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Pathophysiology and treatment of traumatic brain edema

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Abstract: Traumatic brain edema is a secondary phenomenon of traumatic brain injury. It manifests during a time interval by escape of fluid from the vascular compartment to extracellular spaces (vasogenic edema) or due to failure of energy pumps to remove intracellular fluid resulting from hypoxic mitochondrial damage (cellular or cytotoxic edema). The above process is a cascade mechanism mediated by several biochemicals and vasoactive substances.

Keywords: blood brain barrier, brain edema, head injury, intracranial pressure

INTRODUCTION

The tissue damage following brain trauma is a primary injury, whereas secondary mechanisms lead to brain edema.

a) The primary injuries like contusions, lacerations, intracranial hemorrhage, neuronal shearing, transection and axonal injury occur at the time of traumatic event[1] and this can only be prevented by reducing impact force by preventive measures like seat belts and helmet.

b) Brain edema is a secondary injury caused by a cascade of mechanisms initiated at the moment of injury[2]. This secondary injury is to a large extent responsive to timely therapeutic interventions. Understanding of the pathophysiology of the secondary mechanisms may prevent or at least attenuate the progression of brain damage due to edema. If untreated, it leads to raised intracranial pressure (ICP), herniation and death.

BRAIN EDEMA

Brain edema is an excess accumulation of water in the intracellular and/or extracellular spaces of the brain. Brain edema after traumatic brain injury is a frequent finding. Grossly in older terminology of brain edema, the cut surface oozes fluid (*Hirn Edem*). In Brain Swelling, the cut surface is dry (*Hirn Swellung*).

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Basically post-traumatic brain edema is of two types[3]: vasogenic and cytotoxic. Vasogenic brain edema is caused by disruption of the blood brain barrier (BBB)[4,5,6]. Intravascular fluid escapes through endothelium (pinocytosis), or leaky tight junction. Cytotoxic edema is characterized by accumulation of water inside the neurons, microglia and astrocytes[7]. Sometimes they bloat, rupture and fluid escapes into extracellular space. Although cytoxic edema seems more frequent than vasogenic edema in patients after traumatic brain injury (TBI), both entities relate to increased ICP and secondary ischemic events[8,9]. Microscopic and ultrastructural studies reveal increased fluid in interstitial space in vasogenic edema, whereas increased intracellular fluid is present in cellular or cytotoxic edema. Diffusion weighted imaging can differentiate between vasogenic and cytotoxic (cellular) edema by tissue water measurements.

PATHOPHYSIOLOGY

Disruption of the BBB is the most important prerequisite for edema formation. Both vasogenic and cytotoxic edema results in increased intra-cranial pressure and eventually decreased cerebral perfusion pressure. This is in line with the Monroe – Kellie hypothesis which states that 'the sum of the intracranial volumes of blood, brain, CSF and other components is constant and that an in increase in any one of these must be offset by an equal decrease in another[10]. Elevated ICP diminished cerebral perfusion and can lead to tissue ischaemia. Ischaemia in turn may lead to vasodilation via autoregulatory mechanisms designed to restore cerebral perfusion. However vasodilation increases cerebral blood volume, which in turn then increases ICP, lower CPP and provokes further ischaemia[11]. After Traumatic brain injury, CBF autoregulation is impaired or abolished in

most patients. When pressure autoregulation is impaired or absent ICP decreases and increases with change in cerebral perfusion pressure (CPP)[12,13]. Also, autoregulatory vasoconstriction seems to be more resistant compared with autoregulatory vasodilation which indicated that patients are more sensitive to damage from low rather than high CPPs[14].

ROLE OF NEUROTRANSMITTERS AND VASOACTIVE SUBSTANCES IN THE PATHOGENESIS OF BRAIN EDEMA.

Studies on experimental models have shown several neurotransmitters like glutamate, acetylcholine and vasoactive substance i.e., serotonin, histamine, prostaglandins, amino acids, lactic acid etc. to mediate initiation and propagation of brain edema. Platelets are rich source and such substances are released due to their clogging in capillaries[15,16,17]. Serotonin accumulation and diffusion to the surrounding tissue is seen in histoflourescence studies in edematous and contused tissue from human brain. So role of serotonin in pathogenesis of vasogenic cerebral edema is strongly implicated[18,19]. Cortical serotonin (5-HT) metabolism increased following brain injury and this increase is temporarily related to depression of glucose utilization[20,21]. Moreover, Pappius et al showed that administration of the serotonin synthesis inhibitor, P-chlorphenylalamine, attenuated depression of glucose utilization and post injury increases in cortical serotonin[20].

Histamine is released from the mast cells or histaminergic neurons which influence the BBB function. Both H_1 & H_2 receptors are present within the endothelium and Histamine H_2 receptors are known to be involved in the BBB disruption following trauma[22,23]. Histamine has the capacity to induce brain edema by its direct effect on the cerebral endothelial cells to influence nitric oxide (NO) formation probably via histamine H_2 receptors. Since NO is a potential contributor of the BBB breakdown, brain edema and cell injury, blockade of NO by Histamine receptors blockers like ranitidine, cimetidine may provide neuroprotection[24]. Studies conducted by Mohanty et al have shown ranitidine to be more effective than cimetidine in reducing brain edema induced by hyperthermia[25].

Prostaglandins of E series E_1 & E_2 released from the severed blood vessels and damaged platelets[26]. The possible mechanisms by which the released PGs are involved in brain edema are 1) increased permeability of cerebral capillaries. 2) ischemia by vasoconstrictor action[27] and 3) potentiation of action of other chemical agents like serotonin or catecholamines. Treatment with indomethacin a PG synthatase inhibitor led to remarkable reduction of occurrence of edema as a result of injury[28].

