Pathophysiology of Cerebral Edema—A Comprehensive Review

Tara Dalby[1]   Elyana Wohl[2]   Michael Dinsmore[1]   Zoe Unger[1]   Tumul Chowdhury[1]
Lakshmikumar Venkatraghavan[1]

[1]Department of Anesthesia and Pain Medicine, Toronto Western Hospital, University Health Network, University of Toronto, Ontario, Canada
[2]Department of Anesthesia, Notre-Dame Hospital, Montreal, Quebec, Canada

Address for correspondence Lashmi Venkatraghavan, MD, FRCA, FRCPC, Department of Anesthesia and Pain Medicine, Toronto Western Hospital, University Health Network, University of Toronto, University of Toronto 399, Bathurst Street, Toronto Ontario, M5T 2S8, Canada (e-mail: lashmi.venkatraghavan@uhn.ca).

Abstract

Cerebral edema is a condition where an excess of cerebral water accumulates due to primary neurological or non-neurological causes. Cerebral edema complicates many brain pathologies causing additional injury often in excess of the original neurological insult. Classic descriptions divide cerebral edema into cytotoxic, vasogenic, interstitial, and osmotic subtypes. The interplay of different mechanisms is important in the clinical manifestations. Recent research has advanced our understanding of the molecular pathophysiology of cerebral edema, exposing the central role of aquaporins and specific ion channels. The aim of this review is to provide a comprehensive overview of the molecular pathophysiology of cerebral edema including unique disease specific mechanisms.

Keywords
► cerebral edema
► blood–brain barrier
► aquaporins

Introduction

The fluid compartments in the brain and the barriers between them differ significantly from the systemic compartments and are unique to the central nervous system (CNS). Cerebral edema is a condition of excess of fluid in the brain resulting from either neurological or non-neurological causes. Cerebral edema can result from a variety of mechanisms. These include cellular, vasogenic, interstitial, and osmotic mechanisms. Causes of cerebral edema are widespread and can be divided into neurological and non-neurological categories. Neurological causes include ischemia, hemorrhage, hypoxia, trauma, tumors, infections, and hydrocephalus. Common non-neurologic causes include acute hypertension, liver failure, metabolic derangements, and high-altitude cerebral edema (HACE). Cerebral edema affects all age groups, genders, and ethnic groups. Incidence of cerebral edema varies among the individual clinical conditions and the actual frequency is often under-reported due to nonspecific symptoms.

Cerebral edema resulting from various causes have unique patterns based on the interplay of different mechanisms. In addition, in some cases, a combination of these mechanisms can also occur. To understand the different mechanisms for the formation of cerebral edema is crucial for the management of specific types of cerebral edema as well as future developments in disease specific management. Therefore, this review aims to provide a comprehensive overview on the pathophysiology of cerebral edema. In addition, this review also highlights the mechanism of cerebral edema in a few common conditions including focal or global ischemia, intracranial hemorrhage, traumatic brain injury (TBI), liver failure, and high-altitude sickness.

Background

The brain composition has unique anatomical and physiological characteristics.

Fluid Compartments in the Brain

The cerebral fluid compartments have different composition, regulation, and interactions as compared with other body fluids. In contrast to three fluid compartments (intracellular

[ICF], interstitial [ISF], and intravascular) in the systemic circulation, there is an additional cerebrospinal fluid (CSF) compartment in the cerebral circulation (►**Fig. 1A, B**). Among these compartments, the ICF is the largest one accounting for ~70% of the volume,[1] followed by the CSF and intravascular compartments. ISF compartment has negligible volume and it is in continuity with the CSF compartment. The composition and volume of the ICF rely on energy-dependent processes. The Na^+-K^+ ATPase is crucial for maintaining the transmembrane electrochemical gradient that drives other transporters, and thus maintains the cell volume. Cerebral edema occurs when there is expansion of either the ICF and/or ISF, caused by either dysfunction of ion transporter or the membrane barrier. The overall adverse outcomes (morbidity and mortality) of cerebral edema are due to a combination of various mechanisms, including disruption of neuronal transmission, electrolyte derangement, cell death, and ischemia from cerebral compartment syndrome.

