

## The Management of Peritumoral Brain

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### Abstract

Brain edema is classified into four main types: vasogenic, cellular, osmotic, and interstitial. These types may be triggered by various conditions, such as head injuries, vascular ischemia, intracranial lesions, and obstructive hydrocephalus. Several factors are associated with the development of (the swelling of the brain including tumors, physical injuries, insufficient oxygen supply (hypoxia), infections, disruption in metabolism, or acute hypertension. Vasogenic brain edema, the most prevalent form of brain edema, is characterized by a blood-brain barrier (BBB) disorder. When the BBB is compromised, ions and proteins move more easily into the extravascular space, creating an osmotic effect that fluid into the brain's interstitium. In brain tumors, cerebral edema occurs due to leakage of plasma into the parenchyma caused by impaired function of cerebral capillaries. Management of brain edema focuses on two key strategies: preventing further damage caused by the increased fluid in the brain, and addressing the underlying cause of the edema. Corticosteroids are frequently used as a primary therapy for this condition. While low-dose corticosteroids are preferred to minimize serious adverse effects such as myopathy or diabetes, higher doses of dexamethasone-sometimes along with osmotherapy (e.g. mannitol) or surgical interventions- may be necessary in emergency situations. Careful tapering of corticosteroids is essential to prevent dependence or withdrawal symptoms. New therapies, such as vascular endothelial growth factor receptor inhibitors and corticotropin-releasing factor, require additional clinical evaluation. A thorough understanding of pathophysiology of brain edema is crucial for optimizing the treatment strategies both before and after surgical procedures.

**Key words:** Brain edema, brain tumors, corticosteroids, herniation, management, treatment

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### Introduction

Brain edema is characterized by swelling within the brain tissues. It is categorized into four distinct types: vasogenic, cellular, osmotic, and interstitial. Several factors may play role in the development of the cerebral edema, such as head injuries, vascular ischemia, intracranial lesions, or obstructive hydrocephalus.<sup>1-3</sup> Without appropriate treatment, brain edema can lead to fatal outcomes.<sup>1</sup> The Monroe-Kellie doctrine explains how brain edema leads to injury. This principle states that the intracranial space has a

constant volume, comprised of fixed proportion of brain tissue (around 1400 ml), blood (about 150 ml) and cerebrospinal fluid (approximately 150 ml).<sup>1,2</sup> Due to this condition, any increase in one of these components (brain tissue, blood, or cerebrospinal fluid) must be reduced by a decrease in the same number of other components. In brain edema, the swelling of brain tissue increases its relative volume. This, in turn, reduces blood flow (perfusion) into the brain and the pressure can lead to additional damage to both the swollen tissue and healthy brain tissue. The clinical presentation of brain edema varies widely. Individuals may be completely asymptomatic,

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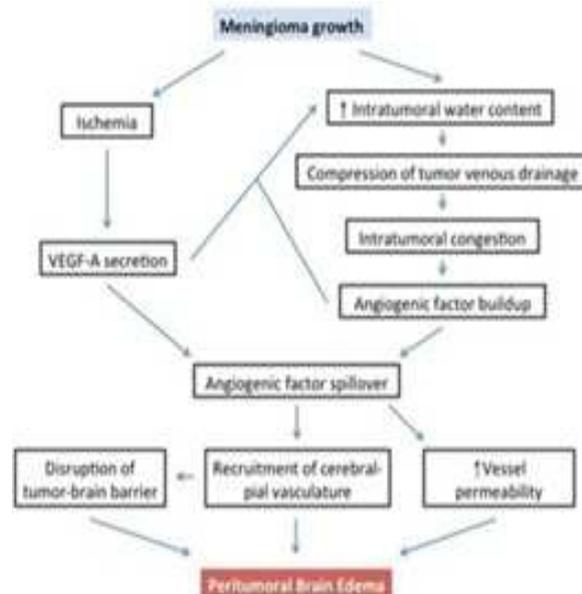
or they may experience dysregulation of the autonomic nervous system, lapse into coma and death. In the majority of cases, symptoms become noticeable when intracranial pressure (ICP) surpasses 20 cm HO (15 mmHg).<sup>1</sup> Treatment strategies for brain edema are directed at both the primary cause and urgent complications. Brain edema therapies involve controlled breathing (hyperventilation), pharmaceutical interventions (osmotherapy, diuretics, corticosteroids), or surgical decompression.<sup>1,4</sup> In brain tumor, brain edema occurs when plasma leaks from dysfunctional cerebral capillaries into the brain tissue. This leakage potentially triggered by vascular endothelial growth factor, causes swelling. Corticosteroids are the standard medical treatment to reduce this swelling. Low-dose corticosteroids, such as 4 mg of dexamethasone per day, are generally preferred to minimize potential side effects (like muscle weakness (myopathy) or diabetes).<sup>1,4</sup> Meanwhile, in urgent situations, higher doses of dexamethasone (16 mg/day or more), may be necessary, sometimes combined with osmotherapy (like mannitol) or surgical intervention.

