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NEUROPATHOLOGICAL ASPECTS OF BRAIN EDEMA [1]

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Neuropathological Aspects of Brain Edema

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Abstract

Edema is characterized by distinct morphological and molecular changes. Currently approved treatments for cerebral edema, decompressive craniectomy and osmotherapy were developed prior to any knowledge of modern cerebral edema pathophysioly. Edema is an abnormal accumulation of fluid within the brain parenchyma it is subdivided into vasogenic and cytotoxic types. The intracellular fluid compartment is the first compartment in the brain that is affected by ischemic insult. Derangements in the energy dependent processes that regulate the volume and solute

composition of the intracellular fluid are primary drivers behind cerebral edema. Cerebral edema accompany ischemic infarcts and intracerebral hemorrhages and when severe may increase mortality to nearly 80%. Cerebral edema after traumatic brain injury is estimated to account for up to 50% of patient mortality. This review is intended to serve as a reference that can contribute in the understanding of formation, types, classification and clinic conditions about cellular and molecular models of the cerebral edema.

Introduction

Reichardt (1905) was the first to introduce the concept of the cerebral edema as a specific reaction of nerve tissue. He defined it as an increase in brain volume in correlation skull capacity. The terms cerebral swelling and cerebral edema are used by both clinicians and pathologists with quite different connotations.

The term cerebral edema is one of long usage. Local edema of the brain has long been recognized as occurring in the vicinity of cerebral neoplasms and abscesses. Diffuse cerebral edema, on the other hand, has been reported in such diverse conditions as cerebral vascular accidents, uremia, severe intoxications and in status epilepticus.

The brain edema is associate traumatic brain injury (TBI), ischemia and tumor, in head injury swelling leads to elevations in intracranial pressure (ICP), which is a frequent cause of death, and to poor prognosis among survivors.

Currently approved treatments for cerebral edema, decompressive craniectomy and osmotherapy were developed prior to any knowledge of modern cerebral edema pathophysioly. These therapies attempt to manage downstream end-stage events without that regulate directy attenuating the underlying molecular mechanisms of cerebral edema. Edema is charactrized by distinct morphological and molecular changes (Stokum et al., 2015).

Edema is an abnormal accumulation of fluid within the brain parenchyma it is subdivided into vasogenic and cytotoxic types. Others labels of edema such as osmotic, interstitial (hydrostatic) or hyperemic refer to etiology rather than physical location. Vasogenic edema is defined as fluid originating from blood vessels that accumulates around cells.

Citotoxic edema is defined as fluid accumulating within cells as a result of injury. The most common cytotoxic edema occurs in cerebral ischemia.

Heretofore, the edema specific to traumatic brain injury (TBI) has generally has been considered to be of vasogenic origin, secondary to traumatic opening of the BBB. However, both forms of edema can coexist. This is a critical problem, as effective treatment will clearly depend on the major type of edema contributing to the swelling process (Marmarou, 2007).

The etiology of cerebral edema is seen in the following neurological and non-neurological

conditions.

Neurological conditions: ischaemic stroke and intracerebral haemorrhage, brain tumours, meningitis and encephalitis of the all etiologies and brain infections like cysticercosis, tuberculosis and toxoplasma.

Non-neurological conditions: diabetic ketoacidosis, lactic acidotic coma, malignant hypertensive, hypertensive encephalopathy, fulminant viral hepatitis, hepatic encephalopathiy, opioid drug abuse and dependence, bites of certain reptiles and marine animals, high altitude cerebral edema.

Computed Tomography (CT) scan provides an excellent tool for in vivo determination of abnormalities in brain water content. The areas of edema appear as low density on unenhanced scan. This is due to the dilution of all the constituents of the white matter. The anatomical specificity of computed tomography permits detection of not only the present but also the type of brain edema. This is helpful in differentiating nature of underlying lesion eg. infarction /tumour (Pollay, 1996).

The importance of cerebral edema in clinical prac detailtice has stimulated the development of experimental models of its various forms: global and regional, complete and incomplete, permanent and transient (Molinari and Laurent, 1976; Katzman et al., 1977).