Anatomy of the Brain Barrier Systems

The fluid compartments in the brain are normally tightly separated from the systemic circulation by physical and chemical barriers. This sustains a constant internal environment optimal for neuronal function. The barriers include the blood–brain barrier (BBB), the blood CSF barrier, and the outer brain barrier (OBB) (►**Fig. 2**).[2] The integrity of the BBB, which isolates the brain parenchyma from systemic vascular circulation, is the key factor implicated in the development of cerebral edema. The BCSFB and OBB isolate the CSF from the systemic circulation and
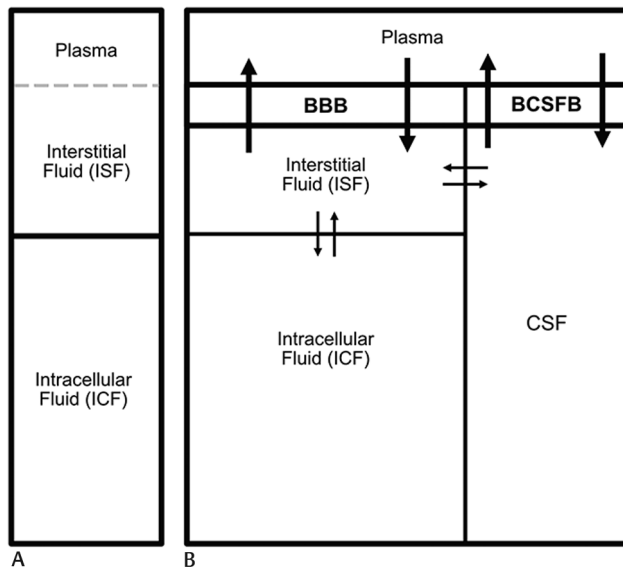
Fig. 2 Fluid compartment barriers within the central nervous system (CNS). The brain barriers isolate the fluid compartments from each other and the systemic circulation. The outer brain barrier (OBB) separates the interstitial fluid from the systemic circulation mainly through the arachnoid barrier cells (ABC), which contain tight junctions (TJ). The blood–brain barrier (BBB) isolates the vascular compartment from the CNS with TJ between endothelial cells. Aquaporin-4 (APQ4) is expressed on the astrocyte foot processes adjacent to the BBB and is involved in water transport intracellularly but not across the BBB. The blood cerebrospinal fluid (CSF) barrier (BCSFC) is formed by TJ between choroid plexus (CP) endothelium. (Reproduced with permission from Nakada T, Kwee IL. Fluid dynamics inside the brain barrier: current concept of interstitial flow, glymphatic flow, and cerebrospinal fluid circulation in the brain. Neuroscientist. 2019; 25:155–166.)

Fig. 1 Systemic and cerebral fluid compartments. Systemic body fluids are separated into 3 compartments (**A**) The majority of water in the body is located in the intracellular fluid compartment (ICF) and the rest is in the extracellular compartment (ECF). The ECF comprises the interstitial fluid (ISF) and the plasma. The brain has 4 fluid compartments, with the additional compartment of the cerebrospinal fluid (CSF) (**B**) The interstitial and CSF compartments freely exchange with one another, not separated by any barrier. The plasma, on the other hand, is tightly separated from the interstitial compartment and the CSF by the blood–brain barrier (BBB) and blood CSF barrier (BSCFB), respectively.
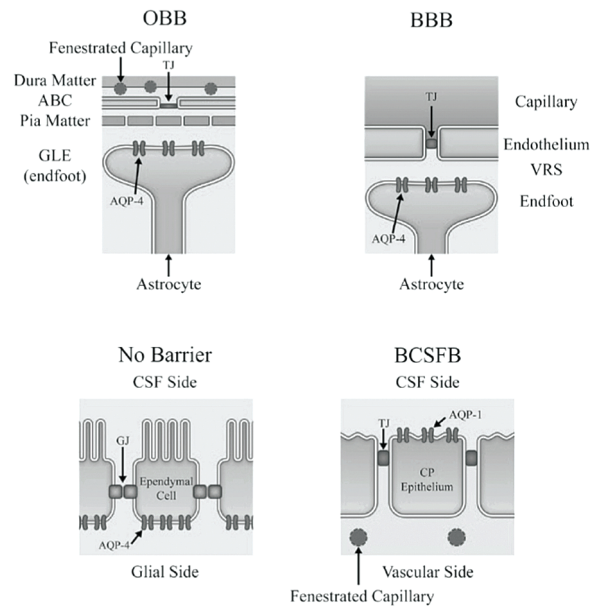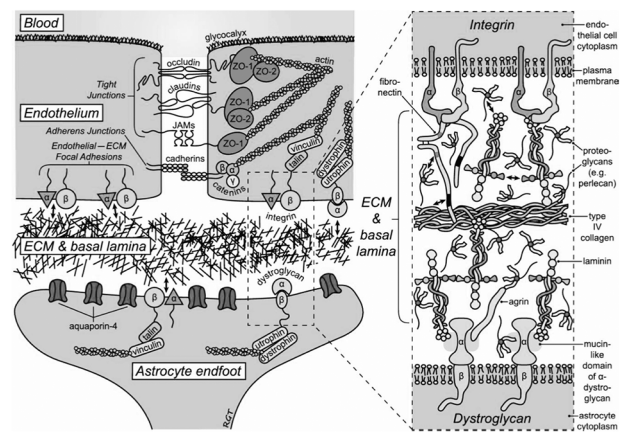
Fig. 3 The blood–brain barrier (BBB). The cerebral endothelium contains tight junctions and has no fenestrations. This restricts paracellular diffusion of water and other molecules from the systemic circulation into the brain. Tight junction proteins such as occludin, claudins, cadherins, zona occludens 1 (ZO-1) and 2 (ZO-2), and junctional adhesion molecules (JAMs) interact with the cytoskeletal components to regulate paracellular diffusion. The glycocalyx provides the first barrier to diffusion, coating the lumen of the endothelium. The final barrier is the extracellular matrix (ECM) and basal lamina, containing type IV collagen. The astrocytes line the BBB with foot processes, expressing aquaporin 4, which permits fluid flux intracellularly. (Reproduced with permission from Abbott NJ, Pizzo ME, Preston JE, et al. The role of brain barriers in fluid movement in the CNS: is there a "glymphatic" system? Acta Neuropathologica. 2018; 135:387–407.)

are formed mainly by the epithelial tight junctions of the choroid plexus, and arachnoid barrier cells, respectively (►**Fig. 2**).[2] The barrier function of the BBB is accomplished by a series of resistors to molecular diffusion, which interact dynamically to regulate the internal environment within the CNS (►**Fig. 3**).

