Cerebral Edema and its Management

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Introduction

Surprising as it may sound cerebral edema is a fairly common pathophysiological entity which is encountered in many clinical conditions. Many of these conditions present as medical and surgical emergencies. By definition cerebral edema is the excess accumulation of water in the intra-and/or extracellular spaces of the brain [1].

Pathophysiology

Pathophysiology of cerebral edema at cellular level is complex. Damaged cells swell, injured blood vessels leak and blocked absorption pathways force fluid to enter brain tissues. Cellular and blood vessel damage follows activation of an injury cascade. The cascade begins with glutamate release into the extracellular space. Calcium and sodium entry channels on cell membranes are opened by glutamate stimulation. Membrane ATPase pumps extrude one calcium ion exchange for 3 sodium ions. Sodium builds up within the cell creating an osmotic gradient and increasing cell volume by entry of water. Increase in water causes dysfunction but not necessarily permanent damage. Finally, hypoxia depletes the cells' energy stores disabling the sodium - potassium ATPase and reducing calcium exchange [2].

Because of failure of the energy-dependent sodium pump in the cellular membrane, sodium accumulates intracellularly and water moves from the extracellular to the intracellular space to maintain osmotic equilibrium [3]. Calcium accumulates inside the cell activating intracellular cytotoxic processes. An inflammatory response is initiated by the formation of immediate early genes such as *c-fos* and *c-jun* and cytokines and other intermediary substances. Microglial cells are activated and release free radicals and proteases which contribute to the attack on cell membranes and capillaries. Once the membranes are disrupted recovery of the cells is impossible [2].

Free radicals are toxic to cells. Reactive oxygen species such as superoxide ion, hydrogen peroxide and hydroxyl ion are produced by the arachidonic acid cascade. Release of fatty acids such as arachidonic

acid provides a supply of damaging molecules [2]. Nitric oxide (NO) is also a source of free radicals. Macrophages and activated microglial cells form NO through the action of inducible or immunological NO synthetase (iNOS) [2].

During injury and ischaemia of the central nervous system (CNS) mediators like glutamate, free fatty acids, or high extracellular potassium compounds are released or activated, which cause secondary swelling and damage of nerve cells. Other substances like histamine, arachidonic acid and free radicals including NO may also be considered mediators of brain edema, but to each of these compounds evidence is less clear than for bradykinin (BK) [4]. A variety of mediators may enhance each other in a cascading manner by various initiating reactions that might be amenable to pharmacologic inhibition. BK may be involved in edema formation after cold lesion, concussive brain injury, traumatic spinal cord and ischaemic brain injury.

In stroke, the molecular cascade initiated by cerebral ischaemia includes the loss of membrane ionic pumps and cell swelling. Secondary formation of free radicals and proteases disrupts brain-cell membranes, causing irreversible damage [5].

To explain the consequences of cerebral edema in the simplest terminology, it is best to take the help of Monro-Kelie hypothesis, which says that the total bulk of three elements (inside the skull) i.e. brain - 1400 ml, cerebral spinal fluid (CSF) 150 ml and blood 150 ml is at all times constant. Since skull is like a rigid box which cannot be stretched - if the volume of one of these components increases, it will force the reduction of volume of the other components. So if there is excessive water, the volume of brain as well as blood inside the skull is compressed. Conversely, primary blood flow disturbances also lead to brain edema [6]. As the brain, blood or CSF volumes continue to increase, the accommodative mechanisms fail and intracranial pressure (ICP) then rises exponentially. Greatly raised ICP eventually causes a reduction in cerebral blood flow throughout the brain. In its most severe form the widespread ischaemia produces brain

death. Lesser degrees of increased ICP and reduced blood flow can cause correspondingly less severe but still extensive cerebral infarction. The numerical difference between raised ICP and mean blood pressure within the cerebral vessels, termed cerebral perfusion pressure and the duration of its reduction are the main determinants of cerebral damage [7]. If these changes continue further, it leads to the disastrous condition of brain herniation, which is the forerunner of irreversible brain damage and death. It must be clearly understood that though raised ICP is the result of cerebral edema of significant magnitude, they are not synonymous as raised ICP can be caused by other mechanisms also.

