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SPECIAL ARTICLE

# Brain Swelling and Brain Edema

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*"There are works which wait, and which one does not understand for a long time; the reason is that they bring answers to questions which have not yet been raised; for the question often arrives a terribly long time after the answer."*

***Oscar Wilde***

Is the term "brain swelling" used to describe the increase in brain bulk or is it traditionally reserved for intracellular distension by hyperhydration of brain parenchyma? If the latter is true should it be synonymous with intracellular type of brain edema or should the term "brain edema" be reserved only for extracellular distension by hyperhydration in brain parenchyma?

For years clinicians have been treating brain edema, be it of any kind, with reasonable efficiency. The administration of steroids, hypertonic solutions and diuretics for example has produced remarkable clinical improvement to the patients[1-13]. However, all those questions have not really been given much thought. In the early literature, brain edema and brain swelling have been differentiated and some restrict the definition of brain swelling to the state in which excess fluid accumulates in the brain cells, mainly in the glial cells; and brain edema means excess fluid in the intercellular space[14-16]. However, there were some who still preferred to use brain swelling as a descriptive term to interpret quite simply an increase in brain bulk[17].

Recently there has been a tendency to use both terms synonymously[18] and at the same time, with the help of more sophisticated investigation tools such as computerised tomography, there has been a sudden rush of interest to try to divide and subdivide brain edema into several categories to correlate with the clinical features, investigative evidence and treatments. Klatzo's classification in 1967 which summarises modern views on brain edema into vasogenic and cytotoxic has often been quoted[19-20]. Adding to these were interstitial edema, signifying periventricular hyperhydration due to obstruction of c.s.f. pathway[18], hydrostatic edema, due to increased pressure in the capillary bed[21,22]; hypo-osmotic edema, in relationship with hyponatremia as in the syndrome of inappropriate ADH secretion[23-24]. There is even further subdivision of cytotoxic edema into type A and B due to hypoxia or poisoning and the delicate specific site of toxicity[25-26].

As a result of wide interest recently paid to brain edema, it is often too liberally used in clinical practice and the term brain swelling has gradually been dropped altogether. We feel that in order to have a clear concept of how to deal with a swollen brain properly, the term brain swelling should be revised again in its clinical descriptive sense, namely the increase in brain bulk of any kind. Thus, brain edema is one cause of brain swelling, but brain swelling can be due to other causes apart from brain edema. It can produce severe intracranial hypertension without the presence of brain edema[18]. With this concept in mind, when a surgeon finds a bulging brain from the craniotomy site, he will describe it simply as brain swelling and follow the line of differential diagnosis and direct the line of management accordingly.

We also feel that by describing the said finding simply as brain swelling, the prompt action that is necessary in the management can be initiated. Treatment of edema, in any clinician's mind will definitely require time, while many causes of brain swelling may be suddenly corrected if the surgeon and anaesthesiologist urgently search for the cause and deal with it properly. Take vascular engorgement for example, it can increase the brain bulk significantly producing brain swelling. However, if left uncorrected, it may advance into vasogenic brain edema or hydrostatic edema[18]. This will be discussed later under the heading of distended vascular bed.

There are numerous causes of brain swelling (Table 1). Each of them is significant in its own way and deserves separate discussion.

## ACUTE DISTENSION OF SUBARACHNOID SPACE BY BLOOD

Perhaps the most obvious example of brain swelling due to acute distension of the subarachnoid space by blood is during surgery of intracranial aneurysm. If a neurosurgeon starts to look for the aneurysm *before* the arachnoid membrane is widely opened and the aneurysm ruptures, he can see with his own eyes that the shrunken brain as prepared by the anaesthesiologist and the surgeon himself by lumbar or ventricular drainage, up to that stage, begins to gradually bulge out, perhaps with every beat of the heart. If the surgeon wastes more time doing something else rather than quickly opening the arachnoid and allowing the extravasated blood out of the subarachnoid space, before long, the brain will swell, due to the