Further to anatomical details, the endothelial surface layer, comprising circulating plasma proteins and the glycocalyx, is the first component of the BBB on the vascular luminal side (►**Fig. 3**).[3] The glycocalyx is a gel-like coating on the endothelial lumen that relies on a constant supply of blood flow for maintenance and regulation, hence blood supply is critical for maintaining a fully functional BBB.[3] The discovery of the glycocalyx has modified our understanding of the Starling forces that drives the diffusion across vascular endothelial walls in vivo. The subglycocalyx has a much lower oncotic pressure than the plasma, and when substituted into the Starling equation, the expected flow with an intact glycocalyx is far less.[4] Interestingly, the cerebral glycocalyx is denser in the brain than in other tissues such as the heart or lungs,[5] suggesting a critical barrier function in the CNS. However, it is also incredibly fragile and can be damaged by ischemia, reperfusion, hyperglycemia, sepsis, inflammation, and shock.[6] Hence, the glycocalyx is implicated in the pathogenesis of cerebral edema of various etiologies.[6]

Fluid flux from the vascular lumen occurs primarily across the interendothelial cell junctions of the capillaries.[3] The capillary endothelial cells are a major component of the physical barrier due to lack of fenestrations and presence of tight junctions and adherent junctions (►**Fig. 3**).[2] Key proteins identified in forming these junctions include claudins, occludins and junctional adhesion molecules.[7] The continuous rather than fenestrated cerebral capillary basement membrane provides yet another barrier fluids must cross to enter the brain.[2] Thus, the endothelial cells provide the major physical barrier in maintaining CNS integrity.

Astrocytes are involved in forming the CNS side of the BBB and additionally provide a lymphatic-like clearance mechanism within the brain (►**Fig. 3**).[1] Each astrocyte extends at least one foot-process to contact and envelop a capillary surface.[1] These end-feet contain transport channels regulating the entry of nutrients into the CNS.[5] The water channel aquaporin 4 (APQ4) is densely expressed on the end-feet, effectively lining the BBB and BCSFB.[2,5,8] APQ4 has a critical roles in water regulation, nutrient sensing, and delivery in the brain.[2,8] The movement of fluid through the brain via astrocytes and specifically the APQ4 has been described as lymphatic-like, or a "glymphatic" system.[1] This system is essential in not only the formation but also the clearance of cerebral edema.

Intracranial Compliance

Cerebral edema can lead to a cerebral compartment syndrome. The intact skull is nonexpandable; therefore, as per the Monro-Kellie doctrine, the net volume of its contents, blood, CSF, and brain tissue, remains constant.[9] In cerebral edema as the volume of brain parenchyma increases, CSF translocation and a reduction in intracranial blood volume occur to compensate. If the increase is rapid, these compensatory mechanisms may be overwhelmed, leading to cerebral ischemia from both reduced blood flow and a sudden increase in intracranial pressure (ICP). It starts a vicious cycle of malignant ICP that can lead to herniation: the compression of vital brain stem structures through the foramen magnum and ultimately death.

Clearance of Fluids from the CNS

The mechanism of fluid clearance from the CNS remains incompletely understood. Fluid clearance is important for protecting against the development of cerebral edema and in promoting its resolution. Excess water may leave the CNS either via bulk flow down a pressure gradient perivascularly,[10] or via the astral-glial, or glymphatic system.[1] One of the important routes for removal of excess ISF from the brain is via fluid tracks along the basement membrane in the walls of capillaries to the cervical lymph nodes.[10] The glymphatic system refers to a dynamic lymphatic-like network of APQ4 expressing astrocytes involved in fluid clearance (►**Fig. 4**). The glymphatic flow has diurnal variations, with flow highest during sleep.[11] APQ4 knockout studies have demonstrated differences in the involvement of APQ4 in the edema formation and clearance between the brain and the spinal cord.[12] In animal models of cerebral edema caused by inflammation, upregulation of APQ4 is associated with worse edema in the acute phase; however, upregulation also promotes the resolution of edema in the subacute phase by increased clearance and inhibition of microglial activation.[13] Clearance of fluid through the glymphatic system may yet prove an important modifiable factor in cerebral edema management.
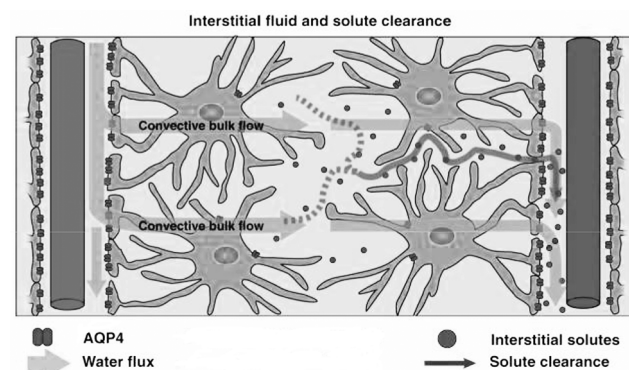

Fig. 4 "Glymphatic" flow of fluid in the brain. Aquaporins are present on the end-feet of astrocytes lining the cerebral capillaries. Water flows from the interstitial space into astrocytes down an osmotic gradient. Water continues to follow the movement of ions within the astrocyte, eventually exiting the intercellular space back into the interstitial space via aquaporins. Excess fluid is eliminated from the brain via a paravenous route, tracking along the basement membrane along the capillary wall eventually draining to the cervical lymph nodes. (Reproduced with permission from Lliff JJ, Wang M, Liao Y et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid B. Sci Transl Med. 2012; 4:147.)