Types

Klatzo specified two categories of cerebral edema - vasogenic and cytotoxic edema. The term cellular edema refers to cytotoxic edema and is preferable to the latter; Fishman accepts these two categories but adds a third, which he calls interstitial cerebral edema. Rarely is the separation into distinct categories possible, there is often overlap between the various types of edema [2].

Vasogenic cerebral edema refers to the influx of fluid and solutes into the brain through an incompetent blood-brain-barrier (BBB) [3]. This is the most common type of brain edema and results from increased permeability of the capillary endothelial cells, the white matter is primarily affected. Breakdown in the blood-brain barrier allows movement of proteins from the intravascular space through the capillary wall into the extracellular space.

Cellular (cytotoxic) cerebral edema refers to a cellular swelling [3]. It is seen in conditions like head injury and hypoxia. It results from the swelling of brain cells, most likely due to the release of toxic factors from neutrophils and /bacteria. Cytotoxic edema is caused by swelling of glia, neurons, endothelial cells and begins within minutes after an insult. Cytotoxic edema affects predominantly the gray matter [3].

Interstitial edema is seen in hydrocephalus when outflow of CSF is obstructed and intraventricular pressure increases. The result is movement of sodium and water across the ventricular wall into the paraventricular space [3]. Interstitial cerebral edema occurring during meningitis is due largely to obstruction of normal CSF pathways, with a resulting increase in the resistance to CSF outflow.

Etiology

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 all etiologies

Other brain infections like cysticercosis, tuberculosis and toxoplasma.

Non-neurological conditions -

Diabetic ketoacidosis, lactic acidotic coma

Malignant hypertension, hypertensive encephalopathy

Fulminant viral hepatitis, hepatic encephalopathy, Reye's syndrome

Systemic poisoning (carbon monoxide and lead)

Hyponatraemia, SIADH

Opioid drug abuse and dependence

Bites of certain reptiles and marine animals

High altitude cerebral edema (HACO)

Clinical Features

A high index of suspicion is very important. The features of cerebral edema add on to and often complicate the clinical features of the primary underlying condition. Until the ICP reaches a level that produces local ischaemia, cerebral edema alone will not produce clinical neurological abnormalities [1]. In a given clinical setting, alteration in level of consciousness, appearance of bradycardia, rise in blood pressure, abnormal breathing patterns evidence of extra ocular movement abnormalities, alteration and inequality of pupillary size and extensor plantar response on the side of the lesion should raise strong suspicion of cerebral edema.

The most common cause of neurological deterioration and death during acute ischaemic stroke is cerebral edema. It occurs in all ischaemic strokes. Ischaemic brain edema is initially cytotoxic because of disturbances in cell membrane. Later vasogenic edema sets in due to disruption of BBB [8]. Cerebral edema usually begins to develop soon after the onset of ischaemia and peaks at 24-96 hours. Usually this is confined to ischaemic region and does not appreciably affect adjacent brain. But, when it progresses it compresses brain regions adjacent to ischaemic zone causing neurological worsening.

Investigations

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 [1]. The anatomical specificity of CT permits detection of not only the presence but also the type of brain edema. This is helpful in differentiating nature of underlying lesion eg. infarction/tumour. In general, the more malignant

primary tumours of the brain and metastatic tumours entail the greatest incidence of cerebral edema, although presence of brain edema does not rule out benign lesions. CT is an excellent method for following the resolution of brain edema following therapeutic intervention. Cerebral edema in acute vascular lesions can be seen in both the cortex and the underlying white matter. The cerebral edema in an epidural and intracerebral haematoma is typically limited to white matter [1].

MRI appears to be more sensitive than CT at detecting brain abscess in the cerebritis phase of its development as well as at detecting associated cerebral edema.

ICP monitoring is an important tool to monitor cases where cerebral edema is present or anticipated and is routinely done in all Neurology and Neurosurgery ICUs. Unfortunately, the direct measurement of ICP and aggressive measures to counteract high pressures have not yielded uniformly beneficial results, and after two decades of popularity - the routine use of ICP monitoring remains controversial. The problem may be partly a matter of the timing of monitoring and the proper selection of patients for aggressive treatment of raised ICP. Only if the ICP measurements are to be used as a guide to medical therapy and the timing of surgical decompression, is the insertion of a monitor justified [7]. Whether ICP monitoring adds much to the management of patients of stroke is still open to question, clinical signs and imaging data on shift of brain tissue are probably more useful [9].