**Table 1** Causes of Brain Swelling (Increase in Brain Bulk)

| Causes | Causative factors and classification | Conditions they occur in | Remarks |
|---|---|---|---|
| Acute distension of subarachnoid space by blood | See text | Rupture of AVM, aneurysm, head injury (H.I.) | |
| Distension of subarachnoid space and/or ventricles by C.S.F. | See text | Communicating hydrocephalus<br>Non-Communicating hydrocephalus | May produce interstitial edema |
| Distension of intravascular compartment (engorgement) | Loss of autoregulation | H.I., normal pressure perfusion break through, hypoxia | May advance and produce vasogenic edema |
| | Increase of $pCO_2$<br>Reduction of $pO_2$ | Respiratory problems | |
| | Poor venous return | Pneumothorax<br>Respirator problems | |
| Mass lesion with or without vasogenic edema | See text | Brain tumour (metastasis)<br>Brain abscess | |
| Brain edema | Vasogenic | See text | Can follow distension of intravascular compartment |
| | Cytotoxic | See text | See text |
| | Interstitial | See text | See text |
| | Hypoosmolar | See text | See text |
| | Hydrostatic | See text | See text |

acutely distended subarachnoid space, and the surgeon will find himself completely at a loss as to what to do for the patient.

No doubt, this can happen during a head injury. With the shearing stress that occurs at the time of head impact, some arteries in the subarachnoid space might be damaged and bleed. The extravasated blood will rapidly distend the arachnoid space with arterial pressure, until hemostasis occurs or equilibrium of pressure between the inside of the lumen of the artery and the subarachnoid space is reached. One can easily visualise how swollen the brain will be if one chooses to do a craniotomy at that acute period. Certainly this is not brain oedema, as there is no hyperhydration of the brain parenchyma and the true volume of the brain is the same or, if anything, smaller but the subarachnoid space has been distended grossly by blood.

During a craniotomy this can be recognised by the widened subarachnoid space in which frank blood stained fluid can be seen through the arachnoid. In some of the cases, wide opening of the arachnoid to let the blood and c.s.f. escape can help to reduce the swelling.

## DISTENSION OF SUBARACHNOID SPACE AND/OR VENTRICLES BY C.S.F.

If hydrocephalus is not recognised preoperatively, operative brain swelling may pressent a big problem. Early hydrocephalus which does not produce obvious structural change may pose a problem here. If the distension is caused by obstructive hydrocephalus, the cortical surface will show widened gyri with very small sulcus in between. If it is by communicating hydrocephalus, the gyri will be widely opened by the c.s.f. and usually opening of the membrane will reduce the total brain volume if a large amount of c.s.f. escapes through the opening. Ventricular drainage is usually the most convenient procedure to correct this kind of swelling during the operation. Lumbar c.s.f. drainage is somewhat more complicated, but may be useful in some cases. Hydrocephalus may produce periventricular edema called interstitial edema[18] which may be seen in the CT scan.

## DISTENSION OF INTRAVASCULAR COMPARTMENT OF THE BRAIN

As the brain is a vascular structure, a large amount of its volume is contributed by the vascular space. The blood vessels of the brain, namely arteries, arterioles, capillary beds and veins are very sensitive to many changes and this is essential in order that the brain will constantly receive adequate oxygenation and also that the volume of the brain and intracranial pressure will be rendered at all times nearly constant. Therefore, a sudden cough, a sudden rise in blood pressure for example will not alter the brain volume beyond the normal limits. However, distension of the vascular space (engorgement) may occur during the following conditions.

### 1. Absence of Autoregulation of Cerebral Blood Flow

The blood pressure varies widely in a normal individual. It is minimal during deep sleep and maximal during physical and mental exertion. In order to preserve constant blood flow despite a large fluctuation of the blood pressure, the brain is equipped with excellent autoregulation. This regulation probably lies at the small arteries and arterioles of the brain and is self-regulated by intraluminal pressure. Constriction will readily occur if the pressure is raised by any cause.

In atherosclerotic patients, this mechanism is to a large extent hampered by the hardening of the arteries and the arterioles and the patient has to learn to live with headache during raised blood pressure due to the increased brain volume. If it becomes too high the smaller arteries, particularly the fragile lenticulostriate ones may rupture and produce the well known cerebral haemorrhage.