Molecular Mechanisms of Cerebral Edema

Accumulation of excess fluid in the brain may arise from dysfunction of the cell membrane (cytotoxic edema), damage to the BBB (vasogenic edema), outflow of CSF from intraventricular space to the interstitial space (interstitial edema), and due to water being pulled from the plasma by the brain cells due to osmotic derangements (osmotic edema) (►Table 1).[1,14,15] Among these mechanisms, cytotoxic and vasogenic processes are the main pathological forces driving common brain pathologies. These mechanisms tend to co-exist due to the symbiotic dependence of an intact BBB with adequate cerebral perfusion and a healthy astro-glial system.

Cytotoxic Cerebral Edema

Cytotoxic edema develops when an osmotic gradient results in water movement from the ISF to the ICF, particularly into the astrocytes.[16] An osmotic gradient is established in the context of an intact BBB from the accumulation of ions within the ICF, due to ion transporter dysfunction, which is characteristic of cerebral ischemia. Failure of the adenosine triphosphate (ATP) dependent Na^+-K^+ ATPase is a common endpoint of many acute CNS pathologies. The Na^+-K^+ATPase is critical for maintaining the transmembrane electrochemical gradient; its subsequent failure leads to membrane depolarization.[17] Following depolarization, excitatory neurotransmitters are released, causing Na^+ and Ca^{2+} influx through ligand gated channels with water following. This leads to volume overload of the cells. Activation of second messenger cascades following Ca^{2+} influx eventually leads to apoptosis.[17] Furthermore, Na^+ continues to enter the CNS (across the endothelial cell) into the ISF by cation channels, with Cl^- and water following their electrochemical and osmotic gradients, respectively.[18] The Na^+-K^+-Cl^-cotransporter-1 (NKCC1) of astrocytes and endothelium is one such important cation channel. NKCC1 is upregulated in acute brain injury and a key molecular target for therapy through the inhibitor bumetanide.[14,15,19] Influx of ions and hence water through this process leads to a net increase in tissue mass despite an intact BBB. The astrocytes, which express APQ4, preferentially swell in cytotoxic edema thus implicating APQ4 in water influx in the acute phase of cytotoxic edema.[20,21] In addition, the monovalent cation channel sulfonylurea receptor 1 transient receptor potential melastatin 4 (SUR1-TRPM4) is involved in cytotoxic edema formation.[22] The TRMP4 pore-forming unit is activated by high intracellular calcium or very low ATP, with pore sensitivity to calcium modulated by transmembrane receptor SUR1.[22] SUR1-TRPM4 normally aids in calcium homeostasis by allowing cation influx when intracellular calcium is high, thus reducing the electrical gradient for further calcium influx. However, under conditions of very low intracellular ATP such as ischemic injury, the channel is activated leading to cell swelling, membrane blebbing, and eventual rupture.[23,24] SUR1-TRPM4 is normally not present in healthy neuronal or vascular tissue but it is upregulated following injury from trauma or ischemia.[22] Further, it is associated with the membrane APQ4, linking the ion and water influx in pathological conditions.[25] Thus, cytotoxic edema is primarily due to failure of ion homeostasis, leading to fluid shifts from the ISF to the ICF.

Vasogenic Cerebral Edema

Vasogenic edema is the result of BBB disruption causing the extravasation of serum proteins into the interstitial

Table 1 Classification of cerebral edema

	Cytotoxic	Vasogenic	Interstitial (hydrocephalic)	Osmotic
Primary mechanism	Metabolic failure	BBB breakdown	CSF accumulation and overflow into extracellular space	Osmotic derangement
Pathophysiology	Failure of the Na^+-K^+ ATPase → influx of ions, (particularly Na^+) & water → expansion of ICF and volume overload occurs in all cells (neurons, glia, endothelial cells)	BBB integrity is disturbed → increased capillary permeability allowing fluid, an ultrafiltrate of plasma, to accumulate in the ISF	Volume of CSF increases due to imbalance of production and clearance → increased intraventricular pressure →transependymal flow of CSF periventricular extracellular space	Relatively lower plasma osmolarity to intracerebral osmolarity creates an osmotic gradient → water diffusion across BBB into ISF
Etiology	Anoxia, ischemia, trauma, liver failure	Tumors, Ischemia (late stages), ICH, trauma, infections, high-altitude Cerebral edema	Hydrocephalus, meningitis, pseudotumor cerebri	Hyponatremia, SIADH and other metabolic pathologies
Contents of edema	Water, sodium, no protein	High protein fluid	CSF, low protein	Water, no protein
Location of edema	Within both gray and white matter	Predominantly in the white matter	Periventricularly and within the white matter	Within the white matter
BBB integrity	Intact	Breakdown	Intact	Intact