Careful monitoring is required when tapering corticosteroid doses due to the potential for dependence or withdrawal effects.<sup>1,4</sup> New treatments, including vascular endothelial growth factor receptor inhibitors and corticotropin-releasing factor, require further clinical trials before they can be widely used.<sup>2-4</sup> Brain edema, regardless of its type, leads to increased pressure within the brain. The most common form of brain edema is vasogenic edema, This occurs when the blood-brain barrier, which normally prevents fluid from entering the brain, becomes compromised, often due to a brain tumor. As a result, fluid accumulates in the extracellular spaces of the brain. Cellular edema occurs when fluid builds up within the brain cells, typically due to brain ischemia (stroke) or oxygen deprivation (hypoxia). Osmotic edema arises from electrolyte imbalance, leading to excessive water absorption by brain cells, and can be linked with medical conditions that disrupts the bodies metabolic functions, such as hyponatremia, and diabetic ketoacidosis. Interstitial edema occurs

when cerebrospinal fluid infiltrates brain tissue, commonly associated with hydrocephalus or meningitis. Lastly, hydrostatic edema develops due to elevated blood pressure (hypertension) in the brain's arteries.<sup>1,5</sup> Cerebral edema can manifest in different forms based on its cause, but all types involve swelling that impairs the brain's access to oxygen and nutrients.<sup>1,5</sup>

### Pathophysiology

The most prevalent form of cerebral edema is vasogenic edema, which arises from a



**Figure 1. Peritumoral Brain Edema Cascade.**<sup>5</sup>

disrupted blood-brain barriers (BBB). A damage BBB allows ions and proteins to leak into the surrounding brain tissue, causing an osmotic gradient that attracts fluid into the brain's interstitial space, resulting edema. In addition to the initial BBB disruption, the productions of vascular endothelial growth factor (VEGF), glutamate, and leukotrienes near tumor sites further enhance vascular permeability.<sup>1,6</sup> These factors, combined with the loss of occluding junctions in vascular endothelial cells around the tumor enhances permeability, which allows the entry of dissolved proteins and fluids into the brain parenchyma, especially in the substantia alba.<sup>7</sup> Peritumoral edema, for instance, results

in cognitive impairment for 65% of patients due to displacement and injury to the substantia alba channel.<sup>1,7</sup> In normal circumstances, minimal flow moves across brain capillaries and tissue. Molecules in the brain's extracellular fluid (ECF) mainly diffuse through this space. The speed of this movement out of the brain is determined by the molecules' size, the difference in concentration of the molecules, and the ability of the molecule to pass through the blood-brain barrier (BBB) and re-enter the vascular system.<sup>1</sup>