EEG is not very helpful in the management of cerebral edema, because the changes which are noted are the sum total of changes due to cerebral edema, raised ICP and the primary lesion superimposed upon each other.

Treatment

Treatment of brain edema has not kept up with the advances in understanding of the mechanism producing the edema [2].

Medical treatment

1. Osmotherapy

The most rapid and effective means of decreasing tissue water and brain bulk is osmotherapy [1]. Osmotic therapy is intended to draw water out of the brain by an osmotic gradient and to decrease blood viscosity. These changes would decrease ICP and increase cerebral blood flow (CBF).

Mannitol is the most popular osmotic agent. Osmotic therapy using mannitol reduces ICP by mechanisms that remain unclear. Mannitol is thought to decrease brain volume by decreasing overall water content, to reduce blood volume by vasoconstriction, to reduce CSF volume

by decreasing water content. Mannitol may also improve cerebral perfusion by decreasing viscosity or altering red blood cell rheology. Lastly, mannitol may exert a protective effect against biochemical injury [10].

There is some evidence that lower dosage is quite effective with less chances of inducing hyperosmolar problems that have been noted with frequent high-dose therapy [1]. IV Mannitol is given in the dosage of 1.0 g/kg, then 50 g every 2-3 hours [9]. When Mannitol is used, one should aim for plasma osmolality 300-310 mOsm/L with maintenance of adequate plasma volume [8]. Prolonged administration of Mannitol results in an electrolyte imbalance that may override its benefits and that must be carefully monitored [2]. Nursing care of the patient receiving Mannitol requires vigilant monitoring of electrolytes and overall fluid balance and observation for the development of cardiopulmonary complications in addition to neurological assessment [10].

Glycerol is another useful agent given in oral doses of 30 ml every 4-6 hour or daily IV 50g in 500 ml of 2.5% saline solution although its effectiveness appears to decrease after few days. It is used in a dose of 0.5-1.0 g/kg body weight. In unconscious or uncooperative patients it is given by nasogastric tube [1].

2. Diuretics - The osmotic effect can be prolonged by the use of loop diuretics (Furosemide) after the osmotic agent infusion. Loop diuretics (Furosemide) can be used as an adjunct. Furosemide (0.7 mg/kg) has been shown to prolong the reversal of blood brain osmotic gradient established with the osmotic agents by preferentially excreting water over solute [1].

3. Corticosteroids - Corticosteroids lower intracranial pressure primarily in vasogenic edema because of their beneficial effect on the blood vessel. They have been less effective in cytotoxic edema, and are not recommended in treatment of edema secondary to stroke or haemorrhage. In fact, systemic complications of steroids can worsen the patient's condition [2]. Corticosteroids have not proven effective in stroke unless stroke is caused by documented cerebral vasculitis. Inj Dexamethasone 4-6 mg IM every 4-6 hours may be useful in these cases. They have also been used in chronic meningitis and in acute bacterial meningitis under cover of antibiotics. Glucocorticoids are used for the management of malignant brain tumours, either primary or secondary, as adjuvant chemotherapy of some CNS tumours and perioperatively in brain surgery. Edema surrounding brain tumours particularly metastatic brain tumours responds dramatically to treatment with high doses of Dexamethasone [2]. Glucocorticoids are believed to exert their influence on brain tumours mainly by reducing tumor-associated vasogenic edema, probably by decreasing the increased capillary permeability of

BBB. The role of corticosteroids in head trauma is uncertain [2].

4. Hyperventilation - Controlled hyperventilation is helpful in reducing the raised ICP. The cerebral vasculature is most sensitive to arterial $p\text{CO}_2$ changes around the normal level of 40 mm Hg. ICP falls within minutes of onset of hyperventilation and although the buffering mechanisms in the CSF and extra cellular fluid soon restore pH to normal the effect may last for many hours. It is important to monitor the effects of ventilation carefully by blood gas analysis and chest radiograph. The $p\text{CO}_2$ should not be reduced below 25 mm Hg. At this point vasoconstrictor effect of hypocarbia itself will cause hypoxia and ischaemic cell damage [11].