Abbreviations: BBB, blood–brain barrier; CSF, cerebrospinal fluid; ICF; intracellular fluid; ISF, interstitial fluid; ICH, intracerebral hemorrhage; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

space.[14] Hydrostatic forces perpetuate vasogenic edema in contrast to osmotic gradients as in cytotoxic edema. Breakdown of the BBB can be due to various causes including uncontrolled hypertension, inflammation, infection, ischemia, and neoplasms. Acute CNS injury, including cytotoxic edema, causes transcriptional changes in the neurovascular unit leading to creation of "endothelial permeability pores"[14] and eventually leading to BBB breakdown. Several vascular permeability factors and membrane receptors have been identified as therapeutic targets. The endothelin-receptor B (ET_B-R) induces a reactive state in astrocytes resulting in the upregulation of matrix-metalloproteinases (MMPs), that degrade extracellular matrix, and vascular endothelial growth factor (VEGF), which disrupts tight junction proteins on endothelial cells.[19] The SUR1-TRPM4 channel is also implicated in the development of vasogenic edema. SUR1-TRPM4 is upregulated in neural and vascular tissues following CNS injury, contributing to BBB dysfunction.[26] Hence, vasogenic and cytotoxic edema often occur together as one leads to the other. The interplay of the molecular mechanisms in various clinical scenarios is summarized in ►Table 2. Differences in imaging between vasogenic and cytotoxic edema are shown in ►Supplementary Figure S1 (available in the online version).

Pathophysiology and Mechanisms of Cerebral Edema in Common Clinical Conditions
Acute Ischemic Stroke

Table 2 Mechanism of cerebral edema in various clinical scenarios

Condition	Type of cerebral edema	Molecular mechanism and evolution
Acute ischemic stroke	Cytotoxic and then vasogenic	• Focal ischemia and damage to cerebral endothelium • Failure of Na^+-K^+ ATPase → Na^+ and Ca^{2+} influx through ligand gated channels with water following • Hypoxia inducible factor gene activation→ upregulation of SUR1-TRMP4 • Vasogenic edema occurs over days to weeks caused by ischemic damage to the BBB • Vasogenic edema is worse if reperfusion occurs after prolonged ischemia
TBI	Vasogenic and then cytotoxic	• Mechanical shearing with primary impact—immediate diffuse BBB disruption—early vasogenic edema (maximal at 4–6 hours) • Early contusional edema from cell necrosis • Late vasogenic edema (5 days)—inflammation due to microglial activation • Cytotoxic edema (hours to days)—neuronal ischemia due to increased ICP from vasogenic edema, deranged neuronal metabolism, exacerbated by hypoxia and hypotension • Upregulation of SUR1-TRMP4 exacerbates ion and water influx
ICH	Vasogenic and cytotoxic	• Hematoma coagulates and retracts–hydrostatic pressure draws in fluid from vasculature (1–4 hours) • BBB breakdown due to inflammation secondary to the presence of blood clot (early vasogenic edema first 72 hours) and breakdown products (late vasogenic edema—after 72 hours) • Increased ICP surrounding hematoma and edema→ microvascular compression → ischemia → cytotoxic edema
SAH	Cytotoxic and vasogenic	• Global cerebral edema not universal-associated with severe ischemic injury on aneurysm rupture • Widespread ischemic injury and microvascular disruption→ cytotoxic edema • Neuroinflammation- microglial activation and leucocyte infiltration→ cytotoxic edema • SUR1-TRMP4 upregulation • Endothelial damage→ vasogenic edema
Peritumoral	Vasogenic	• ↑BBB permeability by substances secreted by tumor cells—mainly VEGF and also by MMPs, leukotrienes, prostaglandins, nitric oxide • ↓ Expression of tight junctional proteins in adjacent endothelium • Mast cell activation→ inflammation → vasogenic edema • Dexamethasone suppresses VEGF production among other mechanisms such as reducing cytokine and inflammatory-mediated BBB breakdown

(*continued*)

Table 2 (*continued*)

Condition	Type of cerebral edema	Molecular mechanism and evolution
Fulminant liver failure	Cytotoxic and vasogenic	• Ammonia accumulation in mitochondria of astrocytes→ oxidative stress • Ammonia→ activates microglia leading to inflammation • Hyponatremia worsens cerebral edema
Global ischemia	Cytotoxic and vasogenic	• Similar to acute ischemic stroke but more diffuse • Following reperfusion-period of mismatched oxygen demand and delivery leads to ongoing ischemia • Vulnerable areas–hippocampi, thalamus, cerebral cortex, corpus striatum and cerebellar vermis
High-altitude cerebral edema	Vasogenic	• ↑ Cerebral blood volume and BBB permeability • ↑ Cerebral blood flow in response to reduced P_aO_2 • ↑ Arterial inflow→ compression of venules ↓ venous outflow • Microbleeds in corpus collosum suggest BBB breakdown
Infectious	Vasogenic, cytotoxic and interstitial	• Encephalitis, meningitis, or abscess→ inflammation →BBB breakdown • Microglial activation and leucocyte infiltration→ cytotoxic edema • Meningitis may→ damage to the CSF outflow pathway → transependymal extravasation of CSF
Hydrocephalus	Interstitial	• Obstruction of CSF efflux→ transependymal extravasation of CSF
Hyponatremia	Osmotic	• Water moves down an osmotic gradient into CNS
Radiation-induced edema	Vasogenic	• Cell death from targeted radiation→ inflammation • Reactive astrocytes express VEGF→ ↑ BBB permeability
Postsurgical edema	Vasogenic and then cytotoxic	• Mechanical disruption of cells and vessels at the time of surgery→ inflammatory cascade → increased BBB permeability • Perilesional hypoxia secondary to vasogenic edema→ cytotoxic edema

