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Outcome biomarkers following severe traumatic brain injury

Biomarcadores prognósticos no traumatismo crânio-encefálico grave

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ABSTRACT

Trauma is the leading cause of death of people from 1 to 44 years of age. Traumatic brain injury is the main determinant for mortality and morbidity caused by trauma. Outcome prediction is one of the major problems related to severe traumatic brain injury because clinical evaluation has an unreliable predictive value and complicates identification of patients with higher risk of developing secondary lesions and fatal outcome. That is why, there is considerable interest in development of biomarkers that reflect the severity of brain injury and correlate with mortality and functional outcome. Proteins S100B and neuron specific enolases are among the markers most studied for this purpose, however some studies

are investigating glial fibrillary acidic protein, creatinine phosphokinase, isoenzyme B, myelin basic protein, plasma desoxiribonucleic acid, heat shock protein 70, von Willebrand factor, metalloproteinases and brain-derived neurotrophic factor, among others. Evidence suggests that inflammation, oxidative stress, excitotoxicity, neuroendocrine responses and apoptosis play an important role in the development of secondary lesions. Markers involved in these processes are being studied in traumatic brain injury. We reviewed these biomarkers, some of which present promising results for future clinical application.

Keywords: Brain injuries/mortality; Brain injuries/complications; Prognosis; Biological markers/blood

INTRODUCTION

Trauma is the leading cause of death for people from 1 to 44 years of age. Traumatic brain injury (TBI) is the main determinant of morbidity, disability and mortality in this group.⁽¹⁾ Severe TBI is associated with a 30 to 70% mortality rate,⁽²⁾ and recovery of survivors is marked by severe neurological sequels and by a very impaired quality of life.⁽³⁾

Severity of TBI is in general established using the Glasgow Coma Scale –GCS). This scale is achieved by observation of three parameters: eye opening, motor response, and verbal response.⁽³⁾ TBI is ranked as severe, with a GCS score of 3 to 8, as moderate from 8 to 12 and as mild from 13 to 15.⁽⁴⁾ The GCS has been used as one of the most important predictors of TBI outcome, although other variables such as age, abnormal motor response, CT findings, pupillary abnormalities and episodes of hypoxia and hypotension have been subsequently introduced in an effort to reach a more precise prognosis. It is often difficult to determine

the GCS score in the emergency room due to intubation or sedation during pre-hospital care.⁽⁵⁾ Interference of alcohol intoxication in decreasing the score of the GCS is controversial.⁽⁶⁾

The functional Glasgow Outcome scale (GOS) is the most used for assessment of the functional prognosis after TBI.⁽⁷⁾ It has five levels, from death to good positive prognosis and is normally obtained 3, 6 and 12 months after trauma.⁽⁸⁾ However it presents important shortcomings and early assessment of brain damage may be very difficult during the patient's stay in the intensive care unit (ICU).⁽⁷⁾

Computed tomography (CT) is the choice image exam in the management of TBI in the emergency room. With this exam, hematomas can be speedily diagnosed, and as required, support early surgical treatment.^(9,10) CT has, however a poor sensitivity for diagnosis of non-hemorrhagic injuries, which explains the poor correlation often observed between the tomography findings and the GCS score.⁽⁹⁾ CT must be repeated if there is a worsening of the clinical condition, diagnosed injuries may expand or new injuries may develop. Mainly for the first 12 to 24 hours after trauma.⁽¹⁰⁾ Marshall et al.⁽¹¹⁾ developed a classification for CT findings in TBI. CT alterations used for the classification are: edema (assessed by compression or absence of cisterns), volume of high or mixed density injuries (blood collections), midline deviation, and evacuation of mass injury.⁽⁸⁾ Various studies have confirmed the prognostic predictive value of the Marshall classification in TBI patients.⁽¹²⁾