For it is in the rat that the most detailed information about the normal organization of the various neurotransmitter systems, neurochemistry, and neuropharmacology has been obtained during the last decade. Moreover, the similarities between the anatomy of the cranial circulation of rat and man, particularly when contrasted with other species such as the gerbil, cat, and dog are important advantage when modelling human cerebrovascular disease (Tamura et al., 1981).

The present study was designed to describe the pathophysiology edematous process.

Material and Methods

To elucidate the effects of the brain edema and anti-edema drugs various experimental animal models have been adopted. The mechanisms of edema are different, thus the choice of experimental models reflects each edema and should be taken into consideration when examining the effects in neuropathological condition.

Historically cerebral edema is considered a clinical condition following acute CNS injury that envolved old experimental study and recent experimental study with continuous advancements in molecular biology to the proteins responsible for understanding of the neurophatologic events.

In our research to review article we select the papers since 1905 to 2016 because of important theme in histology tissue, features neuropathology, etiology, edema types and neuroimaging techiniques. The title Neuropathological Aspects Edema of Brain was chose in according to

authors research line.

This work was accomplished by search eletronic medical dabases on the World Wide Web, PubMed, Scopus and Google Scholar following the keywords: animal models; blood-brain barrier; cellular swelling; traumatic edema; cerebrovascular dysfunction; brain Injury. The web pages of databases were used to get specific published article whereas the download pdf full text, not purchase access content. We did not include articles summaries in our literature review.

A total of 100 articles were selected in different journals (see references) but 19 were properly analyzed and cited in this work. The keywords search with PubMed provided increased frequency and number of citations pdf articles we consider it an excellent research tool for the development of this review.

Studies were included following criterias: experimental models in focal ischemia; rodents experimental models; human stroke models; brain edema; brain oedema; brain swelling; brain injury; transiente and permanent ischemia; middle cerebral artery occlusion (MCA); articles in english; reviews and pdf publications; books chapters (Table 1).

Excluded criterias: models in global ischemia; Nonrodents models; pulmonary edema, macular and foodpat edema; vitro trauma model; vitro ischemia model; stroke embolic middle cerebral artery, stroke cerebrocortical photothrombosis; genetic model of ischemia; blood-brain barrier model; reviews and duplicate publications, articles in french, japanes and german; articles sumaries; newslatter (Table 1).

Table 1. Criterias used to analyse the articles in this work.

INCLUSION CRITERIAS	EXCLUSION CRITERIAS
Articles available in pdf	Articles not published in English
Reviews	Publications abstracts
Books chapters	Duplicate publications
Experimental focal ischemia	Newslatter

Rodents experimental models	Models in global ischemia
Human stroke models	Nonrodents models
Brain edema	Pulmonary edema
Brain oedema	Macular and foodpat edema
Brain swelling	Vitro trauma model
Brain injury	Vitro ischemia model
Transiente and permanent ischemia	Stroke embolic middle cerebral artery
Middle cerebral artery occlusion (MCA)	Stroke cerebrocortical photothrombosis
Articles in English	Genetic model of ischemia
	Blood-brain barrier model
	Reviews and duplicate publications

Results

Edema in Ischemia:

Results of both experimental and clinical studies have indicated that cerebral edema develops following acute regional ischemia and can cause mass effect and herniation that results in a further decrease in cerebral blood flow (CBF).

Complete interruption of cerebral blood, as induced in cardiac arrest, results in the rapid breakdown of all electrophysiological and metabolic functions of the brain. The edema associated with ischemia has a characteristic time course and begins with a cytotoxic phase in which energy failure results in intracellular fluid accumulation associated with shifts in sodium and potassium between intra and extracellular compartments of the brain (Kuroiwa et al., 1985). With ongoing ischemia, the core region the impaired metabolism expands, leading to gradual infarction of the penumbra.

Treatments for the combination of ischemia edema and eventual vasogenic edema secondary to barrier compromise have not only to elucidate the pathophysiology but to better understand the process of the cellular edema resolution (Gasche and Copin, 2003; Marmarou, 2007). Cerebral edema accompany ischemic infarcts and intracerebral hemorrhages and when severe may increase mortality to nearly 80% (Stokum et al., 2015).