Abbreviations: BBB, blood–brain barrier; ICP, intracranial pressure; MMPs, matrix metalloproteinases; SUR1-TRMP4 sulfonylurea receptor 1 transient receptor potential melastatin 4 channel; VEGF, vascular endothelial growth factor.

Cerebral edema remains a leading cause of death in patients with massive ischemic infarcts. The amount and type of edema depend on the ischemic duration, severity, and the presence/timing of reperfusion. Deaths occurring days after stroke are often related to edema and progressive herniation.[27] Cerebral edema due to ischemic stroke is primarily caused by cytotoxic edema, followed, and exacerbated by vasogenic edema. Following acute ischemia, anaerobic metabolism is inadequate to meet metabolic demands and intracellular ATP is rapidly depleted leading to failure of the Na^+-K^+ATPase leading to cytotoxic edema.[17] The SUR1-TRPM4 channel is expressed in human brain specimens postinfarction and is likely a major contributor to the development of cerebral edema following focal ischemia.[26] The underlying mechanism involves activation of the gene hypoxia inducible factor 1.[24] Additionally, promising retrospective studies on humans and animal models of sulfonylurea drugs that inhibit the SUR1-TRPM4 appear to have better outcomes (mortality and functional independence) following ischemic stroke.[23,24]

The edema occurring during ischemia is initially limited by the intact BBB. Animal studies have shown that cytotoxic edema forms within 15 minutes of ischemia onset as water moves into the ICF. This is seen on diffusion-weighted magnetic resonance imaging(MRI) as reduced apparent diffusion coefficient.[28] There is a linear correlation between the extent of reperfusion and the amount of edema formation,[27] likely due to exacerbation of cytotoxic edema from BBB breakdown and vasogenic edema. Animal studies have shown edema is worse if reperfusion occurs after 3 hours of ischemia versus 1 hour.[29] The vasogenic edema follows a different time course, with maximal fluid extravasation 3 days to 2 weeks postischemic insult.[27] The mechanism of BBB damage at the level of the endothelial cell involves tight junction disruption.[27] In embolic stroke, vascular damage also occurs at the site of embolism due to infarction of the vessel wall, and more distally through ischemic damage to the endothelium.[27] Thus, the mechanism of edema in acute ischemic stroke is both cytotoxic and vasogenic, the degree of which is greatly influenced by the timing of reperfusion.

Traumatic Brain Injury

TBI is the result of mechanical and shearing forces in the brain, causing vascular, neuronal, and/or axonal damage. The extent of edema is the biggest predictor of outcome following TBI and accounts for up to half of the associated morbidity and mortality.[30] Here, both vasogenic and cytotoxic mechanisms contribute to the formation of edema at different time points and to varying extents. Mechanical disruption of the BBB occurs immediately during and following primary impact. "Contusional edema" that develops surrounding the damaged necrotic area is from an osmotic gradient established by cellular apoptosis.[29] Endothelial cells undergo cytoskeletal

changes with degradation of tight junction and activation of inflammatory cascades following impact.[31] This causes a diffuse BBB breakdown. Substance P, calcitonin G-related peptide, MMPs, and VEGF are key in producing vasogenic edema through promoting vascular permeability.[29,32] The transient increased BBB permeability is maximal at 4 to 6 hours post injury.[30] The second peak in BBB permeability occurs at 5 days post injury, potentially due to microglia activated by inflammatory cascades.[31]

Neuronal ischemia and metabolic disturbances following TBI lead to cytotoxic edema progressing from 1 hour to 7 days after the injury.[29,30] As in acute ischemic stroke, vasogenic edema exacerbates the cytotoxic edema. The fluid and proteins extravasated into brain ISF and the associated increased ICP lead to the occlusion of small vessels, perpetuating further ischemic damage.[31,33] SUR1-TRPM4 is upregulated in rat models of diffuse TBI, peaking at 6 hours, and its expression associated with astrocyte swelling.[34]

Intracranial Hemorrhage

Intracranial hemorrhage occurs from intracerebral hemorrhage (ICH), bleeding within the brain parenchyma; subarachnoid hemorrhage (SAH), bleeding into the subarachnoid space; or intraventricular hemorrhage (IVH), extension of bleeding into the ventricles mostly associated with ICH or SAH.[7]

Intracerebral Hemorrhage

ICH carries a high burden of morbidity and mortality. The initial injury causes irreversible damage to the surrounding brain parenchyma. The ensuing cerebral edema results in secondary injury of magnitude that may be far greater than the initial cause.[35] Peak perihematomal edema (PHE) correlates with a poor functional outcome.[35]