Recovery after TBI is related to severity of the initial damage (primary lesion) and presence of secondary injury.⁽¹³⁾ An important cause of secondary injury is development of intracranial hypertension (ICH) which may be due to intracranial hematoma or cerebral edema. The traditional goal of management of patients with TBI has been to limit the secondary damage by manipulation of the intracranial pressure and of the cerebral perfusion pressure as well as to avoid aggravating factors such as hypoxemia and hypotension to ameliorate prognosis of these patients.⁽³⁾

The large variety of associated conditions and the variable predictive value of clinical evaluation complicate identification of patients with a higher risk of developing ICH and fatal outcome at the initial stage of the traumatic injury.⁽¹⁴⁾ Due to these issues, there is considerable interest in the development

and later usage of biochemical markers that reflect severity of the cerebral damage and that correlates with development of secondary lesion, short term prognosis (mortality) and long term functional prognosis.^(15,16,17)

A good biomarker for brain injury must be sensitive and with a high specificity for cerebral tissue. It must be measured in serum, as the cephalic-rachidian fluid is not always available and, in severe TBI a rupture of the hematoencephalic barrier takes place.⁽¹⁸⁾ It must have little variability in relation to gender and age. Furthermore, it must have clinical value in patients with associated multiple trauma. Many proteins synthesized in the astroglia cells or in the neurons have been proposed as markers for cell damage of the CNS.⁽¹⁶⁾ Markers related to pathophysiological mechanisms involved in secondary injuries are also being investigated.

TISSUE MARKERS

S100B

This is a small cytosolic dimeric protein of the calcium-binding type.^(15,17) It weights approximately 21kDa⁽¹⁹⁾ and exists in various forms depending upon the structures of its α and β chains. The $\beta\beta$ form, which is named S100B, is found in the astroglia and Schwann cells. The S100B is highly specific for central nervous system tissue, as well as for cells of malignant melanoma.⁽¹⁵⁾ However it may also be found in other tissues such as fatty tissue.⁽¹⁹⁾

Occurrence of S100B may indicate brain damage and increased permeability of the hematoencephalic barrier. Maximum concentration peak occurs after 20 minutes, it is metabolized by the kidney and excreted in urine (half-life of about 30 to 113 minutes).⁽²⁰⁾ It may be measured in arterial or venous blood, is not affected by hemolysis and remains stable for hours. It does not require centrifugation and immediate freezing of the sample.⁽¹⁵⁾ Higher levels of S100B after TBI may also be measured in liquor.⁽¹⁶⁾ Variability of S100B measurement related to gender and age is not significant.⁽¹⁶⁾

High levels of S100B have been reported after TBI, stroke, subarachnoidal hemorrhage and at postoperative from cardiac surgery, if followed by neurological complications.⁽¹⁵⁾ S100B was also high in patients with hemorrhagic shock, related to severity of shock and hypoperfusion.⁽²²⁾ Basic mechanisms that lead to serum increase of S100B in TBI remain

unknown. It is not clear if protein release depends on irreversible cell damage or if it can take place after less severe injury. There is evidence that secretion of S100B by astrocytes might be an active process.⁽¹⁶⁾

In severe TBI, S100B correlates with a short time outcome (death or survival), functional prognosis in 6 months and with severity criteria of TBI such as the Marshall score and the ISS.^(15,23,24) Serum levels of S100B, assessed in the first hours after severe TBI have been better predictors of long term prognosis, when assessed by the GOS scale than the GCS and the CT Marshall scale.⁽²⁵⁾ Because S100B has a half-life of about 2 hours, increased values due to primary brain damage should return to baseline levels in 12 to 24 hours.⁽¹⁵⁾ S100B is a sensitive marker for early prediction of ICH development.⁽¹⁴⁾

Increased levels of S100B were detected in patients with multiple trauma without TBI.^(26,27) In this context we evaluated the role of serum S100B as a predictive marker of the fatal outcome in severe TIB, isolated or associated to multiple trauma. S100B has shown to be a sensitive biomarker of fatal outcome in patients with isolated TBI as well as those with TBI associated to multiple trauma.⁽⁷⁾

