PROTEIN YKL-40 IN SEVERE TRAUMATIC BRAIN INJURY

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Abstract:

Severe traumatic brain/head injury (TBI) is the leading cause of morbidity and mortality among individuals, aged 1 to 45 years, worldwide. Establishment of predictive models or algorithms for action would improve the classification of patients with TBI and could provide detailed information about the mechanisms of the disease.

The purpose of the study is to find specific and reliable biomarkers associated with the outcome in patients with TBI, which could clarify our understanding of the structural damage in the brain or the underlying pathogenic and reparative mechanisms at the cellular level. This information should be of use to conduct future basic and clinical research to optimize the treatment of these patients and to improve clinical outcome.

In recent years, one of the most intensively studied glycoprotein is YKL-40. It is believed to have prognostic value in patients with inflammatory and tumor diseases. Its specific receptor has not been determined yet. YKL-40 is expressed and secreted by activated macrophages and neutrophils, chondrocytes and synovial cells. There is no detailed data available on YKL-40 in TBI. We assume that studies on YKL-40 in parallel with clinical scales would provide new information on the pathogenesis of TBI.

Key words: *YKL-40, brain injury, biomarker*

Severe traumatic brain injury (TBI) is the leading cause of morbidity and mortality among individuals, aged 1 to 45 years, worldwide. It is one of the most common traumatic injuries and the first cause of death among patients with severe multiple injuries (90% of all deaths). More than a third of the surviving patients with TBI (about 3.2 million people in the world) is left with permanent and severe disability (Zaloshnja et al., 2008). The annual cost of their health care exceeds 60 billion dollars (Finkelstein et al., 2006). The trend of increasing its incidence worldwide is worrying due to socio-economic costs too.

Trauma to the head causes primary injury such as skull fracture, cerebral contusion, and haemorrhage that is a direct physical consequence of the impact. Hours or days after the traumatic incident, secondary injury usually occurs which can be in most cases a major determinant of the patient's ultimate neurologic outcome (Vincent JL et al., 2012).

PRIMARY AND SECONDARY INJURY

Injury to the brain is caused by external forces to the head that strain the tissue beyond its structural tolerance (Gennarelli et al., 1996). These forces can be classified as contact or inertial (Graham et al.; 1995). Contact forces typically produce focal injuries such as skull fractures, contusions, and epidural or subdural hematomas. Inertial forces result from the brain undergoing acceleration or deceleration (translational, rotational, or both) and can occur without head impact. Inertial forces can cause focal or diffuse brain injuries: pure translational acceleration leads to focal injuries such as contrecoup contusions, intracerebral hematomas, and subdural hematomas, whereas rotational or angular acceleration, common with high-speed motor vehicle crashes, usually causes diffuse injuries (Vincent JL et al., 2012).

Secondary brain injury includes different pathogenetic mechanisms induced by post traumatic hypoxia and ischemia, which activate a cascade of metabolic changes, leading to production of free oxygen radicals (Ikeda et al., 1990; Kontos et al., 1986; Traystman et al., 1991), secretion of cytokines (Taupin et al., 1993) and other pro-inflammatory mediators (Rostworowski et al., 1997). In addition, accompanying disorders related to trauma such as arterial hypotension, hypercapnia, hyperthermia, hyperglycemia, seizures, are of great impact too (Vincent JL et al., 2012).

A number of pathologic cascades are shared by these important insults in TBI, including excitotoxicity, programmed cell death, axonal injury, and inflammation, along with a spectrum of endogenous neuroprotectant responses (Kochanek et al.; 2000; McIntosh et al., 1993).

BIOMARKERS AND TRAUMATIC BRAIN INJURY

TBIs can be classified by the mechanism of injury, the clinical severity as graded by the Glasgow Coma Scale (GCS), or by the characterization of structural damage. The heterogeneity of the disease makes it difficult to accurately assess the level of trauma and predict the clinical outcome of the patient. Generally, injuries are classified as mild, moderate, or severe depending on the GCS score, which utilizes motor, eye, and verbal responses to evaluate the level of consciousness of the patient. In addition to the GCS, TBI may be classified according to a clinical injury severity score based on the level of injury incurred to various key body regions, according to the level of structural damage, and the patient prognosis based on various prognostic models (Maas et al.; 2008). TBI injury is heterogeneous in nature, and no single classification scheme is sufficient in characterizing injury for the purposes of diagnosis and prognosis. Standard neurological examination and diagnostic imaging techniques (CT and conventional MRI) are able to provide reliable information about the

severity of the initial injury. Unfortunately, these methods could not illustrate biochemical, metabolic and cellular changes related to secondary brain damage and to determine long-term prognosis in this category of patients. Biomarkers, reflecting a biological response to injury or disease, have proven useful for the diagnosis of many pathological conditions including cancer, heart failure, infection, and genetic disorders.