AQP4 channels were first cloned by Peter Agre and co-workers who received the Nobel prize for the same. AQP4 channels is expressed in the astroglial cells end feet membranes adjacent to blood vessels[29]. AQP4 was responsible for the water transport in cultured astroglial cells and might be a primary factor in ischaemia induced ceberal edema[30]. The perivascular pool of AQP4 allows bidirectional water flow and hence is likely to be rate-limiting for both water influx and efflux. Perivascular AQP4 pool is anchored through dystrophin complex (brain dystrophin isoform DP71 and a-syntrophin). Mice with targeted deletion of a-syntrophin displayed a dramatic loss of perivascular AQP4 and a concomitant reduction in the extent of post-ischemic edema[31]. The transgenic mouse studies suggests that aquaporin inhibitors may have clinical indications as diuretics and in the treatment of cerebral edema[32]. Studies conducted on male Sprague-Dawley rats concluded that magnesium decreases brain edema formation after TBI, possibly by restoring the polarized state of astrocytes and by down regulation of AQP4 channels in astrocytes[33].

Trabold et al studied the role of vasopressor receptors for post-traumatic brain edema formation and secondary brain damage in C57\B16 mice and found that inhibition of AVP V1 receptors reduced brain content by 45% ,ICP by 29%, and contusion volume by 18%, while inhibition of AVP V2 receptors had no effect[34].

Erythropoetin is gaining intrest as a neuroprotective agent, apparent diffusion coefficient measurements showed that rhEpo(recombinant human erythropoietin) decreases brain edema early and durably in the rat brain[35]. The mechanism by which it works is still not clear and further studies are needed to know it.

CASCADE OF EVENTS IN THE PATHOPHYSIOLOGY OF TBI

1. Initially there is direct tissue damage and impaired regulation of cerebral blood flow and metabolism.

2. Decreased CBF leads to accumulation of lactic acid due to anerobic glycolysis, increased membrane permeability and consecutive edema formation.
3. Anerobic glycolysis leads to depleted ATP stores and failure of energy dependent brain ion pumps.
4. Hypoxia leads to release of excitatory neurotransmitters like glutamate and aspartate.
5. These and other neurotransmitters activate the ionotropic (NMDA) and metabotropic receptors.
6. Consequently Ca++ and Na+ influx with K+ efflux.
7. Ca++ influx leads to catabolic intracellular processes.
8. Ca++ also activated lipid peroxidase, accumulation of free fatty acids and oxygen free radicals.
9. Prostaglandins and kinins initiate an inflammatory response.
10. Further activations of caspases, translocases and endonucleases initiate progressive structural changes of biological membranes and nucleosomal DNA.
11. There is a depression of metabolic activity of neural tissue resulting in suppressed neuronal activity.
12. Role of aquaporin4 channels, decreased Mg++ levels and vassopressor2 receptor channels and erythropoietin in the pathophysiology of post traumatic brain edema is being studied.

Collectively these events lead to BBB disruption and degradation of cellular structures and ultimately necrotic or programmed cell death

IMAGING TECHNIQUES TO IDENTIFY TYPE OF EDEMA

CT scan is a cost effective technique to distinguish between infarct and hemorrhage. Done within 24 hrs of trauma, it can also identify edema but it cannot distinguish between vasogenic and cellular edema. MR imaging techniques can measure the diffusion of water in the brain tissue. This is usually expressed as the ADC. A reduction in ADC is interpreted as a decrease in diffusion.In cellular edema the water is more closely bound and thus it would be expected to result in a decrease ADC. Proton spectroscopy shows elevated N-acetylaspartate levels indicating tissue damage i.e, mitochondrial damage.

TREATMENT OF BRAIN EDEMA

The goal of medical management of cerebral edema is to maintain regional and global CBF to meet the metabolic requirements of the brain and prevent secondary neuronal injury from cerebral ischaemia. Medical management of cerebral edema (Table 1) involves using a systemic approach, from general measures i.e, optimal head and neck positioning for facilitating intracranial venous outflow, proper airway, avoidance of dehydration and systemic hypotension and maintenance of normothermia to specific therapeutic interventions like controlled hyperventilation, administration of diuretics,osmotherapy and pharmalogical cerebral metabolic suppression.

Surgical decompression and use of osmotherapy to reduce brain edema and its deleterious effect remain the mainstay of treatment even today. This only attenuates the primary injury but cannot abate the secondary cascade of events. Drugs which inhibit or slow the various secondary mechanisms are still in a experimental stage. Few have shown their efficacy in

Table 1: Drugs reducing brain edema

Factors increasing edema	Blocking\inhibitory substances
Free fatty acids	endogenous inhibitors (long chain fatty acids)
Prostaglandins	Indomethacin
Mitochondrial	Cyclosporin A
permeability\damage	Citicholine
Cerebral anerobic metabolism	Lactate
Polyamines	NMDA receptor antagonists Ifenprodil
Free radicals	Scavengers-Vitamin C & E 21 amino steroids Edaravone n-acetyl cysteine Citicholine
Endothelin	Endothelin antagonists – Patent EPO 838223
Chloride transport	Cl transport inhibitor-Torase
Carbonic anhydrase	CA inhibitors-Acetazolamide
Kappa opoid	Agonist-Niravoline
Aquaporin 4	Dexamethasone & hCRF

controlled trails and further research is needed to bring these to the main stream of treatment. The most promising of the studies are the aquaporin 4 channel inhibitors.

CONCLUSION

Post traumatic brain edema is a result of various secondary mechanisms and the treatment options are limited to osmotherapy and surgical decompression. Pharmacological drugs which influence the various secondary mechanisms are still in their infancy, the most promising of them being the aquaporin 4 channel inhibitors. The present concept of therapy has to base on brain volume regulation and improved microcirculation by means of combination therapy.

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