Neuron-specific enolase

Together with S100B, neuron-specific enolase (NSE) is considered one of the most promising markers for brain injury. Enolase is a glycolytic enzyme that converts 2-phospho-D glycerate into phosphoenolpyruvate. It is functionally active as a heterodimer formed by α , β and γ subunits. The neuron-specific enolase isoenzymes are almost exclusively found in the cytoplasm of neurons (isoenzyme γ - γ) and neuroendocrine cells (isoenzyme α - γ).⁽²⁸⁾ The NSF molecular mass is 78kDa and its biological half-life is probably longer than 20 hours.⁽¹⁶⁾

NSE is the only marker that directly assesses functional damage to neurons. It is passively released by cell destruction⁽²⁸⁾ and its increased concentrations after neuron damage may be measured in peripheral blood or liquor.⁽²⁹⁾ NSE specificity is high and variability associated to gender and age is low.⁽¹⁶⁾ One of the main problems associated with use as marker of brain damage is hemolysis. Erythrocytes contain a large amount of NSE and hemolysis may, therefore, cause a marked increase of NSE in the blood.⁽²⁸⁾

Increased levels of NSE were found in blood and liquor of patients with stroke, intracerebral hemorrhage and after cardiopulmonary resuscitation.⁽³⁰⁾

NSE also increases and associates with brain injury in patients with severe sepsis and septic shock.⁽³¹⁾ Tumor cells in APUDomas, neuroblastomas and small cell lung carcinomas are able to produce NSE and increase serum levels of this protein. That is why, serum dosage of NSE has been considered as a diagnostic and prognostic serum marker in the clinical management of these neoplasms.⁽³²⁾

High serum concentrations of NSE are found in TBI correlating with injury severity.⁽²⁹⁾ In severe TBI, NSE correlates with clinical outcome.⁽²⁴⁾ Normally, it increases in the first 12 hours after trauma and then decreases in the hours and days. Secondary increases may take place in patients who evolve to fatal outcome. Presence of NSE, correlation with levels of GCS and CT findings are controversial. Studies that relate NSE level with intracranial pressure (ICP) and with long term functional outcome also disclose conflicting results.⁽¹⁶⁾ NSE may also be high in patients with multiple trauma without TBI (as recorded by TC).⁽²⁸⁾

Glial Fibrillary Acidic Protein

The glial fibrillary acidic protein (GFAP) is an intermediate filamentary monomeric protein with an approximate molecular mass of 40 to 53 kDa.^(16,18) It represents the major part of the cytoskeleton of astroglia and is only found in the central nervous system, therefore, highly specific for brain tissue.⁽¹⁸⁾

Studies have shown the use of measuring the GFAP in the liquor as a specific indicator of a pathologic anomaly of the CNS.^(16,24) High levels of GFAP are found in blood after stroke, correlating to a functional prognosis.⁽³³⁾

GFAP is released in the blood stream soon after TBI. It is related to the TBI level of severity with the Marshall classification and presence of ICH. GFAP is higher in patients with a primary fatal outcome and with a worse neurological outcome, assessed by GOS. GFAP is not released in multiple trauma without TBI.⁽¹⁸⁾

Creatine Kinase BB

Creatine kinase brain isoenzyme (CKBB) is an isoform of creatine-kinase found in the central nervous system. The brain has many isoforms CKBB and mitochondrial-CK but lacks CKMB and CKMM, respectively found in the cardiac and skeletal muscles.⁽³⁴⁾ The molecular mass of CKBB is 40 to 53 kDa.⁽¹⁶⁾

CK-BB is located in the astrocytes and is released

when there is anatomical injury in the brain tissue. Its serum levels increase during the first hours after trauma and drop quickly, unless there is a continued enzyme release. CKBB is found in other organs such as large intestine, prostate, pancreas, uterus, liver and spleen. There is no CKBB in red blood cells and, in physiological conditions, serum concentration of these enzymes is low.⁽¹⁶⁾