For TBI, several proteins synthesized in astroglial cells or neurons have been proposed as potential biomarkers. The presence of these biomarkers in the cerebrospinal fluid and serum of patients with moderate-to-severe TBI, and their correlation with outcome, suggest that they may have utility as surrogate markers in clinical trials. In addition, many of these markers have been found to be sensitive indicators of injury, and therefore may have the potential to diagnose individuals with mild TBI. In addition to biomarkers that correlate with long-term outcome, a few studies have identified prognostic biomarkers for secondary injury that may be useful in personalizing patient management (Hergenroeder et al.; 2008).

The purpose of the study is to summarize data available on YKL-40 as a specific and reliable biomarker, associated with the outcome in patients with TBI. This approach could clarify our understanding of the structural damage in the brain or the underlying pathogenic and reparative mechanisms at the cellular level. This information should be of use to conduct future basic and clinical research to optimize the treatment of these patients and to improve clinical outcome.

In recent years, one of the most intensively studied glycoprotein is YKL-40. It is believed to have prognostic value in patients with inflammatory and tumor diseases. YKL-40 is an extracellular protein, belonging to the mammalian-chitinase like family with not completely defined biological functions. A specific receptor is not determined yet (Schultz et al; 2011). YKL-40 is expressed and secreted by activated macrophages and neutrophils, chondrocytes and synovial cells (Johansen JS; 2006). There is no detailed data available on YKL-40 in TBI. The scientific on the topic are sparse and not thorough enough. The only study published on this issue includes 20 patients and shows that the level of the glycoprotein in cerebrospinal fluid is higher in patients with severe TBI and correlates with the concentration of pro-inflammatory cytokines - IL-1β and TNF-α. The authors suggest that YKL-40 is an indicator reflecting local inflammation (Bonneh-Barkay et al; 2010).

YKL-40 AND INFLAMMATION

Inflammation in TBI appears to have both acute detrimental and subacute/chronic beneficial aspects. There is robust acute inflammation after TBI in both experimental models and in patients. Nuclear factor- κB, TNF-α, interleukin (IL)-1β, eicosanoids, neutrophils, and macrophages contribute to both

secondary damage and repair. Markers of inflammation following TBI have been assessed in humans using two general strategies: examination of inflammation in contused brain tissue or cerebral infarctuses resected from patients with refractory intracranial hypertension, and study of mediator levels in CSF. Consistent with a role for IL-1β in the evolution of tissue damage in cases of human TBI, Clark et al. performed western blot analysis of brain samples resected from adults with refractory intracranial hypertension secondary to severe contusion. The authors suggested that IL-1β is a pivotal pro-inflammatory mediator in the traumatically injured brain in humans. Marion and associates demonstrated increases in IL-1β in CSF after severe TBI in adults. Satchell et al. proved increase in ICE followed by a reduction in pro-IL-1β and an elevation of IL-1β in CSF after severe TBI in children. Contusion and local tissue necrosis appear to be important to trigger neutrophil influx, with resultant secondary tissue damage. Neutrophil influx is accompanied by increases in inducible nitric oxide synthase in brain and is followed by macrophage infiltration, which peaks between 24 and 72 hours after injury. Macrophage infiltration and the differentiation of endogenous microglia into resident macrophages may signal the link between inflammation and regeneration with elaboration of a number of trophic factors.

Kossmann et al. reported a link between IL-6 production and the production of neurotrophins such as NGF in human head injury. Cultured astrocytes treated with either IL-6 or IL-8 in CSF from brain-injured adults produced NGF. Cytokine production after TBI may be important to neuronal plasticity and repair. Studies in models of TBI suggest early detrimental effects of a number of inflammatory mediators but beneficial effects of inflammation on long-term outcome. Although cytokines are shown to function in the pathophysiology of neuroinflammation in TBI, there are controversial reports about the connection between cytokine CSF levels and clinical outcome (Hayakata et al., 2004, Buttram et al., 2007).

YKL-40 transcription levels were induced in reactive atstrocytes and were associated with local inflammation in an acute animal model of TBI. The relationship between YKL-40 and inflammatory mediators was studied in both animal and human TBI (Bonneh-Barkay et al., 2010).

Some researchers demonstrated YKL-40 distribution at the perimeter of contusions and temporal course of expression. They suggested that it might be an important component of the astrocytic response in TBI and modulates CNS inflammation (Wiley CA et al, 2015).

In summary, YKL-40 expression is associated with inflammation in a variety of diseases including TBI. Investigations on the topic are sparse and future work on larger scale should examine the utility of YKL-40 as a biomarker and its role in neuroinflammation. We assume that studies on YKL-40 in parallel with clinical scales would provide new information on the pathogenesis of TBI.

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