Edema in Intracerebral Hemorrhage (ICH):

Major factors contributing to poor prognosis in the initial phase after Intracerebral hemorrhage are hematoma size, early hematoma growth, and presence of additional intracerebral hemorrhage (Xi et al., 2007).

After the initial injury caused by mechanical tissue disruption and mass effect to the hematoma, products of coagulation and clot breakdown initiate a secondary cascade of damage to the perihemorrhagic edema. Although the role of perihemorrhagic edema as a cause of morbidity and mortality after intracerebral hemorrhage in general is still unclear, additional mass effect and increase in intracranial pressure caused by edema may contribute to delayed deterioration in the course of the disease, especially in large hematomas. Cerebral edema after traumatic brain injury are estimated to account for up to 50% of patient mortality (Stokum et al., 2015).

Edema in Traumatic Brain Injury (TBI):

Results of recent studies of traumatic brain injury have indicated that the predominant type of edema in these injuries is cellular.

These results have been confirmed by other investigators. It has been documented that ionic dysfunction occurs with traumatic injury and that extracellular K+ is transiently increased as a result of the depolarization synchronous with mechanical insult (Katayama et al., 1990). This loss of ionic homeostasis should be accompanied by a concomitant movement of sodium.

It is reasonable to suspect that the net balance of ionic movement of cations out of the extracellular space into cells. The movement of Na+ and Ca+ is passively followed by Cl- to maintain electroneutrality and is followed isosmotically by water. If sustained, these ionic disturbances result in cellular swelling and cytotoxic edema, which have shown to be the primary contributor to raised intracranial pressure.

Edema Hydrocephalic (interstitial):

Increased intravascular pressures which cause rupture of the ventricular ependymal lining, transependymal migration (CSF) into the extracellular space, most commonly the periventricular white mater. Fluid composition is identical to CSF with similar ionic concentrations and negligible protein levels.

Various causes of insterstitial edema include obstruction masses, meningitis, subarachnoid hemorrhage. In symptomatic patients, decompression with resection of the obstructing lesion (noncommunitig hydrocephalus) or ventriculostomy catheter placement (communicating hydrocephalus) allows normalization of ventricular pressures (Ho Mai-Lan et al., 2012).

Discussion

Excess accumulation of brain water, cerebral edema, is of central importance in the pathophysiology of a wide range of central nervous system (CNS) abnormalities such as stroke,

tumor, infection, hydrocephalus, and traumatic brain injury.

Cerebral edema produces elevated intracranial pressure potentially leading to brain ischemia, herniation and death.

Despite a large body of empirical data on brain edema and its causes and consequences, current treatments for brain edema such as hyperosmolar agents and surgical decompression have changed little since their introdution more than 80 years ago (Fishman, 1975).

Although brain edema is a pathological state, the development of anti-edema drugs has been stagnant for decades. Understanding the pathogenesis of vasogenic and cytotoxic edema in various brain insults is important for the development of anti-edema drugs. By using experimental animal models for brain edema, key molecules involved in edema formation have been identified.

In experimental animals with traumatic brain injury and cerebral hemorrhage, blood-brain barrier (BBB) hyperpermeability induced is characteristic vasogenic edema. A variety of molecules including vascular permeability factors, membrane channels, transporters and receptors are know to be responsible for brain insult induced vasogenic and cytotoxic edema (Mahajan S. and Bhaghat H, 2016). As inducers of blood-brain barrier hyperpermeability VEGF (vascular endothelial growth factor) and MMP9 (matrixmetalloproteinases) have been the primary focus. Increases in VEGF and MMP9 have been observed, and the inhibition of VEGF and MMP9 attenuates BBB disruption and reduces vasogenic edema in brain injury animals (Michinaga and Koyama, 2015).