PHE develops from a conglomeration of hydrostatic, cytotoxic, and vasogenic mechanisms with a distinctive time-course.[36,37] The early (1 to 4 hours) phase of edema is due to perihematomal hydrostatic pressure changes.[36,37] The coagulation cascade is activated causing the blood to clot and retract. Hydrostatic pressure reduces surrounding the clot, leading to fluid influx from the vasculature.[36] In addition, microvascular compression from raised ICP leads to hypoperfusion that then triggers cytotoxic mechanisms.[37] The initial breach in BBB and extravasation of blood products activates mast cells within seconds, leading to inflammatory cascades involving activated microglia, astrocytes and driving neutrophil and leukocyte infiltration.[38] In the intermediate period (4–72 hours), thrombin activation is the major driving force behind inflammatory cascades and also directly interfering with endothelial cell interactions disrupting the BBB, perpetuating vasogenic edema.[36] The inflammatory response is important in hematoma resolution in addition to exacerbating edema.

The late stage (>72 hours) of PHE is due to the toxic breakdown products of the clot.[37] Erythrocyte lysis occurs following complement activation, leading to the presence of free hemoglobin, a potent neurotoxin.[39] Cell death occurs through inhibition of the Na^+-K^+ ATPase, free radical formation, and lipid peroxidation.[36] Peak PHE volume is reached between day 8 and 12 post initial injury,[7,35] with the PHE causing the volume of the lesion to increase as much to 150%.[36]

Subarachnoid Hemorrhage

SAH is most often the results from the rupture of an aneurysm. Acute injury is associated with a surge in ICP, followed by secondary or delayed injury.[40] Global cerebral edema occurs in a subset of patients and is an independent predictor of mortality.[41] The mechanism of global cerebral edema following SAH is unclear, and an MRI study 72 hours post injury suggests a combination of vasogenic and cytotoxic mechanisms.[41,42] It may have a biphasic time course, with some patients showing edema on initial presentation (6–8%) and others developing edema later in the course of the disease (12%).[41] At the time of aneurysm rupture, ICP surges, causing a temporary arrest of cerebral perfusion causing widespread ischemic injury and leading to global edema.[40,43,44] The causative factors for edema may relate to the ischemic tissue and microvascular injury during cerebral circulatory arrest.[41] Delayed cerebral edema is positively associated with the use of hypertensive therapies, and is potentially caused by cerebral ischemia.[41] Another causative mechanism may be "neuroinflammation," manifest as microglial activation and leucocyte infiltration leading to cytotoxic edema independent of ischemia.[43] Widespread endothelial damage occurring immediately after SAH results in vasogenic edema.[44] Expression of integral BBB proteins is reduced in animal models of SAH, such as endothelial tight junction proteins (occludins, claudin 5 and zona occludens-1 [ZO-1]) maximal at 24 to 48 hours post ictus, with ZO-1 and occludins having a second reduction after 72 hours.[7] MMP blockade reduces the vasogenic edema associated with SAH.[43] Early vasogenic edema seen on diffusion weighted MRI correlates with the Fischer grade, implicating the presence of blood products in developing vasogenic edema.[42] The SUR1-TRMP4 channel is also upregulated in both human and animals following SAH.[45] Inhibition of the channel with glibenclamide in a rat model of SAH leads to reduction in inflammatory markers such as tumor necrosis factor α (TNF-α) expression, SAH-induced immunoglobulin G, and post SAH cognitive impairment.[45] While APQ4 is upregulated in animals and humans following SAH, animal knockout models and blockade experiments show conflicting results regarding edema formation.[43] The cerebral edema associated with SAH is a mixture of cytotoxic and vasogenic mechanisms, caused by widespread ischemic and inflammatory insults.

A major complication of SAH is delayed cerebral ischemia (DCI) occurring at 5 to 14 days after initial injury and responsible for a large amount of the associated morbidity and mortality.[40,41] Etiopathogenesis of DCI may be related to increased BBB permeability, spreading cortical depolarization, loss of cerebral autoregulation, microthrombosis, and microcirculatory changes.[46,47] The relationship with cerebral edema is unclear; however, early brain edema is a predictive factor for the development of DCI.[48]

Intraventricular Hemorrhage

IVH, rarely an isolated occurrence, is usually an extension of SAH or ICH into the ventricles.[7] IVH may occur in the premature infant, as the periventricular germinal matrix is fragile with an immature BBB; a deficient basement membrane, underdeveloped endothelial tight junctions, and incomplete coverage of capillaries by astrocyte end feet.[7,42] The main pathophysiological consequence leading to edema is hydrocephalus—accumulation of CSF due to impaired drainage. Vasogenic edema may also occur, as animal models of IVH through injection of blood or collagenase into the ventricles result in BBB disruption.[7]

Brain Tumors

Brain tumors (malignant gliomas, metastases, and meningiomas) are associated with cerebral edema. The amount of cerebral edema can be extensive, leading to focal neurological deficits, coma, and the patient demise. Vasogenic edema from disruption of the microvasculature appears to be the primary mechanism in peri-tumoral cerebral edema (PTE).[49]