5. Other agents - Barbiturates, Procaine derivatives, Indomethacin, Propofol and THAM (Thrometamine) are some other agents which have been tried and used in the past but are not being used routinely in present practice [12,13,14].

Barbiturates produce a marked decrease in metabolic rate and it seems likely that the fall in cerebral blood flow and ICP is secondary. Complication of barbiturate therapy, in particular systemic hypotension and pulmonary failure, have caused concern and careful monitoring with a Swan Ganz catheter is recommended [11].

Lidocaine will prevent a rise in ICP during intubation. It may act directly on brain stem vasomotor centre. However, there is no present evidence that it reduces ICP already raised [11]. THAM has been used to regulate the acidotic impairment of cerebral autoregulation and the response of the vascular system to hypocapnia can be improved [13].

Surgical treatment

Surgical treatment is occasionally recommended for large hemispherical infarcts with edema and life threatening brain-shifts. Temporary ventriculostomy or craniectomy may prevent deterioration and may be lifesaving. Decompressive craniectomy in the setting of acute brain swelling from cerebral infarction is a life saving procedure and should be considered in younger patients who have a rapidly deteriorating neurological status [15]. Also, in large cerebellar infarcts with cerebral edema surgical decompression is life saving [16]. The surgical removal of lesions responsible for cerebral edema results in resolution of cerebral edema. In cases of severe hydrocephalus VP shunt is very helpful [1].

General measures

When signs of elevated ICP are present certain

measures for management should be initiated.

Position of the patient - Elevation of head end of bed 15-30 degrees to promote cerebral venous drainage is advisable and head is kept in midline to limit neck vein compression. However, in acute carotid or basilar artery occlusion bed is not tilted to avoid hypoperfusion distal to occlusion [8].

Correction of contributory factors - Correction of factors increasing ICP e.g. hypercarbia, hypoxia, hyperthermia, acidosis, hypotension and hypovolaemia is helpful. Endotracheal intubation and mechanical ventilation to hyperventilate to PaCO_2 of 25 mm Hg is helpful in impending herniation [8].

Fluid restriction - Fluid restriction minimally affects cerebral edema and, if pursued to excess, may result in episodes of hypotension, which may increase ICP and is associated with worse neurologic outcome [16]. Glucose containing solutions should be avoided; euvoalaemia should be maintained, N or N/2 saline should be used; urinary losses should be replaced with N saline in patients receiving Mannitol [8].

Hypothermia - Multiple mechanisms for reduced brain temperature-induced neuroprotection have been identified and include reduced metabolic rate and energy depletion, decreased excitatory transmitter release, reduced alterations in ion flux, reduced vascular permeability, edema and BBB disruption [17]. Recent studies have led to the hypothesis that changes in post-ischaemic cerebral temperature can critically modulate encephalopathic processes which are initiated during the primary phase of hypoxia-ischaemia, but which extend into the secondary phase of cerebral injury. Randomised clinical trials are in progress to establish the safety and efficacy of prolonged cerebral hypothermia [18]. Suarez JJ has shown that a body temperature $>37.5^\circ\text{C}$ and blood glucose >150 mg/dl are related to worsening of the cerebral edema. The measures necessary for good cerebral reanimation are the following : evaluation of the airway, controlled hyperventilation, maintenance of the cerebral perfusion pressure >70 mm Hg, suitable position of the head, administration of hypertonic solutions, Dexamethasone, and possibly barbiturates [19].

Blood pressure needs to be monitored carefully in cases with cerebral edema. When cerebral edema causes raised ICP, systemic blood pressure rises as a compensatory phenomenon to ensure adequate cerebral perfusion. Hence, under these circumstances bringing down the raised blood pressure will increase the extent of cerebral ischaemic damage and will be counter productive.

Management of cerebral edema in specific conditions

Stroke

In 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 [3]. As the molecular events become clearer, novel treatments that block different stages of the injury cascade will be available for clinical testing [5].

Cerebral edema in bacterial meningitis

Initial management of increased ICP is intubation and controlled hyperventilation to reduce $p\text{CO}_2$ to 25 mm Hg [20]. However, the effect of hyperventilation is transient. Hypotension should be avoided to maintain cerebral perfusion. Mannitol may enter brain through partially open BBB and therefore is less effective. Corticosteroids have shown no benefit in 24 hours over non-corticosteroid treated patients. Lasix and fluid restriction produces dehydration, fall of blood pressure, low cerebral perfusion pressure and increased risk of cerebral thrombosis. If severe hydrocephalus is present VP shunt should be considered [8].

