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REVIEW ARTICLE

Post-Traumatic Cerebral Edema: Pathophysiology, Key Contributors, and Contemporary Management

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ABSTRACT

The development of cerebral edema following traumatic brain injury is one of the most significant predictors of outcome and is associated with high rates of morbidity and mortality. A prominent focus of neurosurgical and neurocritical care is the evaluation and aggressive management of cerebral edema and subsequent intracranial hypertension. Despite numerous advances and capabilities in neurocritical care, treatments remain primarily reactive and are instituted only after secondary pathophysiological pathways have culminated in an intracranial pressure crisis. Recent reviews have focused on several key molecular contributors to post-traumatic cerebral edema and on several potential anti-edema therapeutic targets. The present article provides a contemporary overview of post-traumatic cerebral edema by reviewing important historical concepts, fundamental pathophysiological mechanisms, various causes and key contributors specific to traumatic brain injury, and established treatments of downstream intracranial hypertension.

1. Introduction

Traumatic brain injury (TBI) is a leading cause of death and disability worldwide.[1] Each year in the United States, nearly 2 million individuals sustain a TBI resulting in nearly 52,000 deaths.[2] Post-traumatic brain swelling accounts for nearly 50% of all TBI mortalities, and cerebral edema (CE) remains the leading cause of in-hospital mortality despite numerous neurosurgical and neurocritical care advances.[3] Established early interventions aim to minimize the downstream consequences of CE by prioritizing intracranial pressure (ICP) monitoring and optimization of body temperature, analgesia, ventilation, and electrolytes. While these interventions have possibly improved patient outcomes over the past 50 years, they remain largely non-specific for the underlying driving forces that promote edema formation.[4-6]

Post-traumatic edema formation is a complex heterogenous process influenced by the nature of the primary injury, patient characteristics, and additional systemic injuries. Numerous advances have improved our understanding of edema formation following TBI. Yet, a comprehensive understanding of the networks underling CE in TBI remains in an early stage of development. This, in turn, translates to a paucity of anti-edema drugs available in clinical practice with no targeted treatments for post-traumatic CE currently available. Several recent reviews have introduced novel pathways implicated in edema formation and drugs with theoretical benefit for targeting edema in TBI.[2,7] In this review, we discuss established and proposed molecular contributors to post-traumatic CE, as well as review standard practices to mitigate and treat downstream intracranial hypertension. Potential anti-edema drugs will be briefly introduced, highlighting future therapeutic targets. We thus aim to provide contemporary overview of the pathophysiology and treatment of post-traumatic CE and highlight the complexity that has limited the development of targeted therapeutics.

2. History

The challenges confronting physicians and patients combating malignant post-traumatic CE have been described since the inception of neurosurgery and neurocritical care.[4] In 1942, G.F. Rowbotham wrote "I have occasionally found the brain, in the acute phases of a head injury, under such great tension that it bulged into the wound as soon as the dura was opened".[8] In 1901, Cannon proposed that increased ICP can impair cerebral blood flow (CBF) and that the injured brain has increased osmotic pressure resulting in an influx of water. The first use of hypertonic saline to "shrink" brain tissue was reported by Weed and McKibben in 1919.[9] Wise and Charter first described the use of mannitol to decrease brain mass in 1962.[10] The pathophysiology of brain edema in the first half of the 1900s remained poorly understood, but in 1967 Igor Klatzo described the concept of "cytotoxic" and "vasogenic" edema – nomenclature that remains widely used today.[11] The development of molecular biology techniques in the 1980s catalyzed the investigation of molecular mediators of

cerebral edema. With regards the TBI, the heterogeneity of insults, patient characteristics (including host-response), and systemic injuries have limited the development of a unified pathophysiological understanding of post-traumatic CE. Throughout the 2000s and today, numerous investigations continue, aimed at establishing a mechanistic approach to understanding and ultimately treating CE in TBI.[12]

3. Cerebral Edema in Traumatic Brain Injury – An Overview

Post-traumatic neurological dysfunction results from a complex cascade of pathophysiological pathways leading to the evolution of brain injury. Direct impact, rotational forces, penetrating trauma, and/or blast waves cause immediate, primary injury characterized by extra- and intra-axial hemorrhages, diffuse axonal injury, tissue crushing wounds, and cerebral vasculature dysfunction. This primary injury then catalyzes diverse pathophysiological responses in the ensuing hours to days, collectively termed secondary injury. While primary injury, short of prevention, is largely non-modifiable, the secondary injury cascades present multiple potential therapeutic targets. Importantly, the end result of many secondary injury cascades is a pathologic net increase in brain tissue water content, otherwise known as CE, which has a profound impact on prognosis including mortality following TBI.[13]

