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The Modern Approach to Treating Brain Swelling in the Neuro ICU

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Abstract

Brain swelling is an urgent clinical problem that frequently accompanies ischemic stroke, brain hemorrhage and traumatic brain injury, and it increases morbidity and mortality associated with them. It occurs due to failure of membrane transporters and the blood-brain barrier (BBB), resulting in combination of cytotoxic, ionic and vasogenic edema. Currently, decompressive craniectomy and osmotherapy are the mainstays of management, but these therapies do not halt the underlying molecular cascade leading to brain swelling. Recent advances in the molecular underpinnings of cerebral edema have opened up possibilities of newer targeted therapeutic options. Here we outline the current approach for rapid diagnosis and intervention to reduce mortality and morbidity associated with brain swelling.

Keywords

Brain swelling; cerebral edema; diagnosis; treatment

INTRODUCTION

Unchecked brain swelling can increase mortality in large hemispheric stroke patients, and its presence predicts poor outcome in moderate sized strokes[1, 2]. Development of brain swelling following traumatic brain injury is the most significant predictor of outcome, and account for up to 50% of mortality[3]. Brain swelling seen in acute liver failure, anoxic brain injury and toxin exposure also presents a significant clinical problem. Recent advances in monitoring capabilities and molecular understanding have led to increased interest in brain swelling. While the therapeutic options are still limited and only mitigate downstream

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effects, a systematic approach aimed at early detection can provide a window of opportunity to initiate therapies while the harmful effects of brain swelling are still manageable. Other medical topics important in the treatment of brain swelling include prevention of secondary brain injuries caused by seizures, hyperglycemia or hyperthermia. With continued advancements in Neuro ICU care, further improvement in survival and reduction in disability is possible in patients with brain swelling.

PATHOPHYSIOLOGY

While the terms “brain swelling” and “cerebral edema” are often used interchangeably, they do have different pathological connotations. Brain swelling refers to increase in brain volume, and can result from hemorrhage, tumor or cerebral edema. Cerebral edema refers to abnormal accumulation of water within the brain tissue and is a prime example of treatable causes of secondary neurological deterioration in patients with brain injury. As modern day neurointensivists spend significant amounts of time monitoring for the presence of cerebral edema and managing its consequences, this is the focus of the current review.

Cerebral edema is a stepwise process in which acute injury can lead to the formation of cytotoxic, ionic and/or vasogenic edema. Cytotoxic edema is characterized by the depletion of intracellular adenosine triphosphate (ATP), which disrupts active transport of osmolites across cell membranes and drives Na^+ and water intracellularly, causing cell swelling[4]. Cytotoxic edema subsequently leads to the disruption of the transendothelial Na^+ gradient. This leads to the accumulation of Na^+, Cl^- and water in the extracellular compartment of brain parenchyma and promotes the movement of water from the intravascular to extracellular spaces, a process termed “ionic edema[5].” Increased upregulation of the Sur1-Trpm4 channel in endothelial cells in response to brain injury contributes to formation of ionic edema and represents a highly promising therapeutic target[6]. Separate to these two forms of cerebral edema (i.e. cytotoxic and ionic edema), increased the permeability of the blood brain barrier (BBB) following brain injury by inflammatory mediators and oxidative stress permits extravasation of water and plasma proteins and causes extracellular edema commonly known as vasogenic edema[7].

As brain injury evolves in a complex spatiotemporal pattern, these three forms of cerebral edema are likely to overlap significantly, instead of evolving in a sequential manner, and contribute to brain swelling. As postulated by the Monro-Kellie doctrine, brain swelling causes an increase in intracranial pressure (ICP) because of the fixed volume of the enclosed cranial cavity[8]. Raised ICP in turn forces reduction in capillary perfusion and leads to tissue hypoxemia.

MANAGEMENT

Identification of high risk patients

Vigilant recognition of high risk patient populations likely to develop brain swelling serve as a cornerstone of the modern approach to brain swelling in the Neuro ICU. Early recognition of impending brain swelling can guide the frequency of neurological examinations, initiation of medical and surgical therapies, and communication with family members about the

anticipated clinical course. Patients at high risk of developing brain swelling should be promptly considered for transfer to a center with multidisciplinary expertise in neurocritical care and neurosurgery[9]. Tables 1 and 2 shows the risk factors for developing brain swelling following ischemic stroke and ICH, respectively. Thrombolysis risk using the modified Rankin Scale (mRS) and NIH Stroke Scale (NIHSS) (TURN) score is a tool described recently that can predict the development of cerebral edema within 24 hours after ischemic stroke with good sensitivity and specificity[10].