Various situations of brain injury such as cardiac arrest and subarachnoid hemorrhage may lead to release of CKBB in the liquor.⁽³⁴⁾ High CKBB serum levels are also found in adenocarcinomas of the prostate, breast, ovary, colon, other adenocarcinomas of the gastrointestinal tract and also in small cell anaplastic carcinoma of the lungs.⁽³⁵⁾

Severe TBI studies have disclosed correlation of the severity score assessed by GCS with serum levels of CKBB. However, specificity and sensitivity of the serum determination of CKBB as a predictor of brain injuries remains controversial.⁽¹⁶⁾

Brain-derived neurotrophic factor

Brain-derived neurotrophic factor (BDNF) is a key molecule for neuroplasticity.⁽³⁶⁾ It is expressed in many cell types, including neurons and glia cells. Increased expression of BDNF in the central nervous system, in response to various stimuli, suggests a neuroprotector role for this neurotrophine. Especially, inflammatory responses seem to be involved in the increased expression of BDNF.⁽³⁷⁾

BDNF has been researched in various neurological and psychiatric disorders. In TBI, experimental studies in rats disclosed an increased RNAm of BDNF in the hippocampus within the first 24 hours following trauma.⁽³⁶⁾ Thereupon we studied the serum levels of BDNF patients, victims of severe TBI. We found high serum levels of BDNF in the first hours after TBI, with a correlation of the serum levels of BDNF and fatal outcome in patients with isolated severe TBI.⁽³⁸⁾

Mielin Basic Protein

Mielin basic protein (MBP) is a specific protein of mielin with a molecular weight of 18.5kDa. It may be released to the blood after brain injury or in demyelinating disease.⁽¹⁶⁾ Serum and liquor concentrations of MBP were found in children with suspicion of inflicted TBI.⁽³⁹⁾ The MPB was elevated in patients with severe TBI relating to the degree of severity and mortality.⁽¹⁶⁾

EXCITOTOXICITY AND PROTEOLISIS MARKERS

Cell excitotoxicity is a key event in the pathophysiology of TBI. Because it is well known that the glutamate excitatory amino acid is rapidly released after cell damage and that high glutamate concentrations lead to depolarization of neighboring cells, glutamate release is believed to be the sentinel event for injury by excitotoxicity.⁽⁸⁾ Part of this process is mediated by the n-methyl-D-aspartate (NMDA) receptor.^(3, 40)

Calcium influx to the cell triggers reactions that, in turn, activate calcium-dependant enzymes. Caspase-3 is a member of the caspases family of the cysteine proteases that may induce apoptosis mechanisms. Increase of caspase-3 as well as that of calpain was documented *in vivo* after TBI. The α -spectrin is the main action substrate of calpains and of caspase-3 cysteine proteases and products of degradation of the α -II-spectrin may also be viewed as biomarkers in the context of TBI.⁽⁴¹⁾ In liquor, Pineda et al.⁽⁴²⁾ recorded increased concentrations of α -II-spectrin degradation products, which correlated to severity of the injury, CT findings and functional outcome after severe TBI. The α -II-spectrin degradation product generated by action of the caspase-3 had a temporal release curve different from the calpain, suggesting that mechanisms of necrotic as well as apoptotic cell death are activated in humans after TBI, but at different points in time. Raghupathi⁽⁴³⁾ suggests that cell death mechanisms after TBI may represent a continuum between the apoptotic and necrotic pathways.

CELL DEATH MARKERS

Apoptosis markers

Growing evidence has disclosed that apoptosis occurs after TBI.⁽⁴¹⁾ Onset of apoptotic cell death may be activated in two distinct pathways, normally referred as intrinsic and extrinsic. The intrinsic begins with release of cytochrome c from the mitochondrial intermembrane space to the cytosol, leading to activation of a cascade of caspases and amplification of the apoptotic signal. Cytochrome c was high in the liquor of children with TBI.⁽⁴⁴⁾ On the other hand, the extrinsic pathway may be activated by binding to a Fas/Apo-1/CD95 receptor of the transmembrane cell surface, receptor-1 of the tu-

mor necrosis factor (TNF-1), DR3, DR4 and DR5 and their corresponding ligands.^(45,46) The Fas (FasL) ligand binds to the Fas receptor resulting in multimerization, recruiting of adaptor molecules and formation of a caspase activating complex. Fas/FasL is a key regulator of apoptosis.⁽⁴⁷⁾ Fas may also take a soluble form (sFas) deprived of a transmembrane region that may prevent cells from the FasL-induced apoptosis.⁽⁴⁸⁾ There is abundant evidence suggesting that apoptosis receptors participate in neuron death after CNS injury.⁽⁴⁹⁻⁵¹⁾ Our research group assessed the role of sFas and of TNF- α as predictive markers of fatal outcome in adult men with isolated TBI. We detected high levels of serum sFas and TNF- α in victims of severe TBI, however no correlation was found between high levels and fatal outcome.⁽⁵²⁾

Plasma desoxyribonucleic acid

Dosage of plasma desoxyribonucleic acid (DNA) in serum or plasma for clinical diagnosis, study of prognosis and monitoring of a range of conditions has been investigated. DNA sequences, derived from tumors, fetuses and donors have been detected in plasma and in serum of patients with cancer, of pregnant women and transplanted patients respectively.⁽⁵³⁻⁵⁵⁾

Significant increases in circulating DNA have been detected in plasma of trauma patients and have been shown as a promising biomarker for stratification of trauma severity. The increase in the concentration of plasma DNA was correlated with level of severity and development of post-trauma complications.^(56,57) High plasma DNA concentrations were also related to severity of strokes.⁽⁵⁸⁾

Mechanisms by which free circulating DNA increases after trauma have not been established. High concentrations observed very early after injury, suggest that the extra-cell DNA originates from tissue damage (necrosis) while apoptosis mechanisms may contribute to persistent increases, in addition to a DNA clearance, probably impaired by commitment of the responsible organs due to systemic inflammation.⁽⁵⁷⁾

Our group published a study evaluating the role of plasma DNA dosage as a predictive marker for the fatal outcome of severe TBI victims. We showed that significantly high concentrations of plasma DNA 35.7 \pm 5.2 hours after trauma correlated with mortality. No correlation was found between DNA concentrations and presence of associated extracranial injuries.⁽⁵⁹⁾

INFLAMMATORY MARKERS

In TBI, there is a frequent systemic intense inflammatory response that affects the injured cerebral tissue as well as the healthy one. Response to inflammatory stress includes activation of the complement and up-regulation of endothelial cell adhesion molecules of cerebral vessels, associated with accumulation of neutrophils and production of cytokines.⁽⁶⁰⁾ Role of inflammatory mediators in the development of a secondary lesion has been investigated. A series of mediators is involved, including cytokines.⁽³⁾ Among the cytokines are chiefly focused interleukin 1 β (IL-1 β), tumor necrosis factor (TNF α), interleukin 6 (IL-6) and interleukin 8 (IL-8).^(3,20,60)

Interleukin 8 (IL-8) is considered one of the main cytokines involved in the physiopathology of TBI. It is produced by various cell types including neutrophils, endothelial cells, astrocytes and microglia cells. Release of IL-8 is stimulated by other cytokines such as IL-1, and by ischemic hypoxia and re-perfusion, which are the basic mechanisms of oxidative post-traumatic stress. Many experimental studies indicated that IL-8 plays a crucial role in inflammatory response to stress in TBI.⁽⁶⁰⁾ Studies in humans also suggest that IL-8 plasma levels have a predictive parameter for mortality in severe, isolated TBI.^(20,60)

Astrocytes and microglia soon after trauma release IL-1 β and TNF α , lead to additional release of cytokines and to production of peripheral immune system mediators. Clinical studies have shown high levels of TNF α in TBI patients.^(3,52)

The role of the IL-6 is more ambiguous as it has a pro- as well as an anti-inflammatory action. High levels of IL-6 in plasma and liquor are found after TBI.⁽³⁾ IL-6 might stimulate vasopressin secretion and may be involved in the pathogenesis of the syndrome of inappropriate hormone secretion (ADH-antidiuretic hormone) after TBI⁽⁶¹⁾.

OXIDATIVE STRESS MARKERS

Oxidative stress seems to be a key event in the post TBI neuron degeneration, when increase of free radicals leads to proteic oxidation, lipid peroxidation and DNA damage.⁽³⁶⁾ They are produced during normal aerobic metabolism and in physiological concentration do not have destructive effects on the cell. However, at the acute stage of TBI, associated to hypoperfusion and cell ischemia, increased concen-

trations of free radicals may bring about structural instability of many molecular components of the cell. The brain is particularly vulnerable to oxidative stress due to high oxygen demand, intense production of free radicals and high levels of transition metals such as iron that may catalyze production of free radicals. Furthermore, neuron membranes have an abundance of polyunsaturated fatty acids, which are the source for lipid peroxidation reactions.⁽⁶²⁾ Membrane lipid peroxidation by free radicals is quite common in patients with TBI. The membrane becomes dysfunctional and lysis and cell death may occur.⁽⁸⁾ Free radicals can also injure endothelial cells, contributing to vasogenic and cytotoxic edema.⁽³⁾ When tissues are exposed to oxidative stress, activity and expression of antioxidant enzymes are increased. The superoxide dismutase (SOD) and the glutathione peroxidase Gpx are cerebral antioxidant enzymes. On studies with TBI, activity of these enzymes has shown changes.^(63,64)

MARKERS OF VASCULAR INJURY

The Von Willebrand Factor (VWF) is a known marker for endothelial injury, and its concentration increases in response to different stimuli.⁽⁶⁵⁾ This factor is an adhesive protein that prompts onset and progression of thrombus formation on the site of vascular damage by interacting with components of the extracellular matrix and platelets receptors.⁽⁶⁶⁾ Recent studies were carried out aiming to correlate VWF plasma level with prognosis of trauma. Yokota et al.⁽⁶⁵⁾ in a study related two markers, thrombomodulin and the VWF with severe TBI. They concluded that both are good indicators of brain injury and brain activation in trauma. A study that assessed coagulation and fibrinolysis in post-TBI children disclosed increase of hypercoagulability in the first 24 hours, with significant increase of VWF and fibrinogen with a peak in the second week.⁽⁶⁷⁾ We studied the role of VWF as potential prognostic marker in patients with severe TBI, comparing their plasma levels with clinical diagnostic criteria and imaging with a short term outcome (death or survival). Our study showed that VWF plasma levels increased significantly in individuals that suffered severe TBI and that they correlated with the Marshall Classification score suggesting that VWF might be a marker for unfavorable prognosis.⁽⁶⁸⁾

Matrix metalloproteinases (MMPs) are zinc-de-

pendent endopeptidases responsible for the degradation of most components of the extracellular matrix such as collagen, fibronectins and elastins. During normal cell development and physiology the activated metalloproteinases are needed for the extracellular matrix degradation, permitting cell migration.⁽⁶⁹⁾ Experimental studies have shown that MMP-9 levels increase after TBI degrading components of the basal layer and breaking the hematic-encephalic barrier.⁽⁷⁰⁾ Wang et al.⁽⁷¹⁾ in studies with rats showed that the MMP-9 levels after TBI presented a persistent elevation for one week and that this elevation also takes place in the contralateral hemisphere suggesting that after trauma changes in the cerebral status are not limited to the injured zone. In this same study it was shown that weak activity zones presented a limited level of MMP-2, suggesting that small elevation of MMP-2 may take place, contrary to studies related to encephalic ischemia, where a major elevation of the MMP-2 activity is detected.⁽⁷¹⁾ Suehiro et al.⁽⁷⁰⁾ found high levels of MMP-9 in patients with acute stage TBI, which correlate with high levels of IL-6 suggesting that MMP-9 may play an important role in injury by TBI and that it is associated to post-TBI inflammatory events.

The role of endothelin 1 (Et-1), a vasoactive peptide very potent in the deterioration of brain perfusion after trauma remains uncertain.⁽⁷²⁾ It may represent a cellular manifestation of the self-regulatory mechanisms' failure.⁽³⁾ Maier et al.⁽⁷²⁾ showed that an increase of the serum and liquor levels of Et-1 took place in patients with severe TBI at the acute stage.

CELLULAR STRESS PROTEINS

Heat shock proteins HSP are highly conserved molecules that play a significant role in the protein folding and unfolding as well as in the assembly and disassembly of protein complexes. Due to these auxiliary functions some Hsps have been called chaperone molecules, as they protect cells from damage by environmental stress. The Hsps are designated according to their molecular weight. The Hsp70kDa family regulates cerebral processes in normal or stress conditions. In the brain, Hsp70 may be induced by a series of pathological stimuli including ischemia, excitotoxicity and inflammatory responses.⁽⁷³⁾

Pittet et al.⁽⁷⁴⁾ showed that the Hsp72 (member of the Hsp70 family) can be detected in the serum of patients with severe trauma within 30 minutes after

trauma and that high levels are associated with favorable outcome after trauma. Recently we investigated the role of the Hsp70 protein as a predictive marker of mortality for severe TBI in men. We proved that high serum levels of Hsp70 may be a promising biomarker for cases of severe TBI. ⁽⁷³⁾

NEUROENDOCRINE MARKERS

In the last few years various studies have shown that hypopituitarism is a common TBI complication. From 23 to 69% of patients show some degree of hypopituitarism during the first 12 months after the TBI. ⁽⁷⁵⁾ Growth hormone (GH) deficiency is the most common hypophysiary deficiency induced by TBI isolated or associated to other hypophysis deficiencies. ⁽⁷⁶⁾ Next, the luteinizing hormone (LH) and follicular stimulating hormone (FSH) deficiencies are significantly more common than deficiencies of the adrenocorticotrophic hormone (ACTH) which are significantly more common than deficiencies of the thyroid stimulating hormone (TSH). ⁽⁷⁷⁾ The pituitary gland responds to acute traumatic events and many changes in hormone levels become apparent in the first hours or days after trauma. ^(61,78) Recent studies have shown that various inflammatory mediators including cytokines and free radicals may affect endocrine function at the acute stage of TBI. ⁽⁷⁸⁾ Such changes represent part of the acute adaptive response to trauma and may also be influenced by medication administered at this stage such as glucocorticoids, narcotics or dopaminergic agents. ⁽⁶¹⁾ Hormone changes of the acute stage after TBI generally do not predict hypophysiary dysfunction after one year. ⁽⁷⁸⁾ Hypophysiary function in TBI patient can improve with time, suggesting that isolated or even multiple failures diagnosed in the short time are transient. On the other hand, a normal pituitary function may in the short term, albeit seldom, decrease in 12 months after trauma. ⁽⁷⁶⁾

Agha et al., ⁽⁷⁹⁾ studying patients with TBI after admission in the ICU found 56.5% of hypophysiary dysfunction at the acute stage of TBI. These results were confirmed by Dimopoulou et al. ⁽⁸⁰⁾ in a study carried out under similar conditions, showed that 53% of the patients had at least one deficiency in the hormone axis, and the most frequent were hypoadrenalism and gonadal dysfunction. Tanriverdi et al. ⁽⁷⁸⁾ found a positive correlation between the testosterone levels at the acute stage of TBI and the GCS

score. In this same study, levels of GH and IGF-I did not correlate with severity of TBI.