The close relationship between CE, intracranial hypertension, and functional outcome in TBI has been recognized for centuries.[14] In accordance with the Monro-Kellie doctrine, an increase in brain volume as a result of CE can rapidly lead to increased ICP. The extent and time course may vary based on individual compliance/elastance curves. However, unchecked ICP ultimately compresses brain vasculature and reduces cerebral perfusion, eventually causing ischemia, irreversible brain injury, herniation, and death.[15] In severe TBI, increased ICP and radiographic measures of CE correlate with increased mortality and poor functional outcome.[13,16-21] ICP elevations following TBI are common. As many as 45–80% of TBI patients subsequently develop ICP elevations above the accepted threshold of 20–22 mmHg.[22] In addition, the "dose" of elevated ICP appears significant. In a retrospective study of 135 patients with severe TBI, Vik et al. reported a significant relationship between the "dose" of ICP, worse CT findings, and unfavorable patient outcomes including death and disability.[23]

Today, the downstream effects of CE, namely intracranial hypertension and mass effect, remain the target of approved interventions and a mainstay of the Brain Trauma Foundation guidelines.[24] But while ICP-focused treatment has reduced mortality, benefits regarding functional outcome remain unclear.[25-29] It is possible that the treatment of elevated ICP by itself incompletely addresses the multiple mechanisms underlying CE, and a paradigm shift to include treatments addressing CE-specific pathways may present new therapeutic targets. Indeed, depending on cerebral compliance, CE may not manifest as intracranial hypertension despite

deleterious molecular cascades causing secondary injury. To better understand contemporary management of post-traumatic CE, the following sections will discuss CE as a direct result of several pathophysiological processes, discuss some of the better studied contributors specific to trauma, and review established treatments.

4. Pathophysiology of Cerebral Edema

CE is the manifestation of several processes including a maladaptive program of protein expression and function, triggered by acute CNS injury. These go beyond the acute osmolar forces of central necrotic tissue from primary injury described in the 1990s.[30,31] In TBI specifically, it is important to acknowledge the role of additional contributors to CE such as mechanical disruption/shearing forces and neuroinflammation. Generally, CE is separated into three stages: cytotoxic, ionic, and vasogenic edema. While these stages are typically presented sequentially, in reality, they represent a continuum and often occur simultaneously.[32] Together, they form a pathophysiological phenomenon whereby fluid and ion dysregulation within various compartments lead to an abnormal accumulation of fluid within perfused brain tissue, i.e., CE.

Cytotoxic edema, the first stage of CE formation, describes the cellular swelling response that many brain cells exhibit after an acute injury. While all cell types exhibit cytotoxic edema, astrocytes exhibit particularly marked swelling.[33] Cell swelling results from several mechanisms causing influx of osmolytes and water; this influx can be driven by various ion channels and transporters and can also be a consequence of energy failure.[32] Importantly, cytotoxic edema represents a rearrangement of brain osmolyte and water content. During this process, no new water is added to the tissue, and no tissue swelling occurs.[32]

In contrast to cytotoxic edema, ionic and vasogenic edema represent progressive forms of endothelial dysfunction and ultimately result in net influx of water into brain tissue with resultant tissue swelling. Ionic edema formation is primarily driven by forces generated during cytotoxic edema formation, whereby cellular uptake of interstitial ions creates a trans-endothelial ionic gradient that favors influx of circulating ions into brain tissues.[34] Ionic influx occurs across the blood-brain barrier (BBB) through various ion channels and transporters expressed by brain endothelium, which osmotically drives trans-BBB uptake of circulating water. Vasogenic edema represents further breakdown of the BBB, wherein serum proteins such as albumin are extravasated as part of the edema fluid.[11] Multiple mechanisms participate in the formation of vasogenic edema, including increased pinocytosis, endothelial retraction, and loss of endothelial tight junctions.[32] During vasogenic edema, the BBB continues to exclude erythrocytes. However, progressive, severe endothelial dysfunction and oncotic endothelial cell death may eventually render the cerebral vasculature permeable to all circulating contents, including erythrocytes, thereby contributing to hemorrhagic transformation.[35]

4.1 Pathways Involved in Cytotoxic, Ionic, and Vasogenic Edema

During cytotoxic edema, cellular mechanisms that are normally involved in astrocyte-mediated homeostasis of the brain microenvironment become dysregulated, resulting in astrocytic sodium overload and swelling. For example, extracellular potassium and glutamate rise dramatically after acute CNS injury,[36,37] which stimulates the activity of the Na^+-K^+-$2Cl^-$ cotransporter (NKCC1) and the excitatory amino acid transporter (EAAT), resulting in cytotoxic edema formation.[38-40] Interstitial pH also declines after injury and can drive cytotoxic edema formation through activation of the Na^+/H^+ exchanger (NHE) and the $Na^+/HCO3^-$ transporter (NBC).[41,42] In addition to these constitutively expressed channels and transporters, the sulfonylurea receptor 1 – transient receptor potential melastatin 4 (SUR1-TRPM4) channel is upregulated *de novo* by astrocytes after injury and is a major mediator of cytotoxic edema formation.[43-46]

During ionic edema formation, a variety of plasmalemma channels and transporters contribute to influx of circulating ions into the brain parenchyma. Channels and transporters including the sodium-hydrogen antiporter (NHE), the cation-chloride transporter NKCC1, and the SUR1-TRPM4 channel all contribute to maladaptive influx of solutes, which ultimately drive water influx.[47,48]