Over 70% of fluid in the central nervous system (CNS) is contained in the intracellular fluid compartment. Compared with the interstitial fluid has a much higher level of potassium and a much lower level of sodium and calcium. Because of these ion gradients, under physiological conditions, the flux of sodium and calcium into cells, and the flux of potassium out of cells, are balanced with efflux of these ions against their electrochemical gradients by active, energy dependent ion pumps such as the Na K-ATPase and Ca-ATPase. The Na K-ATPase prevents the intracellular accumulation of sodium ions, thus preventing an influx of solute and water that would result in cell swelling, the associated loss of cytoskeletal integrity, and oncotic cell death (edema). The activity of the Na K-ATPase also generates the electrochemical gradiient necessary for secondary active and passive ion transport process. The intracellular fluid compartment is the first compartment in the brain that is affected by ischemic insult.

Derangements in the energy dependent processes that regulate the volume and solute composition of the intracellular fluid are primary drivers behind cerebral edema (Kahle et al., 2009).

As in other tissues, water is in thermodynamic equilibrium across the plasma membranes of all brain cells. Because cell membranes are freely permeable to water, changes in the intracellular or extracellular content of solutes establish transmembrane osmotic gradients that result in the flow of water into or out of cells. As a result, transmembrane osmotic gradients trigger the flow of water, which causes cell swelling.

A variety of physiological and pathophysiological conditions can alter this balance Isosmotic cell

volume challenges are a problem in the brain because transmembrane change during the generation and propagation of action potentials (Iwasa et al., 1980).

Moreover, neuronal activity also causes transient changes in the extracellular pH and levels of potassium, sodium, chloride and calcium, which can alter neuronal and glial volume by alteration of ionic gradients across the cell membrane. The cell swelling that occurs secondary to ischemic injury causes isosmotic volume increases due to the intracellular accumulation of sodium, chloride and other solutes.

In ischemic stroke 5% - 10% patients develop symptomatic cerebral edema resulting in obtundation with its attendant consequences or brain herniation. Edema peaks on the second or third day but causes mass effect for 10 days. The larger the infarct, the more likely edema will be a problem. Even small amounts of edema from a cerebellar stroke can raise intracranial pressure in the posterior fossa. Restriction of free water and intravenous mannitol may be useful. As the molecular events become clearer, novel treatments that block different stages of the injury cascade will be available for clinical testing (Murr et al., 1993).

Brain edema formation after intracerebral hemmorrhage causes herniation related death and severe neurological deficits. Although the mechanisms of edema formation after intracerebral hemmorrhage are not fully determined studies indicated that erythrocyte lysis and hemoglobin toxicity contribute to delayed brain edema. Intracerebral hemorrhage is the most devastating subtype of stroke, causing high mortality, morbidity, and disability.

After initial hemorrhage, continued bleeding is observed and hematoma expansion is induced, which is consequently associated with adverse outcomes. In the area surrounding hematoma, secondary injury is induced by disturbance of neuronal and glial functions.

These events cause glutamate release, membrane depolarization and mitochondrial dysfunction and cellular swelling. In addition, because activated glia release products that induce blood-brain barrier breakdown, dysfunction is deteriorated, resulting in extravasation of blood components (thrombin and hemoglobin) and inflammatory responses (Michinaga and Koyama, 2015).

Traumatic brain injury is thought to trigger a cascade of events, including mechanical deformation, neurotransmitter release, mitochondrial dysfunction, and membrane depolarization, that can lead to alterations in normal ionic gradients. In addition, membrane depolarization resulting from ionic flux and trauma may trigger voltage-sensitive ion channels, providing further routes for ionic movement.

These ionic disturbances are identified by an increase in extracellular Na+, Ca2+, and Cl-. Restoration of ionic homeostasis can either occur via energy dependent co and countertransport processes such as the Na+-K+ adenosina triphosphatase (Betz, 1986).

In conclusion, the edema develop early after intracerebral hemorrhage, traumatic brain and brain ischemia injury can increases within the first 7 to 11 days promoting molecular events, changes in the extracellular pH and levels of potassium, sodium, chloride and calcium which can alter of ionic

gradients across the cell membrane. This additional mass effect may contribute to secondary clinical deterioration and mortality, especially in larger intracerebral hemorrhage.

Keywords: animal models; blood-brain barrier; cellular swelling; stroke edema; cerebrovascular dysfunction; brain Injury.

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