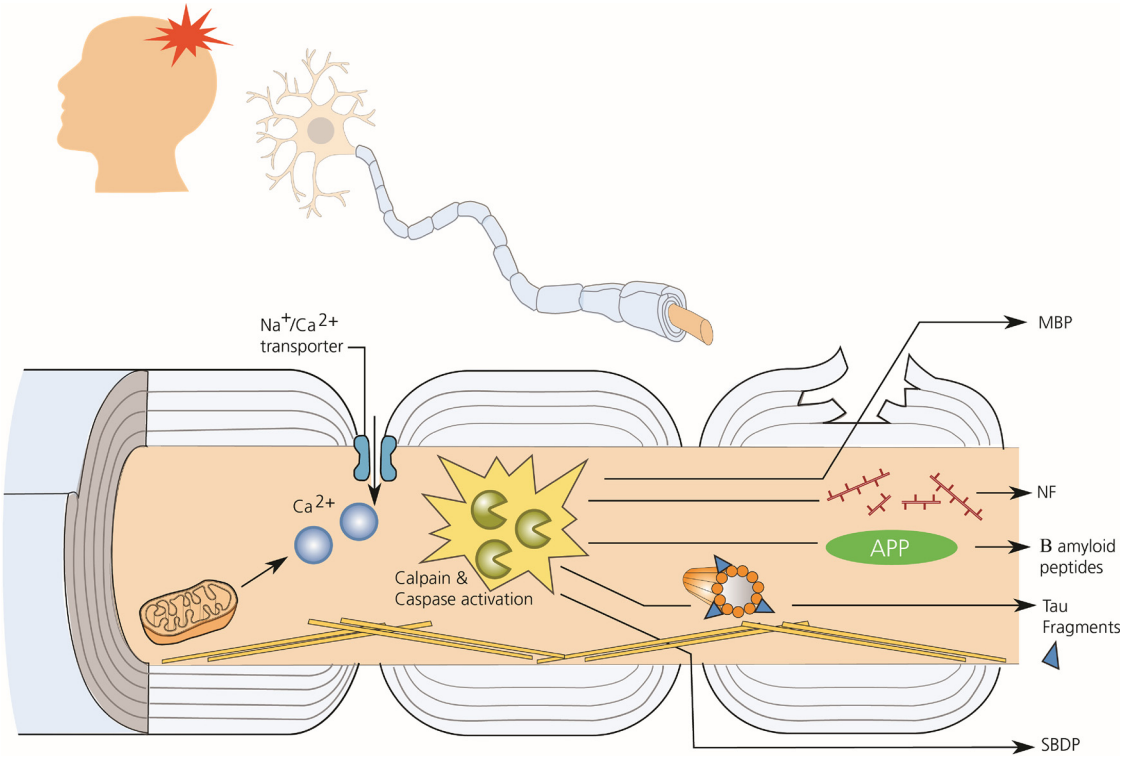

Fig. 1. Pathogenesis of TBI and the generation of biomarkers. Acceleration/ deceleration forces during TBI results in axonal undulations demonstrated above. Intra-axonal calcium concentrations then rise due to (i) influx from extracellular sources via transporters and due to mechanoporation, and (ii) intracellularly from mitochondria under oxidative stress following injury. Increase in intracellular calcium then causes activation of calpains and caspases, which then contribute to breakdown of: (i) myelin sheath, releasing MBP, (ii) neurofilaments, releasing NF chains of varying weights, (iii) APP, releasing B amyloid peptides of various weights, (iv) tau, a microtubule associated protein, into various fragments, and (v) spectrin, a cytoskeletal protein contributing to axonal morphology, into a collection of products known as SBDP. Abbreviations: APP- amyloid precursor protein, MBP- myelin basic protein, NF- neurofilaments, SBDP- spectrin breakdown products, TBI- traumatic brain injury.

communication between neuroanatomically distinct regions, facilitating connectivity and the formation of large-scale networks. Whilst axonal injury has long been appreciated on neuropathological examination of post TBI brains through observation of signs such as axonal 'retraction bulbs', varicosities, and white matter damage [14–16], understanding its functional effect on networks in the brain *in vivo* has yet to be fully explored. However, more recent advances in network science and imaging have enabled visualization and analysis of the large-scale structural and functional connectivity of the brain. The 'default mode network' and 'salience network' are examples of networks in the brain that have been extensively studied in the normal healthy population, which provides a reference point for comparisons in pathological disease states [17]. By studying the level of activity in such networks, the severity and specific distributions of DAI have been elegantly demonstrated to correlate with several cognitive impairments seen post-TBI, including attention [18], memory [19], and executive function [20] (for review see Sharp et al [17]).

Hence there is a need for additional clinical tools in the diagnosis and prognosis of TAI. By understanding the mechanisms underlying TAI, specific proteins released during axonal injury can be characterised and measured, serving as biomarkers.

This can potentially aid patient healthcare by (i) increasing speed of diagnosis in the acute setting owing to accessibility of potential fluid biomarker assays, (ii) improving accuracy of diagnosis since the short half life of several biomarkers mean that they reflect a specific part of the TBI process, (iii) providing more certainty to the outlook of victims on their future quality of life, (iv) focusing rehabilitation services to those with poorer prognostic indicators, and (v) providing potential therapeutic targets (see review by Hill et al [21]). Such biomarkers may exist in several bodily fluids including CSF, blood, and saliva [22]. Extensive research has been carried on the use of biomarkers in TBI, but there has been little appreciation for their use in the context of TAI.

From a clinical perspective, biomarkers can be any quantifiable product serving as a marker of insult. This definition, however, does not appreciate the direct pathophysiological link between the site and nature of injury, and biomarker measured. For instance, there are several biomarkers that may reflect TAI but cannot be realized conceptually from a pathological perspective. Neuron specific enolase (NSE), S-100B, and glial fibrillary acidic protein (GFAP) are all examples of promising biomarkers for TBI [23]. GFAP, as the name suggests, is of glial origin and shown to rise acutely in severe TBI, peaking during the first few days post injury before gradually decreasing, and demonstrated to predict clinical outcome [24]. This was corroborated by further evidence of the use of both serum S-100B, a calcium binding protein found in Schwann cells and glia, and GFAP as successful diagnostic indicators of TBI severity [25]. NSE, an enzyme found in the neuronal soma, along with S-100B and myelin basic protein (MBP), could be used to predict outcomes in paediatric TBI [26]. Whilst all of these biomarkers demonstrate clinical validity, their origins mean that they share no direct conceptual link with the axon itself. Indeed, evaluation of biomarkers in this fashion results in a broad classification of direct and indirect biomarkers of axonal injury. In this review we will focus on direct biomarkers of axonal injury because it facilitates an explanation of effect-causal relationships, and signifies the meeting point of basic scientific understanding and translation to the clinical setting. For a more general account of the use of biomarkers in TBI, please see the review by Kawata et al [27].