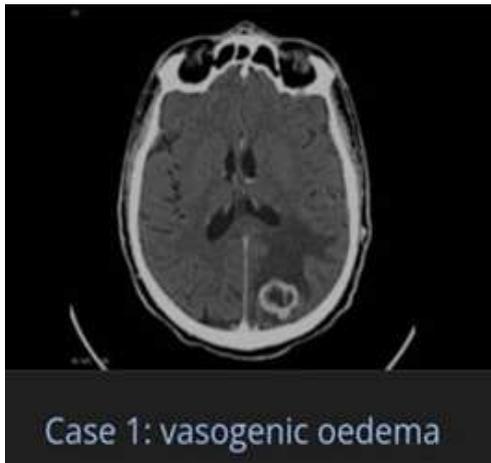
The accumulation of vasogenic fluid in the brain is caused by injury to the brain vessels. This type of edema is partially resolved when the excess fluid moves into the ventricular cerebrospinal fluid (CSF). Two key factors facilitate the removal of fluid from the brain's extracellular fluid (ECF): the pressure difference between swollen brain tissue and CSF; the CSF's "sink" mechanism, which aids in fluid absorption. Research indicates that reducing intracranial pressure (ICP) enhances the clearance of edematous fluid, possibly due to an increased pressure gradient between the edematous tissue and CSF. Additionally, the removal of proteins from the brain's ECF occurs through intragial uptake, a process believed to be critical in resolving vasogenic brain edema.<sup>1,2</sup> Cerebral edema, or brain swelling, is characterized by excess fluid within the brain tissue, resulting in increased volume in one area of the brain, consequently reducing the space available in other areas. It is generally categorized into cytotoxic, interstitial, or vasogenic types:<sup>1-3</sup>

1. Typically seen in cases of, brain metastases, abscesses, trauma, and hemorrhages, vasogenic edema results from structural damage to the blood vessel lining or impaired tight junctions. Furthermore, fluid shifts through a mass flow mechanism, induced by a transmural pressure gradient that causes fluid to escape from cerebral vessels into the brain's extracellular space. This type of edema mainly affects the substantia alba.<sup>3,4</sup>
2. Cytotoxic (intracellular) edema is characterized by the accumulation of fluid within cells due to injury, typically result from exposure to toxic substances (toxicity), a reduction in blood flow to the

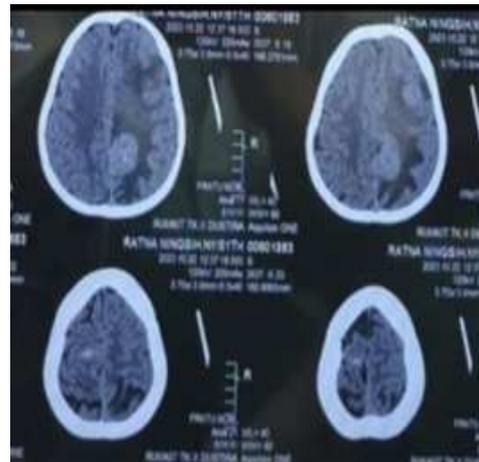
brain (ischemia), or a deficiency of oxygen (hypoxia). Cellular injury disrupts energy production, due to the failure of the sodium-potassium ATPase-dependent pump. This pump failure causes fluid to build up within the cells, resulting in cytotoxic edema.

3. Unlike vasogenic edema, cytotoxic edema affects both substantia grisea and substantia alba. Furthermore, cytotoxic edema can also be triggered by conditions that cause low sodium levels in the blood such as dilutional hyponatremia, acute sodium depletion, inappropriate antidiuretic hormone (ADH) syndrome or by osmotic imbalances within the body, like hemodialysis, or diabetic ketoacidosis. In the early stages, fluid shifts from the extracellular space into the intracellular compartment, without altering brain volume, but eventually, the extracellular and intravascular compartment balance. Cytotoxic edema, which is commonly associated with ischemia and infarction, has a vascular distribution and causes less brain compression.<sup>3,4</sup>
4. Interstitial edema develops when cerebrospinal fluid (CSF) moves into the periventricular substantia alba, usually as a result of obstruction in CSF circulation or issues with its absorption.<sup>3,4</sup>