In animal experiments enlargement of brain volume does not occur after severe head injury if the blood pressure is kept normal or subnormal, but if, for any reason, it is raised, the injured brain will suddenly start to swell[21]. In real life, we see this many times during removal of post-traumatic haematomas of any kind. If, say, we remove a large subdural haematoma in an acutely ill patient not long after head injury, due to his serious condition, prior to the surgery his blood pressure may be in the vicinity of 80-90 mm.Hg systolic. After the removal, the surgeon sees sunken brain well away from the dura. However, if the anaesthesiologist is over-anxious and with blood transfusion or other means raises the blood pressure to the vicinity of 130-140, the brain will gradually swell and may reach the level where the bone flap cannot be replaced. More often than not the conscious level of the patient which should be improved after the clot removal becomes worse after the surgery because of the swelling. To my mind, the blood pressure should be kept at that low level for a length of time, provided that the patient does not show signs of subclinical shock such as oliguria, rapid pulse and cold clammy skin, until the autoregulation resumes its normal activity to cope with the rise of blood pressure. Then we may allow the blood pressure to swing naturally.

After a successful removal of intracranial AVM sudden brain swelling may occur due to "normal pressure perfusion breakthrough" which may also be due to the loss of autoregulation[27].

### 2. Partial Pressure of $O_2$ and $CO_2$

It is well known that the rise of $pCO_2$ and fall of $pO_2$ will increase blood flow and distend the cerebral vascular bed[28-32]. Adequate ventilation must be maintained at all times during the care of a patient with brain swelling. If the patient's consciousness deteriorates, the skin becomes warm and excessive sweating is shown on the fore-head. All clinicians should be aware of this condition, otherwise known as "$CO_2$ narcosis". If this is not recognised it will not only allow brain edema to form but will also accelerate the progress of the edema.

### 3. Venous Return from the Brain to the Heart

The is one of the most dangerous causes of congestion of the cerebral vascular bed and is also often missed. Tension pneumothorax, prolonged application of a respirator using intermittent positive pressure are some of the usual causes. With normal respiration, the intrathoracic great veins particularly the ones from the head, superior vena cava, will decrease in calibre during expiration, coughing and straining and increase in calibre during inspiration when the intrathoracic pressure is negative. With constant positive pressure in the case of tension pneumothorax or with no negative pressure at all in the case of improper use of the respirator will definitely embarrass the venous return[6,17,19,45] .

There is a condition, which is not well known, but very often occurs after injury known as thrombosis of the large dural venous sinuses. This condition can be a result of a fracture that runs across the sinus and partially damages its wall. The thrombosis of the sinus can produce brain swelling due to congestion of the vascular bed. It may also produce another intermediate or longterm complication, namely communicating hydrocephalus due to failure of the function of arachnoid granulation.

## MASS LESION

A mass lesion which is not at the site of craniotomy can produce excessive brain swelling. Unrecognised hematoma on the opposite side, multiple brain metastasis are such examples. The metastatic tumour may not only be multiple, but also may be small and, being foreign to the brain, produces a large amount of vasogenic brain oedema around the lesion. Even very careful exploration may miss the small tumour and only oedematous brain tissue is obtained. Reexamination of all investigations including cerebral angiography is again necessary. With CT scan the localisation is easier but not altogether reliable. Iso-density lesion may be completely missed by the scan.

## BRAIN EDEMA

Brain edema is caused by an increase in the outflow of water from the vascular bed. Since the passage of water across the capillary bed is governed by Starling equilibrium, it is useful to consider edema as a result of this equilibrium being disturbed although the actual situation in the cerebral vascular bed is much more complex.

The three most important factors that disturb the equilibrium are increased intravascular hydrostatic pressure, damage to the vascular endothelium and reduction of plasma colloid osmotic pressure[25] .

As said earlier, Klatzo's classification of brain edema into vasogenic and cytotoxic has been widely adopted. These two types have a clear cut pathophysiological change at the level of capillary endothelium, its "tight junctions", neuroglia cells and blood-brain-barrier. Other types of edema were added on later in order to cover the whole scope of brain edema.

***Vasogenic Brain Edema*** : This kind of edema is by far the most common. The fluid, proteins and electrolytes escape from the damaged vessels and spread through the brain parenchyma[33-36]. It is believed that the blood-brain-barrier which is at the tight

**Table 2** Types of Brain Edema

| Type | Cellular change | Location | Spread | Edema fluid | Causes |
|---|---|---|---|---|---|
| Vasogenic | Extracellular | White matter | Localised | Plasma like | Damage of capillary endothelium at tight junctions, BBB |
| Cytotoxic | Intracellular | Grey & White matters | Diffused but may be localised | Water & Sodium | Hypoxia and metabolic inhibitors |
| Interstitial | Extracellular | Periventricular | Localised | C.S.F. | Hydrocephalus |
| Hypo-osmotic | Intracellular | Grey & White matters | Diffused | Water | Low plasma colloid osmotic pressure |
| Hydrostatic | Extracellular | White matter | Diffused | Water | loss of auto-regulation, Hypertension |

junctions formed by endothelial cells lining the cerebral capillaries[37-39] is disturbed thus allowing leakage of serum protein and edema fluid. This type of edema occurs in many conditions such as brain tumour, local injury[38,40-43], brain abscess, intracerebral hematoma and experimental application of intense cold to the cortex[25]. Essentially this type of edema is extracellular and tends to be localised, and limited to the white matter.

Most important of all, the clinician must always bear in mind that vasogenic edema may develop from the congestion of distension of the vascular bed and once this is allowed to happen, a longer time is required to reverse the process.

*Cytotoxic Edema* : At cellular level this type of edema is different from the vasogenic type. There is usually no leakage of the blood-brain-barrier. The endothelial cells swell due to the failure of ATP-dependent sodium pump in the cells. The sodium accumulates within the cells and water follows to maintain osmotic equilibrium. The neuroglia and neurones then will show the same intracellular change. The causes of cytotoxic edema mainly are hypoxia, but in experiments it can be induced by many metabolic inhibitors[18-20]. This type of edema is usually generalised involving both gray and white matter. The edema fluid contains no protein. Because it is intracellular in nature hypo-osmolar type of edema (see below) is sometimes included in this category[18].

*Interstitial Edema* : Because some fluid is found in the periventricular region in the case of hydrocephalus or benign intracranial hypertension and does not seem to fall into vasogenic or cytotoxic categories a new type has been described[18]. It seems that the c.s.f. is forced into the brain parenchyma by the hydrostatic pressure in the ventricle. It may be of some diagnostic value, but the treatment consists essentially of treatment of the hydrocephalus.

*Hypo-osmotic Edema* : When there is reduction of the plasma colloid osmotic pressure of any kind, generalised intracellular swelling may occur[25]. Clinically it is significant as the syndrome of inappropriate ADH secretion is common in neurosurgical practice[12] and can produce this type of edema which, if undetected, may be fatal.

*Hydrostatic Edema* : Although it occurs in direct trauma as in vasogenic edema, it so happens that this type of edema contains no protein in the edema fluid and a new type of edema has been described[21,22,25]. It is claimed that there is no endothelial damage and the tight junctions are well preserved, therefore only water is extravasated. High intravascular hydrostatic pressure is said to be the cause. It is also found in excessive hypertension, hypercapnia and hypoxia.

### Progress and Resolution of Brain Edema

Although in experiments, vasogenic edema is localised, once the process has started it is increased by arterial hypertension and by all agents that decrease cerebrovascular resistance permitting transmission of higher intravascular pressure more distally in the vascular bed. Hypercapnia, hypoxaemia, hyperthermia and volatile anaesthetics all augment the formation of edema[19,20,44]. Clinicians should try their best to avoid all the agents. The edema fluid finally resolves into the ventricle through the ependyma[13,25]. If intracranial hypertension persists, the edema will not be resolved easily. Therefore, clinicians should do their best to reduce intracranial pressure[25].

## THE MANAGEMENT OF BRAIN SWELLING

### Diagnosis

Before we treat brain swelling, every effort must be made to determine its causative factors. This may be difficult because usually there are multiple factors involved at the same time. Sometimes the diagnosis can be done by exclusion and inference, particularly during surgery. Proper anaesthetic control must be ensured and thereby coughs, strains and retention of carbon dioxide can be avoided. The ventilation must be adequate and allow good venous return to the heart. The blood pressure must be kept optimal as hypertension in the abscence of autoregulation is undesirable. If this is achieved but the problem is not yet solved, the surgeon must then make sure that he is operating at the right location, he is not dealing with a multiple mass lesion such as bilateral hematomas or multiple small metastases. Obstruction of c.s.f. pathway must be excluded and distension of subarachnoid space by blood must be recognised. When all of these are done and the brain swelling remains unchanged, inferential diagnosis of brain edema is justified.