Evaluation

Frequent assessments can aid in rapid diagnosis and timely management of brain swelling to improve outcomes. Early diagnosis of brain swelling is a key to reducing mortality and improving functional outcomes in ischemic stroke, as shown by clinical trials of decompressive hemicraniectomy [11]. Worsening brain swelling should be considered in patients with signs or symptoms of rising ICP, such as decreased level of consciousness, vomiting, headache, gaze deviation and hemiparesis. Of these signs, level of consciousness, which results from damage to the ascending reticular activating system and thalamo-hypothalamic-cortical projections, is the most important clinical parameter to detect brain swelling. Assessment scales that evaluated the level of consciousness, including the Glasgow Coma Scale (GCS) and The Full Outline of UnResponsiveness (FOUR) Score are most commonly used to monitor for signs of worsening brain swelling [12]. Use of such scales can improve communication across multi-disciplinary providers in the Neuro ICU and facilitate appropriate clinical responses.

Confounders to the level of alertness are commonly present in the ICU setting, such as use of sedatives, fever, post-ictal state and metabolic causes such as hypercarbia, hypoglycemia or uremic encephalopathy should be eliminated before attributing decreased arousal to brain swelling. Accurate assessment for the presence of brain swelling thus requires integration of information from multiple clinical sources and clinical judgment. Several different quantitative methods based on electroencephalography (EEG) are in development to assist with interpretation of the clinical exam and can aid in diagnosis of worsening level of consciousness. Alpha to delta ratio (ADR) and Bispectral (BIS) monitoring are examples of such quantitative tools [13, 14]. Use of these techniques to detect a decreased level of arousal in the setting of developing brain swelling should be still considered investigational.

Diagnosis

Development of clinically significant brain swelling can be observed with a rapid course over 24–48 hours from the initial brain injury, or more gradually over days. While several different neuroimaging modalities are useful to detect the presence of brain swelling, computed tomography (CT) imaging is most widely used because of easy availability. A baseline non-contrast head CT should be obtained on arrival in all patients at risk of brain swelling for reference purposes. Following that, serial CT scans should be evaluated for signs of mass effect, like loss of sulci, compression of the ventricular system and midline shift. In instances where the neurological exam is confounded by sedatives or fever, surrogate markers of edema such as neuroimaging findings can play an important role is diagnosis.

Contrast-enhanced CT and MRI are used to assess BBB permeability and can be helpful in predicting the development of edema. Requirement of the use of a contrast agent often limits use of these modalities in clinical settings [15]. Near infrared spectroscopy (NIRS) provides continuous, direct and noninvasive monitoring of cerebral oxygenation and cerebral blood volume. Bilateral frontal NIRS measuring regional cerebral oxygen saturation has been shown to accurately predict worsening brain swelling[16]. Currently, it is an experimental technology with limited use in the Neuro ICU, but it has potential as a clinical tool for bedside measurement of brain swelling.

Medical Management

Initial medical management of patients with or at risk for brain swelling focuses on protecting the airway, breathing and circulation. Important considerations for this patient population include use of minimal amounts of sedation to prevent a confounding effect of sedation on the assessment of level of consciousness. State of the art Neuro ICU care should incorporate all essential aspects of critical care management, including maintenance of normothermia, normoglycemia, euvolemia, eucarbia and eunatremia. Proper head positioning in the midline with head elevation to 30 degrees can ensure maximal cerebral venous outflow Hyperventilation can be used as a short term measure to counter ICP crisis, but its effects are transient [17]. Hypercarbia should generally be avoided to prevent cerebral vasoconstriction, which can exacerbate tissue injury. Pharmacological prophylactic therapy against stress ulcers and venous thromboembolism are part of good clinical practice in this high risk group of patients. Early enteral nutrition support within 24 hours of admission can lead to improved outcome, and placement of nasogastric tube may be needed [18, 19].

Osmotherapy is the mainstay of medical therapy for brain swelling, but its prophylactic use should be avoided, as its efficacy is limited and could be exhausted if initiated too early. The mechanisms by which hyperosmolar therapy provides benefit in brain swelling are several fold. It reduces brain swelling by creating an intravascular osmotic gradient which in turn facilitates water extraction. Influx of water into brain vessels can improve cerebral compliance [20]. Mannitol and hypertonic saline are two of the most widely used hyperosmolar agents. A meta-analysis comparing equi-osmolar doses of hypertonic sodium solutions to mannitol showed that hypertonic saline may be superior to mannitol for treatment of elevated ICP [21]. Hypertonic solutions containing sodium chloride have a theoretical advantage of low BBB permeability and a higher reflection coefficient, making it an attractive osmotic agent [22]. Potential advantages of hypertonic saline include expansion of the intravascular volume, increase in cardiac contractility and improvement in intracranial compliance [23].

A wide variety of dosing regimens and different strengths of hypertonic saline are currently used, driven primarily by institutional practice pattern, and no strong data is available to suggest that one particular regimen is better than others. Mannitol dosing is weight-based, and usually bolus doses of 1–1.5 g/kg IV are repeated every 4 to 6 hours. Serum osmolarity of 320 mOsm/kg or an osmole gap of 10–15 mOsm/kg is usually considered to be an upper limit for use of mannitol. Hypertonic saline is commonly given as a 30 ml bolus of 23.4% saline, although preparations of different strengths are available and used. Continuous

infusion of hypertonic saline (such as 3% saline) is frequently used to titrate up to or maintain hypernatremia. Continuous hypertonic saline infusions are generally well tolerated and may be an effective method of reducing ICP and edema formation [24]. Although there are few studies comparing this strategy to bolus dosing [25], early continuous hypertonic saline may nevertheless be used to reduce cerebral edema and ICP [26–28], with bolus osmotherapy reserved for clinically symptomatic brain swelling.

Osmotic therapy does have significant systemic side effects. Osmotic diuresis with mannitol can cause intravascular dehydration and hypotension. Adequate fluid replacement with isotonic solutions should be provided after osmotic diuresis to preserve euvolemia. Another potential toxicity of mannitol is that upon prolonged use it can cross the BBB and accumulate in the brain tissue, causing a reverse osmotic shift, thus increasing ICP [29, 30]. Other side effects of mannitol are pre-renal azotemia, hyperkalemia, development of pulmonary edema and heart failure in patients with renal failure. Side effects of hypertonic saline are an increased rate of heart failure because of volume overload, acute renal failure, thrombocytopenia and acute respiratory distress syndrome. These are most commonly seen after the serum sodium is increased to > 170 mEq/L [31], which is above the standard target levels used to control brain swelling. Central pontine myelinolysis, a syndrome often seen with rapid correction of chronic hyponatremia, has not been reported with the use of hypertonic saline for brain swelling, but is a theoretical risk. Prolong repeated use of hypertonic saline will lead to development of a hyperchloremic metabolic acidosis and may limit its continued use. Hyperchloremic acidosis can be prevented by using hypertonic sodium/acetate solutions [27]. Hypertonic saline and mannitol can be used in an alternating fashion to treat symptomatic brain edema.

Another important consideration in the use of hyperosmolar therapy is careful weaning. Weaning should be initiated cautiously and in a stepwise manner following the peak edema period, and the patient should be closely monitored for signs of rebound edema. Barbiturates are sometimes tried as a last medical resort for the treatment of brain swelling, but their use is often associated with cardiovascular depression, immunosuppression and loss of the neurological examination.

Surgical Management

While surgical decompression has been shown to provide a clear survival benefit in large hemispheric stroke, its role in the management of brain swelling associated with trauma and ICH is still uncertain (see discussion below). A pooled analysis of three randomized control trials of decompressive hemicraniectomy showed that patients under 60 years of age with large hemispheric stroke have significant improvement in mortality when they had the surgical procedure done within 48 hours of symptom onset, compared to medical therapy alone [11]. A follow up study demonstrated a similar mortality benefit in a patient population above the age of 60, but had much fewer favorable functional outcomes [32]. Since evidence of benefit from decompressive surgery is most clear when it is done early and is done in a generous fashion (e.g., a bone flap of at least 12-cm in diameter), formation of consensus guidelines at an institutional level can facilitate rapid identification and triage of patients in a timely manner for surgical therapies [33]. Following decompression, patients

should be watched for the development of subdural hemorrhage, external hydrocephalus, wound infection and dehiscence[34].

While decompression does offer benefit in quality-adjusted life-years, functional recovery following devastating stroke is usually incomplete and often leaves patients with significant disability [35]. Because of concerns about long-term quality of life, a very important challenge for modern day neurointensivists involves providing a helpful framework for decision-making by effectively incorporating available quantitative data into communication with surrogate decision makers [36].