Blood-brain barrier (BBB) is susceptible to alterations caused by intracranial pathological conditions. Usually, the BBB restricts the passage of large or polar molecules while allowing selective permeability for small hydrophilic ions and nonelectrolytes. However, when the blood-brain barrier (BBB) is compromised, water, electrolytes, and large hydrophilic molecules can infiltrate the brain tissue surrounding blood vessels, resulting in vasogenic edema. In such scenarios, the amount of fluid that leaks into the brain tissue directly correlated to cerebral perfusion pressure (CPP). Vasogenic edema should be distinguished from osmotic edema (resulting from reduced serum osmolality) and cytotoxic edema (caused by ischemic injury). Blood osmolality is a critical factor influencing cerebral edema, as a 19-mmHg pressure gradient across the blood-brain barrier is created for every



**Figure 2: Vasogenic Edema Gaillard F, et al. Radiopedia.org.<sup>7</sup>**



**Vasogenic Edema  
Hospital Data Where We Work**

milliosmole change. On the contrary, oncotic pressure has a minimal impact. Neuroimaging techniques often reveal BBB disruption in various brain tumors. Researchers are exploring new methods to deliver therapeutic drugs directly to the tumor site. Emerging therapies aimed at modulating BBB permeability-such as osmotic BBB disorders and intra-arterial chemotherapy-are under investigation and may significantly influence perioperative management in the future.<sup>3</sup>

Cerebral edema significantly contributes to the symptoms observed in brain tumor patients. While the use of corticosteroids has significantly initially make the management of newly diagnosed tumors much easier, their long-term administration- are often required in cases of relapse-is associated with significant side effects. Consequently, a deeper understanding of the mechanisms underlying the development and resolution of tumor-related edema, aided by advanced imaging and molecular methodologies, is urgently needed. Recently, research has focused on the molecular pathways involved in edema progression, highlighting potential therapeutic targets including the use of vascular endothelial growth factor receptor inhibitors – explored to treat edema.<sup>12</sup>

As previously mentioned, the primary mechanism behind vasogenic edema is increased permeability of blood vessels. A key role of the

blood- brain barrier (BBB) is to stop plasma fluid and proteins from leaking into the brain tissue. This is accomplished by a complex system of endothelial cells, pericytes, and astrocyte end-feet, which form tight junctions that greatly limit

permeability. In addition, these cells exhibit minimal pinocytosis activity. Normally, the brain-blood barrier selectively prevents the passive entry of exogenous hydrophilic molecules exceeding 180 Da into the central nervous system (CNS). However, in pathological states involving BBB disorders, like brain tumors, plasma fluid and proteins can leak out through the disrupted barrier. This leads to swelling, elevated fluid pressure in the tumor, and higher pressure inside the skull.<sup>7</sup> Brain tumors disrupt the balanced interaction of BBB cells disrupted, resulting in the breakdown of this critical protective function. Microscopic examination of the BBB in both primary and metastatic brain tumors have identified abnormalities, including tight junctions, elevated pinocytosis activity, and the presence of fenestration. In addition, the basement membrane becomes thickened and uneven, with weakened pericytes-astrocytes interaction. These changes result in a dysfunctional, hyperpermeable BBB characterized by pores as large as 550 nm in diameter, allowing the leakage of plasma fluid into the central nervous system (CNS).<sup>8</sup>

The exact cause of blood-brain barrier (BBB) disruption brain tumors is still unknown. In the

early stage, brain tumor within the central nervous system expands by growing alongside existing blood vessels, a process called vascular co-option. However, once the tumor reaches a size of 1-2 millimeters, it must induce the formation of new blood vessels, a process known as angiogenesis, in order to continue growing. Tumor-associated angiogenesis is primarily driven by hypoxia, as the existing vascular network becomes insufficient to support the growing tumor mass.<sup>8</sup>

VEGF is the primary proangiogenic peptide contributes to the loss of BBB integrity in brain tumors. Its regulation is observed in gliomas, meningiomas, and metastatic tumors. In addition to hypoxia, excessive VEGF expression can also be triggered by gene mutations and low pH environment. VEGF is generated by both tumor cells and host stromal cells, binding to VEGFR1/2 receptors on endothelial cells. This interaction promotes the formation of gaps between endothelial cells (interendothelial fissures), the breaking apart of endothelial cells (fragmentation), and the development of pores (fenestration). These changes are linked to the deterioration of the basal membrane. These changes lead to fluid leakage into the brain tissue, resulting in edema and elevated interstitial fluid pressure (IFP). In gliomas, levels of VEGF mRNA are strongly associated with capillary permeability and blood vessel density. As the malignancy grade glioma rises, VEGF expression also increases, with high-grade tumors typically exhibiting more significant edema compared to low-grade tumors.<sup>7</sup> The pressure from interstitial fluid caused by edema can result in severe neurological symptoms that are often more debilitating compared to those caused by the tumor itself. This edema may induce specific neurological deficits, and also cause more general symptoms, such as headaches and confusion. In severe cases of increased intracranial pressure, brain herniation and death can occur. Steroid medications help alleviate edema by decreasing vascular permeability, partly by suppressing VEGF expression.

While corticosteroids effectively alleviate brain swelling, their use is associated with many side

effects including sleep disorder (insomnia), mental status changes, muscle weakness (myopathy), bone thinning (osteopenia), high blood sugar (hyperglycemia), and irritation of the gastrointestinal tract. These side effects can significantly impair the quality of life of patients with brain tumors. In addition, higher and potentially more harmful doses of corticosteroids are often necessary to maintain antiedematous effects, underscoring the need for alternative treatments for cerebral edema.<sup>7</sup>

A number of neurological injuries can cause brain swelling. These include traumatic brain injury (TBI), stroke, bleeding in the brain, brain aneurysm, tumors, and infections such as meningitis or encephalitis, as well as seizures. Additionally, certain non-neurological conditions and environmental factors, such as hypertension, hepatitis, Reye's syndrome, carbon monoxide poisoning, and lead poisoning can also contribute to cerebral edema. Certain environmental factors, like exposure to high altitudes, have also been linked to the development of cerebral edema.<sup>7</sup>

### Treatment Protocols and Care Plans

Cerebral edema linked to brain tumors is highly prevalent and can develop in both primary and metastatic tumors. This edema arises from plasma leakage through vessel walls into the brain parenchyma due to blood-brain barrier dysfunction. The clinical manifestations of tumor-related edema depend on the tumor's location and the severity of edema, which often surpasses the mass effect of the tumor itself. If left untreated, brain swelling can cause elevated pressure within the skull (intracranial pressure) and acute herniation syndrome, potentially causing permanent neurological damage or fatal herniation. The care plan for increased intracranial pressure includes: general management, medical treatments, and surgical intervention. While surgical tumor resection remains the definitive treatment for, the role of critical care management is equally critical, requiring vigilant monitoring of patients in the intensive care unit.<sup>7</sup> For decades, glucocorticoids have played a critical role in the management of brain tumor

patients. As one of the most potent classes of drugs, they effectively reduce tumor-induced edema and help mitigate the side effects and risk of encephalopathy in patients receiving radiation therapy. Unfortunately, corticosteroids are linked to numerous adverse effects, posing a significant challenge for patients who require prolonged corticosteroid therapy.<sup>3,4,9</sup> New angiogenesis inhibitors like bevacizumab (Avastin®), which have been increasingly used in cancer patients, are linked to significant steroid-sparing effects. This allows neuro-oncologists to reduce overall corticosteroid use in patients with advancing malignant brain tumors. Recent experimental research has provided new insights into the mechanisms and impacts of corticosteroids in cancer patients, including their effects on tumor biology, angiogenesis and steroid-related neurotoxicity.<sup>10</sup>

Treatment of brain edema involves two key approaches: preventing additional damage caused by the edema and addressing the underlying cause of the brain edema. Ongoing interventions may include correcting metabolic imbalances, managing hypertension, removing intracranial lesions, or shunting hydrocephalus, depending on the etiology of the edema. Edema must be managed to prevent additional damage, and complications including elevated intracranial pressure (ICP) should be minimized.<sup>9</sup> Glucocorticoids therapy has demonstrated promise in treating brain swelling associated with vasogenic mechanism. However, their effectiveness is limited other types of edemas.

They are also generally contraindicated in trauma cases. Additionally, the use of hypotonic fluids is strongly discouraged in patients with cerebral edema, as they can exacerbate the condition and contribute to increased ICP. If cerebral edema leads to elevated ICP, several strategies can be employed to manage ICP. These include positioning, hyperosmolar therapy, antipyretics, sedatives, muscle paralysis, PCO<sub>2</sub> modulation, and surgical intervention.<sup>2,3,10</sup> In cases of severe brain edema following a malignant middle cerebral artery stroke, osmotic agents, like mannitol, can be administered. These agents c

create an osmotic gradient across the blood-brain barrier, which helps to draw fluid from the brain tissue back into the bloodstream, thus reducing the swelling. Mannitol is the primary osmotic agent used, and it is typically given at doses ranging from 0.25 to 1 gram per kilogram of the patient's body weight. Its therapeutic effects are primarily attributed to reducing blood viscosity and, to a lesser degree, decreasing blood volume. However, the use of mannitol can lead to side effects such as osmotic diuresis, dehydration, and kidney injury, particularly if serum osmolality surpasses 320 mOsm.<sup>4,10</sup>

Three percent hypertonic saline is also commonly used treatment for reducing brain edema. It can be administered as a 5 ml/kg bolus or via continuous infusion, with close monitoring of serum sodium levels. This treatment is generally considered safe as long as serum sodium remains below 160mEq/dl and serum osmolality of less than 340 mOsm.<sup>4,10</sup> Decompression craniectomy is a neurosurgical procedure involving the removal of a portion of the skull and dura, creating space for the brain to expand without compression. This intervention is usually reserved as a last resort when all other measures to reduce ICP pressure have failed. When deemed necessary, early implementation of this procedure is recommended for better outcomes. In addition to mannitol, hypertonic saline is a treatment option for cerebral edema, and it is often chosen over diuretics due to its effectiveness.<sup>2,3,10</sup> Other supportive management of cerebral edema includes: extra ventricular drainage of cerebrospinal fluid (CSF), preventing straining and coughing, inducing muscle paralysis in intubated patients, maintaining a straight and elevated neck position to facilitate cerebral blood flow, administering barbiturates to induce coma, minimizing the use of positive end-expiratory pressure (PEEP), and implementing therapeutic hypothermia to reduce brain metabolism. Hypothermia is typically maintained for several days; however, prolonged use increases the risk of systemic infection and hypotension.<sup>2,3,10</sup>

### **Complication**

Cerebral edema can vary from minor cognitive

impairment to life-threatening outcomes. If left untreated, severe brain edema may result in death due to the compression or herniation of the brainstem. Furthermore, significant brain edema can induce widespread brain injury, initiate seizures in susceptible individuals, or cause extensive ischemic brain damage. One of the most life-threatening consequences of cerebral edema is elevated ICP, which can result in herniation and brainstem injury. Severe cases may also cause permanent neurological damage. Furthermore, many of these issues are closely linked to the root causes of the swelling.<sup>1</sup>

### Conclusion

Brain tumor patients frequently suffer complications from, vasogenic brain edema, contributing substantially to morbidity. This is attributable to both the direct pathological effects of edema and the iatrogenic effects of prolonged corticosteroid administration. Peritumoral vasogenic brain edema, in particular, is a significant contributor to both illness and death among individuals with brain tumors. It increases interstitial fluid pressure, which compromises chemotherapy delivery and fosters resistance to therapy.

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