Traumatic brain injury (TBI) is a leading cause of death and disability in children and young adults. It constitutes a major health and socioeconomic problem throughout the world (1-2). The World Health Organization (WHO) has projected that by 2020 road traffic injuries will be the third global burden of disease, well ahead of HIV and tuberculosis (3). In Australia, there are an estimated 2500 new cases of moderate to severe TBI per year, primarily young males aged between 15–19 years involved in motor vehicle accidents. The financial burden of TBI, in both lost productivity and the cost of medical care, is enormous with the total lifetime cost for TBI patients in Australia estimated at $8.6 billion (4). With no effective therapies for the treatment of severe brain injuries and despite progress in critical care, mortality rates remain at nearly 30% (5-6).

Primary brain damage occurs immediately at the time of impact and involves mechanical cell destruction. Secondary brain damage develops within minutes to months after the injury and is mediated by multiple physiological and molecular cascades leading to ongoing neuronal damage (7). Inflammatory mediators, excitatory amino acids, and free radicals have been shown to play key roles in the exacerbation of neural injury following TBI through the initiation of various neurotoxic pathways, contributing to cell membrane breakdown and cell death (8). In addition, a study on 8000 TBI patients showed that imbalance in systemic physiological conditions like hypertension and hypoxia are linked with the worst outcome in severe diffuse brain injury (9).

The long-established approach in the development of efficacious therapeutics in humans and animal models of TBI aims at inhibiting the molecular pathways leading to secondary brain damage. The inflammatory response is an important component of TBI and is characterized by the release of pro- and anti-inflammatory mediators with dual and opposing roles: the enhancement of brain damage through the release of neurotoxic substances contrasting the neurotrophin-mediated repair of the injured tissue. This harmful–beneficial dual aspect makes the neuroinflammatory cascade a challenging therapeutic target.

Several approaches have been used over the years to monitor and elucidate the role of neuroinflammation in TBI patients:

1) The first and most accessible approach has involved the analysis of cytokines in cerebrospinal fluid (CSF), which is thought to mirror brain production. The most
interesting finding of all studies utilising this approach was that the cytokine levels detected in the CSF were far higher than those detected in blood serum (7). This suggests that neural cells themselves are the source of intrathecal cytokine production. These early findings also demonstrated that the secretion of cytokines in the CSF remained elevated for a longer period of time as compared with rodent brain.

2) A second experimental approach developed in the clinic in recent years relies on the insertion of a microdialysis catheter in the frontal cerebral cortex of TBI patients. Despite the controversies surrounding the use of a somewhat invasive procedure, which may itself cause damage, this technique allows for in situ measurement of cytokines produced by the brain parenchyma.

3) The third approach used in humans is the examination of contused brain biopsies obtained from patients undergoing surgery to evacuate the injured tissue. Even though this approach provides valuable information at the tissue level, it presents a few technical limitations (low efficiency of cytokine retrieval), which may not reflect accurately the events occurring in the whole injured brain.

4) The final approach used in humans is the examination of post mortem brain tissue. Trauma brain samples of individuals who died after severe closed head injury are now available from the Australian Neurotrauma Tissue Bank. In recent years, a number of seminal studies have been published confirming and extending previous observations on the inflammatory cascade following TBI in animal and human studies (10-12).

Traumatic brain injury is an extremely complex condition with multiple molecular events contributing to the neuronal damage in humans. To date there are no efficient therapies for the treatment of patients. The simplicity and inability of animal models to reflect the complexity of clinical head injury in humans highlight the importance of studying these pathways in human tissue if therapeutic targets are going to be identified. Limiting secondary damage is crucial for improved quality of life of TBI patients and reduced socio-economic burden on Australian society.

References:


