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Understanding head injury: A prelude ?

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Abstract: There is a vast accumulated data on the current understanding of head injury. Concepts on early prehospital care and transport, imaging, surgical management and multimodality monitoring have firmly established themselves in the overall management of head injury. However, data on genetic and biochemical markers and cerebral protection has not yet translated into full fledged clinical application. Probably the current situation is at the threshold of the neurochemical markers, neuroprotective pharmacological agents and advanced neuroimaging being woven into the overall head injury management.

Keywords: biomarkers; cerebral protection; head injury

INTRODUCTION

Head injury is an age-old, world-wide problem, yet so little is known about the pathophysiological processes that follow head injury. The information so far available is yet to be translated into improved outcome. Research in animal models has helped researchers to work out improved treatment targets in head injury, but definite neurological improvement is still linked to improved prehospital management and resuscitation. Although there are exciting and novel approaches emerging, there is yet no substitute for meticulous initial resuscitation. Research on head injury over the last one decade has thrown some very promising and challenging results. This article reviews the current developments in the diagnosis & management of head injuries.

ETIOLOGY AND RISK FACTORS

An interesting etiological factor determining prognosis is the mode of injury. People sustaining a head injury from an assault or from being struck with a falling object have a markedly greater likelihood of poorer neurological outcomes than patients sustaining the more common acceleration/deceleration injuries, presumably because the former injury types entail greater axonal damage[1].

Genetic Expression

Although presence of *APOE4* alleles is not an established risk factor for head injury, presence of even one of these alleles increases the risk of a poor outcome. Football players and boxers with an *APOE4* allele are at greater risk for posttraumatic cognitive problems than *APOE4* - negative athletes[2,3]. Genes either regulating or having associations with interleukin, dopamine, apoptotic systems, angiotensin converting enzyme and calcium channel polymorphisms have all been implicated in head injury outcomes, and mystery of these genetic markers will be unraveled in future research[4].

Alcohol

Although alcohol increases the risk of incurring head injury, recent studies paradoxically indicate that high blood alcohol levels could improve outcome in patients with severe head injury[1,5,6]. This beneficial effect lies probably in the inhibition of excitotoxicity by alcohol.

Medications

People on antiplatelet and anticoagulants medications and clopidogrel are at a higher risk of intracranial bleeding with even trivial head injuries[7,8].

PATHOPHYSIOLOGY

Cerebral edema following head injury can occur even in the absence of intracranial bleeding. Severe brain edema occurs more often in children than in adults[9]. A recent pathological study found that quantitative loss of neurons from the dorsal thalamus correlated with severe disability and vegetative state outcomes in patients with closed head injuries[10]. A prominent locus of axonal damage has been the fornices, which are important for memory and cognition[11]. More severe and diffuse axonal injury has been found to correlate with vegetative states and the acute onset of coma following injury[12].

Neurological Examination

Glasgow coma scale continues to be the standard for rapid initial & post-resuscitation neurological assessment

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in acute head injury. Both initial and post-resuscitation low GCS scores have correlated significantly with 1-year outcomes following severe head injury. Abnormal post-resuscitation pupillary reactivity correlates with a poor 1-year outcome. Although a 2006 study showed 100% mortality in a group of 173 patients who presented with a GCS of 3 & fixed dilated pupils, a subsequent study, of 92 such patients has shown that 9% had a good outcome[13,14].

LABORATORY STUDIES

Coagulopathy

Trauma-induced coagulopathy with prolongation of prothrombin time, which normalizes within 12 hours has been found in patients hospitalized for head injury[15]. Elevated D-dimer level following head injury has been considered as a poor prognostic factor. A recent study has proposed a high risk of progressive hemorrhagic injury when the plasma D-dimer level was above 5.00 mg/L; such a value alone may be an appropriate reason for a follow-up CT scan[16].

Neuroimmunochemistry

Following traumatic brain injury, high CSF levels of catecholamine and 5-hydroxyindole acetic acid (HIAA), the serotonin metabolite, have correlated with worse outcomes[17]. Microdialysis techniques have also shown high CSF levels of excitotoxic amino acids to be associated with poor outcomes[18].

Prostaglandins are also elevated dramatically in moderate-to-severe head trauma during the first 2 weeks after injury. Higher prostaglandin level have correlated with worse outcomes. Furthermore high thromboxane levels have been suggested as the underlying cause of posttraumatic vasospasm, which has been documented in some patients with closed head injuries, even in patients without traumatic subarachnoid bleeds[19]. A recent study of a small group of patients with severe head injury has shown that those with increased T cell reactivity against myelin antigens had improved outcomes thereby suggesting a beneficial autoimmune response[20].

Biomarkers

The commonly used biomarkers are S-100B, GFAP, NSE, SBDP, Beta Amyloid. S100B is a calcium-binding protein found primarily in the cytoplasm of astroglia and Schwann cells, but also in non-nervous cells such as adipocytes, chondrocytes and melanoma cells. S100B is not a reliable marker of brain damage in the early post-traumatic setting, which is frequently associated with hemorrhagic shock, local ischemia and/or open fractures. In contrast, GFAP is not found outside the central nervous system and is thus considered to be highly brain-specific. Moreover, unlike S100B, which is a marker of activation but not necessarily of cell *damage*, GFAP does indeed appear to be a marker of actual cell damage. Serum GFAP levels over 0.033µg/L are considered pathologic. GFAP is not only brain-specific, but also related to the severity of brain injury and to outcome after TBI. Further clinical research will be required to support this evidence[21,22].

NSE is found in platelets and erythrocytes as well. NSE is passively released by cell destruction only - it is not actively secreted into the extracellular space. Serum NSE levels over 10µg/L are considered pathologic. However a serious drawback is that it is found in erythrocytes and is thus released into the blood during hemolysis. Recent research is directed towards detection of mild head injury with the help of this biomarkers even before subjecting patient to neuroimaging. A systematic review of the literature indicates that intensive work needs to be done in the future to improve the utility of markers in clinical decision making. Biomarkers are not recommended in the BTF Guidelines of 2007.

Microdialysis

In theory, any substance small enough to diffuse through the dialysis membrane can be measured, but the key substances can be categorised as follows:

1. Energy related metabolites e.g. glucose, lactate, pyruvate, adenosine, xanthine. The lactate/pyruvate ratio is a better marker of ischaemia, than lactate alone.
2. Neurotransmitters - glutamate, aspartate, GABA
3. Markers of tissue damage and inflammation - glycerol, potassium, cytokines
4. Exogenous substances - administered drugs[23]

Multimodality monitoring

In a multimodality approach, it must be remembered that each modality measures independent variables and increases the complexity and the potential to generate artefacts. However, the artefacts are unlikely to occur at the same time in each modality. The use of more than one method of monitoring will therefore help differentiate real events from an artefact. enhancing the accuracy of

interpretation of events and may help in targeting treatment more appropriately. As experience in these techniques grows, it will become apparent which of these modalities are required to provide the most accurate reflection of intracranial events and monitor subsequent therapy[24].

Neuroimaging

Newer modalities have been developed to detect mild head injury which would otherwise be undetectable by conventional CT or MRI. Using innovative fibre tracking methodology, actual disruption of cortical fibres can be visualized in 19% of TBI. Similarly attention impairment in patients with mild head injuries have recently been correlated with diffusion abnormalities in cortical projection fibres[25,26]. Proton Magnetic resonance spectroscopy of frontal white matter that appears normal on MRI has shown a decrease in neuronal N-acetylaspartate spectra in patients with head injuries indicating aberrant metabolism[27].

ICP Monitoring

A 2008 study utilizing the National Trauma Data Bank retrospectively uncovered a 45% reduction in survival in patients who underwent intracranial pressure monitoring. These results have been called into question, however, because of a dearth of clinical and neuroimaging data[28,29].

MANAGEMENT STRATEGIES

Saline Vs Albumin

Saline appears to have a better long term result as compared to albumin. In a large, double-blind, randomized controlled study of 460 patients with Glasgow Coma Scale scores <13 who also had abnormal head CT scan results, 2-year follow-up demonstrated increased mortality in those receiving albumin as opposed to saline[30].

Hypothermia

Contrary to popular perception, a current review of 23 randomized, controlled trials concluded that this therapy was of no benefit[31,32]. In addition, a post-hoc analysis found that rewarming of patients with head injury who arrived in the emergency department already hypothermic is likely to be detrimental.

Nutrition

Enteral alimentation is as important as controlling of cerebral perfusion pressure in management of severe head injury. A recently concluded study has shown that early enteral alimentation can reduce the mortality by 50% in severe head injury[33].

Neuroprotective Agents

The first successful clinical trial for the treatment of TBI in more than 30 years of research was recently completed. This NINDS-sponsored, Phase IIa single-center clinical trial for progesterone in the treatment of moderate to severe adult TBI found that the mortality rate among patients given intravenous progesterone for 3 days post-injury was less than half that of controls given standard of practice care but no hormone (13.6% versus 30.4%). Thirty-day functional outcomes for moderately injured patients in the progesterone group were significantly better than those for the placebo group. It is of interest to note that an NIH-appointed Data Safety Monitoring Board found no serious adverse events attributable to PROG treatment in this trial[34]. Statins, melatonin, cyclosporine and dietary supplements like creatinine have shown a lot of promise but further studies are needed to validate their efficacy[35].

Cognitive Enhancing medication

Donepezil treatment significantly improves visual and verbal memory as well as attentional deployment[36].
Reports claiming dramatic response with levadopa need validation.

Non Medical therapy

Constrained induced movement therapy, in-hospital rehabilitation programmes for severe head injury, music therapy, yoga have been found to be beneficial in various studies. Whether these observations have a scientific basis remains unproven.

Stem Cells

Although this field looks promising their efficacy has yet to be translated from animal models to humans. Some advances have recently been made in genetically engineered human neural stem cells that permit cell proliferation and differentiation in-vivo and in-vitro. Also, there is incorporation of superparamagnetic iron oxide nanocomposites into these cells that can permit MRI tracking in-vivo without impacting their survival or ability to differentiate[37].

Surgery

The operative and non-operative management of

intracranial injuries is an ever-evolving area of study and, at present, more a matter of neurosurgical judgment than hard and fast decision rules[38,39,40].

POSTTRAUMATIC HEADACHE

Posttraumatic headache occurs in 30-90% cases of head injury, which seems to have a vascular component. A recent controversial study claims analgesic overuse as the cause of these posttraumatic headaches[41,42].

PROGNOSTIC FACTORS

Most important prognostic factors are probably age, mechanism of injury, post-resuscitation GCS score, post-resuscitation pupillary reactivity, post-resuscitation blood pressures, intracranial pressures, duration of posttraumatic amnesia or confusion, sitting balance, and intracranial pathology identified on neuroimaging. Further studies are needed to determine whether these have universal validity[43].

CONCLUSION

Despite all these advances, the basic principles of resuscitation, carried out in the universal "airway, breathing, circulation" manner as advocated for any trauma, are vital for a good outcome. No amount of sophisticated critical care treatment can be substituted for this initial management in arresting the effect of primary injury. This is the "platinum 10 minutes" and the ''golden hour'' of intervention. The current concepts are novel & exciting. They will go a long way in our understanding & management of the critically ill patient.

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