Tumor cells secrete VEGF that increases BBB permeability.[49,50] VEGF expression is also upregulated in brain tumors that are prone to edema.[51] Notably, messenger ribonucleic acid levels of VEGF correlate with edema severity in meningioma.[50] Conditions within the tumors, such as hypoxia and acidosis, can further increase VEGF expression, leading to widening of interendothelial gaps and creating fenestrations in the basement membrane.[49,52] Dexamethasone suppresses VEGF production[50] among other mechanisms such as reducing cytokine and inflammatory-mediated BBB breakdown.[49] This may account for the unique role of steroids in cerebral edema-associated with tumors. Other factors contributing to increased BBB permeability in PTE are the leukotrienes, prostaglandins, nitric oxide MMPs, and mast cells activation.[53]

The vasculature of malignant tumors has abnormal structure, contributing to vasogenic edema. Endothelium adjacent to high-grade glial tumors has reduced expression of the tight junction proteins claudins and occludins, abnormal tight junctions as well as fenestrations that are incompletely covered by an irregular basal lamina.[51] Aggressiveness of the tumor correlates better with the volume of the edema than the size of the tumor itself.[51,54] Dexamethasone treatment has been shown to upregulate tight junction proteins such as claudin, occludin, and ZO-1 in vitro,[49] which may be an additional mechanism for its profound effect on PTE. Aquaporins of various subtypes tend to be overexpressed in brain tumors and their adjacent vasculature,[49] with a strong correlation between aquaporin expression and tumor grade.[55] In addition to water balance regulation, aquaporins have been shown to facilitate cell migration, proliferation and cell adhesion, which is pertinent to tumor biology.

Fulminant Liver Failure

Cerebral edema occurs in 80% of patients with fulminant liver failure and is a leading cause of death.[56] Although ammonia accumulation in the astrocytes is the most vital factor in the pathophysiology of cerebral edema in fulminant liver failure,[56] other factors including damage to the BBB, inflammation, and hyponatremia also play an important role.[57]

Accumulation of ammonia in astrocytes follows the failure of hepatic detoxification mechanisms. Astrocytes contain the enzyme glutamine synthetase, which converts ammonia to glutamine, a precursor for the excitatory neurotransmitter glutamate.[56] Accumulation of ammonia within the mitochondria leads to oxidative stress, and release of reactive oxygen species.[58] Additionally, microglia in contact with ammonia release proinflammatory cytokines TNF-α, interleukin-1, and interleukin-6 leading to activation of further microglia and establishing an inflammatory cascade, ultimately causing disruption of the BBB and promoting further cytotoxicity.[56,57] The contribution of vasogenic edema in the setting of fulminant liver failure remains inconclusive, as animal models have not yet demonstrated clear evidence of BBB breakdown.[59]

Hypoxic–Ischemic Cerebral Edema

Hypoxic–ischemic injury occurs following a sufficient period of asphyxia depriving the brain of oxygen. These events occur in situations such as adult cardiac arrest, or perinatally during complicated labor and delivery (e.g., umbilical cord around the neck), potentially leading to life-long neurological deficits. The resultant cerebral edema is by both cytotoxic and vasogenic mechanisms similar to acute ischemic stroke, but occurs more diffusely. The brain is subject to ongoing ischemic injury even after flow is re-established due to mismatch in demand and delivery of oxygen. This phenomenon, called "no-reflow," may be due to disruption of microvascular control mechanisms and/or vasoconstrictive levels of extracellular K^+.[60] Highly metabolically active areas such as hippocampi, thalamus, cerebral cortex, corpus striatum, and cerebellar vermis are particularly vulnerable to damage.[60] Activated microglia, microvascular thrombi, and inflammatory cytokines exacerbate vasogenic edema.[61] The length of circulatory arrest is the most important marker of extent and severity of cerebral damage. During fetal development, cerebral autoregulation develops between 23 and 33 weeks, placing premature infants at higher risk of ischemic damage than term infants.[62]

High-Altitude Cerebral Edema

HACE is a severe consequence of acute mountain sickness, caused by low partial pressure of oxygen at altitude, resulting in a hypoxic hypoxemia in un-acclimatized individuals. This may adversely affect those with reduced ability to compensate for the hypoxia induced increase in cerebral blood volume.[63] The disease is rare, difficult to investigate, and the mechanisms are therefore not fully understood.

HACE appears to be vasogenically mediated through increased cerebral blood volume and BBB permeability. The vasogenic nature is supported by the extensive microhemorrhages within the corpus callosum and good response to steroids,[64,65] with inflammatory pathways involving VEGF, nitric oxide, and vasopressin playing a role.[64] A study by Sagoo et al[63] has significantly increased our understanding

of this disease. They studied the MRI of 12 human subjects breathing a hypoxic oxygen mixture over a period of 22 hours, simulating the conditions inducing HACE. The first observation was an increase in arterial inflow, preceding the development of cerebral edema. The authors also found a reduction in venous outflow, likely due to compression of small intracerebral venules and veins as edema develops, contributing to and exacerbating the edema. HACE is a potentially fatal, severe consequence of high altitude, with a unique pathophysiology.

Conclusion

Cerebral edema is the endpoint of a vast number of brain pathologies and causes secondary neurological damage, which is potentially fatal. Cytotoxic and vasogenic mechanisms synergistically produce the clinical picture of cerebral edema associated with the various etiologies. In-depth understanding of pathophysiology of cerebral edema remains the cornerstone for managing such cases and this knowledge is also crucial to develop future diagnostic as well as therapeutic modalities for patients with cerebral edema and related disorders.

Conflict of Interest
None declared.

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