On the other hand, high serum concentrations of cortisol are usually present during the initial stage of trauma and are associated to increased ACTH release which, supposedly results from cytokines activation of the noradrenergic system and from corticotrophin release. ⁽⁶¹⁾ In some cases, abnormalities in the cortisol secretion dynamics (fasting hypercortisolemia, abolition of normal day rhythm and inadequate suppression after dexamethasone) may persist for many months after TBI ⁽⁷⁸⁾. Tanriverdi et al. ⁽⁷⁸⁾ in a prospective study, in which dosages were measured during the first 24 hours after admission in the ICU and 12 months later, found that mean levels of cortisol were significantly higher at the acute stage in comparison to the levels of the ACTH triggering a central activation of the hypothalamus-hypophysis-adrenal axis. However, no correlation was found between cortisol level and severity of injury, although some authors have shown correlation between the GCS and initial levels of cortisol and between cortisol levels and prognosis. Serum levels of cortisol-binding globulin to cortisol may be decreased in catabolic conditions resulting in disproportionately low total cortisol levels when compared to free cortisol (biologically active). ^(77,81)

Hyperprolactinemia is present in more than 50% of the patients at the acute post-TBI stage. Proof of a negative correlation between prolactine concentrations and TBI severity suggests a good prognostic role for prolactine responses at the acute stage after TBI. ^(61,81) Posterior hypopituitarism can also be present after TBI with central diabetes insipidus. Prevalence of diabetes insipidus after TBI at the acute stage may reach 26%. ⁽⁷⁷⁾

Experimental studies have shown increases of leptin RNAm in the brain of rats, during the first hours after TBI. ⁽⁸²⁾ Leptin is a hormone produced by adipocytes that regulates satiation and energy metabolism by activating receptors expressed in the hypothalamus. Recent evidence indicates that leptin may be a neuronal protector. ⁽⁸³⁾ High levels of leptin were found in male patients with spinomedullary injury. ⁽⁸⁴⁾

Aldosterone has already been studied as a biochemical marker of the acute stage of TBI. ⁽⁸⁵⁾

CONCLUSION

Research on biomarkers with a prognostic value in severe TBI is a promising domain for the im-

proved management of TBI. Some biomarkers such as S100B and NSE are at a clinical study stage. However, evidence has disclosed promising new biomarkers among which plasma DNA, HSP70 and von Willebrand factor, also BDNF are noteworthy.

RESUMO

O trauma é a principal causa de morte em pessoas entre 1 e 44 anos de idade. O traumatismo crânio-encefálico é o principal fator determinante da mortalidade e da morbidade decorrentes do trauma. A predição do prognóstico é um dos principais problemas associados ao traumatismo crânio-encefálico grave, já que o valor preditivo variável da avaliação clínica complica a identificação de pacientes com maior risco para desenvolvimento de lesões secundárias e desfecho fatal. Devido a estas questões, há considerável interesse no desenvolvimento de biomarcadores que reflitam a gravidade do dano cerebral e que se correlacionem com

mortalidade e prognóstico funcional em longo prazo. As proteínas S100B e enolase neuronal específica estão entre os marcadores mais estudados para este fim, mas há também estudos com a proteína glial fibrilar ácida, a creatinina quinase cerebral, a proteína mielina básica, o ácido desoxirribonucléico plasmático, a proteína de choque quente 70, o fator von Willebrand, as metaloproteinases, o fator neurotrófico derivado do cérebro, dentre outros. Evidências sugerem que a inflamação, o estresse oxidativo, a excitotoxicidade, as respostas neuroendócrinas e a apoptose têm um importante papel no desenvolvimento de lesões secundárias. Marcadores envolvidos nestes processos também estão sendo estudados no traumatismo crânio-encefálico. Revisamos estes marcadores, muitos dos quais apresentam resultados promissores para uma futura aplicação clínica.

Descritores: Traumatismos encefálicos/mortalidade; Traumatismos encefálicos/complicações; Prognóstico; Marcadores biológicos/sangue

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