Special Considerations for Brain Swelling in TBI

ICP monitoring is a cornerstone of TBI management as practiced currently [37]. While several different ICP monitors are available, including ones that can be placed in the subdural, subarachnoid and parenchymal locations, intraventricular catheters are preferred in most situations as they allow therapeutic CSF drainage to control raised ICP. Although ICP monitoring has become an integral part of managing patients with severe TBI, and even short durations of increased ICP has been shown to have unfavorable effects, trials comparing the use of hyperosmolar therapies driven by ICP monitoring versus the clinical exam/imaging have not shown a difference in outcomes [38, 39].

The role of decompressive craniectomy also remains uncertain in the management of refractory intracranial hypertension in TBI [40]. The decompressive craniectomy in diffuse traumatic brain injury (DECRA) study, which was designed to compare bifrontal decompressive craniectomy and standard medical management, showed that early surgery is not superior to medical management for patients with diffuse TBI [41]. Efforts are ongoing to develop the evidence base for indications and optimal timing for decompressive craniectomy in TBI.

Special Considerations for Brain Swelling in ICH

Brain swelling in ICH is the result of a combination of hematoma and perihematomal edema (PHE). Expansion of hematoma volume or an increase in PHE can cause worsening brain swelling. PHE can develop in the hyperacute phase and reach a peak in the second week after initial hemorrhage [42]. The basic principles and options for medical management for brain swelling associated with ICH are the same as above for ischemic stroke [43]. Surgical evacuation of the hematoma is clearly indicated for moderate to large posterior fossa hemorrhage, but its role in supratentorial ICH is less clear [44]. Based on the results of the Surgical Trial in Intracerebral Hemorrhage 2 (STICH2) trial, there may be a small survival benefit for superficial lobar ICH [45], although the role of surgical evacuation remains controversial in the ICH population. Currently, two ongoing clinical trials are evaluating the effectiveness of minimally invasive clot evacuation strategies using stereotactic or endoscopic aspiration [46, 47].

EMERGING THERAPIES

Brain swelling represents an important target for basic science research and therapeutic intervention in recent years. The SUR1 receptor blocker glibenclamide (Glyburide) is

undergoing evaluation in patients with large territory infarction [48]. The anti-inflammatory drug glycyrrhizin is shown to prevent BBB breakdown and vasogenic edema by inhibiting HMGB-1 [49]. Bumetanide, an inhibitor of NKCC1 and clinically used a loop diuretic, has been shown to have promise targeting brain edema following ischemia, TBI and acute liver failure [50–52]. Other promising molecular targets include TLR4 and AQP4 [53, 54].

CONCLUSION

Development of brain swelling puts patients at risk of neurological deterioration, and accordingly represents a therapeutic opportunity to improve outcomes from acute brain injury. Modern approaches to brain swelling in Neuro ICU consist of early identification of high risk patients and timely initiation of available therapeutic options. Recent discoveries of key molecular pathways involved in cerebral edema formation hold promise for the development of effective treatment strategies to further mitigate brain swelling.

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Table 1

Risk Factors to Identify Ischemic Stroke Patients at High Risk of Brain Swelling

Epidemiological
History of hypertension[55]
History of heart failure[55]
Clinical
NIHSS > 20 in dominant hemisphere or NIHSS > 15 in nondominant hemisphere[55]
Early decline in level of arousal[55]
Development of nausea or vomiting in first 24 hours[55]
Systolic blood pressure > 180 mm Hg in first 12 hours[55]
Radiological
Presence of hyperdense middle cerebral artery on noncontrast head CT[56]
Presence of large vessel occlusion
Involvement of multiple vascular territories[55]
Incomplete circle of Willis[55]
Infarct volume of > 82 ml on DWI MRI within 6 hours of symptom onset[57]
Infarct volume of > 145 ml on DWI within 14 hours of symptom onset[58]

NIHSS = National Institutes of Health Stroke Scale
MRI = Magnetic Resonance Imaging
DWI = Diffusion Weighted Imaging

Table 2

Risk Factors to Identify ICH Patients at High Risk of Brain Swelling

Risk Factors for Hematoma Expansion
Initial ICH volume[59]
Early presentation after symptom onset[59]
Anticoagulation use[60]
CTA spot sign[61]
Risk Factors for Worsening Perihematomal Edema (PHE)
Hyperglycemia[62]
Persistently increased systolic blood pressure[63]
Hematoma volume[64]
Elevated PTT at admission[42]
Increased serum concentration of MMP-9[65]

ICH = Intracerebral Hemorrhage
CTA = Computed Tomography Angiography