Tuberculous Meningitis and Tuberculoma

Glucocorticoids are a useful adjunct to chemotherapy, clinical trials have demonstrated that patients treated with adjunctive glucocorticoids experience a significantly faster resolution of CSF abnormalities and elevated CSF pressure. Adjunctive glucocorticoids enhance survival and reduce the frequency of neurologic sequelae especially in cases with cerebral edema [21].

Toxoplasmosis

Glucocorticoids are recommended for the management of patients with cerebral edema [22].

Cryptococcosis

Daily lumbar puncture or CSF shunting has been advocated in the hope of averting permanent blindness for patients with marked cerebral edema who have incipient blurred vision [23].

Diabetic Ketoacidosis

When the plasma glucose level falls to about 17 mmol/L (300 mg/dL), 5% glucose solutions should be added, both as a source of free water and as a prophylactic measure to prevent the late cerebral edema syndrome.

In children, cerebral edema is a common cause of death (less frequent in adults). The exact cause of the brain swelling is not known, however, in a recent study Glaser et al found that children with diabetic ketoacidosis with low partial pressures of arterial carbon dioxide and high serum urea nitrogen and treatment with bicarbonate therapy are at an increased risk of cerebral edema [24]. Theories include osmotic disequilibrium between brain and plasma as glucose is rapidly lowered, decreased plasma oncotic pressure due to infusion of large amounts of saline, and insulin-induced ion flux across the BBB. Whatever the mechanism, mortality rates are high. Treatment involves the bolus infusion of 1 g Mannitol per kilogram of body weight in the form of 20% solution. The major nonembolic complication of DKA therapy is cerebral edema, which most often develops in children as DKA is resolving. The etiology and optimal therapy for cerebral edema are not well established but over replacement of free water should be avoided.

Reye's syndrome (Fatty Liver with Encephalopathy)

Fatty changes of the renal tubular cells, cerebral edema, and neuronal degeneration of the brain are the major extra hepatic changes in Reye's syndrome. Therapy consists of infusion of glucose and fresh frozen plasma, as well as intravenous. Mannitol to reduce the cerebral edema [25].

Cirrhosis of Liver

Cerebral edema is frequently present and contributes to the clinical picture and overall mortality in patients with both acute and chronic encephalopathy. Hemoperfusion to remove toxic substances and therapy directed primarily towards coincident cerebral edema in acute encephalopathy are also of unproven value [26].

High Altitude Cerebral Edema

High altitude cerebral edema is a clinical diagnosis, defined as the onset of ataxia, altered consciousness, or both, in someone with acute mountain sickness or high altitude pulmonary edema [27]. Global encephalopathy rather than focal findings, characterizes high - altitude cerebral edema [27]. Despite normal cerebral oxygenation and normal global cerebral metabolism, vasogenic edema develops in humans (and sheep) who become moderately ill with acute mountain sickness / high altitude cerebral edema during 24 hour or more of hypoxic exposure [28]. The exact cause of high altitude cerebral edema is not known. Possible mediators, some triggered by endothelial activation, include vascular endothelial growth factor, inducible nitric oxide synthase and bradykinin [27].

Treatment requires descent and gradual

acclimatization provides the most effective prevention [29]. Acetazolamide is an effective preventive aid and can be used in certain conditions as treatment [29]. Simulated descent with portable hyperbaric chambers, now commonly used in remote locations, is also effective [27]. Education should include information about rate of ascent, diet, alcohol intake, physical activity, and preventive medications, including Acetazolamide, Nifedipine, and Dexamethasone in selected cases [30].

Conclusion

Though there has been good progress in our understanding of pathophysiological mechanisms associated with cerebral edema more effective treatment is required and is still awaited. Certainly, the “ideal” agent for the treatment of cerebral edema- one that would selectively mobilize and / or prevent the formation of edema fluid with a rapid onset and prolonged duration of action, and with minimal side effects, remains to be discovered. Probably in the days to come we can look forward to newer agents specifically acting on the various chemical mediators involved in the pathogenesis of cerebral edema.

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