### Treatment of Brain Edema

It is important that clinicians must treat not only brain edema, but also prevent its progress. All the factors that accelerate the progress of edema must be eliminated. Hypoxia and hypercapnia must be corrected. The blood pressure is kept at optimal level. Hyperthermia must be controlled. Constant reappraisal of the general condition must be done, this also includes regular check-up of electrolyte and fluid balance.

*Ventilation* : Apart from the correction of respiratory problems which may arise as mentioned earlier, a ventilator can be useful in the treatment of brain

edema. It can promote better venous return to the heart by negative expiratory phase[45]. Hyperventilation and reduction of $pCO_2$ has also been proven beneficial in brain edema, particularly in association with vascular engorgement. The effect of hyperventilation is not only the reduction of intracranial pressure, but also a more favourable perfusion in the edematous brain[25,46]. However, $pCO_2$ must not be lower than 25-30 mmHg as brain ischaemia and infarct may result[47].

*Restriction of Fluid* : In our experience hyponatremia occurs very frequently in association with brain lesions. Some of the patients develop a full blown syndrome of inappropriate ADH secretion. We find it useful to prevent this by restriction of fluid to 1500 ml per day during the acute period and 500 ml per day if the syndrome occurs, as advised in the literature[12]. Hypo-osmotic edema is most efficiently dealt with by this measure.

*Steroid Therapy* : It has been generally accepted that glucocorticoid dexamthasone is most potent in treating brain edema[2-8,13,48]. However, this is true in vasogenic edema only[18,25]. As it is the most common form of edema, dexamethasone is now widely used by clinicians. The most dramatic response can be seen in metastatic brain tumour, where the peritumoural vasogenic edema resolves rapidly after the administration of dexamethasone and clinical improvement can be dramatic.

The mode of action is not known. "Membrane stabilisation" has often been quoted and reduction of formation of c.s.f. has been suggested but they are still controversial[49,50].

The usual dosage of dexamethasone is a starting dose of 10 mg and 4 mg four times a day thereafter.

*Osmotherapy* : Much has been written about the effects of a variety of hypertonic solutions, including glucose, sucrose, urea, mannitol and recently, glycerol[51-57]. It is very difficult to evaluate the effect of each agent. We use only mannitol in the dosage of 1 mg per kg body weight only when we want a quick and transient reduction of brain volume in order to facilitate other procedures such as removal of a tumour or surgical decompression. The osmotherapy is effective only in the part of brain where the capillary permeability is normal. Therefore, if it is used in vasogenic edema only the normal part of the brain will shrink. Furthermore, the hypertonic agent leaks into the edematous area, due to damaged endothelial tight junctions, and remains there. The rebound in severity in the edema may follow because the hypertonic agent is not excluded from the edematous tissue[18].

In conclusion osmotherapy has a very limited place in brain edema. It is used only when indicated as described above.

*Newer Mediation* : Furosemide has been shown to reduce intracranial pressure and diminish brain edema in patients and experimental studies. It also appears to reduce the rate of c.s.f. formation[1,3,4,13,29]. During surgery we have been impressed by the usefulness of Furosemide at the dosage of 1 mg/kg. It is as effective as mannitol. It may be proven to have a signigicant place in the treatment of brain edema as it does not produce rebound effects in osmotherapy.

Acetazolamide causes about a 50 per cent reduction in the rate of c.s.f. formation within the ventricle[18]. If used discriminately it may be useful in the treatment of certain types of brain edema such as interstitial edema.

*Surgical Decompression* : The external decompression by temporary removal of a large bone flap has less and less place in the treatment of edema. It has been gradually replaced by more efficient medication.

However, internal decompression is still very useful particularly in head injuries where there is a large amount of necrotic material and clots in the intracranial cavity. Their removal will provide more available space for the edematous brain until resolution takes place. Internal decompression is also very useful when a mass lesion is the basic cause of perifocal brain edema. The removal of the mass lesion will also help to accelerate the resolution of the edema.

## SUMMARY

It is important to have a clear concept in dealing with an increase in brain bulk. It may be due to several causes and brain edema is one of them. The authors suggest the term brain swelling be used in the clinical descriptive sense and various causes of brain swelling have been discussed. Brain edema is discussed in detail.

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