Vasogenic edema is exacerbated by secretion of multiple permeability factors from adjacent cells following injury. For example, pro-inflammatory cytokines are released following CNS injury and promote BBB dysfunction via increased matrix metalloproteinase expression,[49-51] leukocyte infiltration with loss of tight-junction proteins,[52] increased production of substance P and bradykinin,[53] and expression of inflammatory cell adhesion molecules.[2,54] Overall, numerous molecular mediators and pathways contribute to cytotoxic, ionic, and vasogenic edema and are reviewed extensively in recent works.[2,7] While our understanding of the relative role of each pathways in the development of CE in TBI remains in its infancy, these molecular pathways represent an important and exciting area of future research.

5 Cerebral Edema Patterns in Traumatic Brain Injury

Historically, BBB injury resulting from direct mechanical trauma was thought to be the main contributor to edema after TBI.[55] For example, in models of cerebral contusion, Katayama et al. demonstrated that mechanical disruption of the BBB increased peri-contusional water content due to the osmotic potential between the central necrotic core and surrounding brain.[31] Imaging studies also support the prominent role of BBB injury in early edema following brain trauma. Barzo et al. measured the apparent diffusion coefficient (ADC) by MRI imaging in rats subjected to closed head injury and reported significant increases in ADC and brain water content measured by T1 weighted imaging during the first 60 minutes post-injury, consistent with vasogenic edema

due to BBB compromise.[56] Mechanical injury, although an immediate cause of BBB disruption, is not the sole mechanism of BBB breakdown. The secondary injury cascades noted above promote a leaky endothelium 6–24 hours post-injury.[2] This incompetent BBB persists for up to 3-4 days after injury and may worsen 5–7 days later due to microglial activation.[2,57,58]

CE following traumatic injury is not solely vasogenic but consists of more mixed edema patterns.[2,59] Recent models suggest a biphasic component of vasogenic and cytotoxic edema following TBI. Barzo et al. found that cellular edema in rodent models began 40–60 minutes post-injury and became dominant at 1–2 weeks post-injury.[56] This finding has been supported in human studies wherein MRI data after closed head injuries also suggest a mixed edema pattern. Hudak et al. used Fluid-Attenuated Inversion Recovering (FLAIR) imaging in combination with Diffusion Weighted Imaging (DWI) to characterize cytotoxic and vasogenic edema patterns following TBI, and reported significant contributions of both edema subtypes.[18] This variability in edema subtypes and timing post-injury likely reflects the continuum between cytotoxic, ionic, and vasogenic edema which, as noted, occur simultaneously.[32]

6 Causes of Edema in Traumatic Brain Injury

6.1 Ischemia

Ischemic brain injury is a well-established cause of CE in other forms of neurological injury and mediates CE through a variety of mechanisms, including ion channel dysfunction with cellular edema.[60] The role of ischemia in TBI remains incompletely understood. Pathological studies have long identified ischemic injury in fatal cases of TBI. In 263 fatal head injuries, Graham et al. found ischemic damage in the brains of >88% of cases.[61] Similar findings are suggested based on measurements of cerebrovascular physiology. A recent study comparing CBF, CBV, cerebral oxygen metabolism ($CMRO_2$), and oxygen extraction fractions (OEF) between TBI patients and controls reported increased ischemic brain volume highest in the first 24 hours post-injury.[62] Ischemia was identified even in the absence of increased ICP, remained detectable up to 10 days post-injury, and was inconsistently detected by jugular or brain tissue oximetry.[62] A study by Bouma et al. found lower CBF in all brain regions in comatose patients with CE compared to those without CE, with a significant portion of patients exhibiting cerebral ischemia.[63] The clinical consequence of reduced CBF, however, is not established. Positron emission tomography (PET) studies after severe TBI demonstrate large reductions of CBF without energy failure.[64] It is therefore possible that oxygen metabolism is preserve due to low baseline metabolic rate and compensatory increases in oxygen extraction.

6.2 Hemorrhagic Blood Products and Peri-contusional Edema

Extravasated blood harbors numerous neurotoxic elements, including thrombin, fibrinogen, complement, leukocytes,

platelets, and hemoglobin breakdown products.[65] Therefore, hemorrhage itself may be viewed as a primary form of CNS injury following trauma, resulting in the formation of a shell of edema surrounding the traumatic hematoma. Perihematomal edema formation occurs in three stages: ionic edema, vasogenic edema, and delayed vasogenic edema. The forces governing its formation are mostly similar to those that contribute to the phases of endothelial dysregulation. However, there are several mechanisms unique to the formation of perihematomal edema.

Perihematomal ionic edema is generated through two major forces. First, after hemorrhage, cytotoxic edema forms in the perihematomal shell and drives ionic edema formation as described above. Second, perihematomal ionic edema is also generated by a phenomenon called clot retraction. In clot retraction, the coagulation cascade results in exudation of serum proteins by the clot, increasing the osmotic pressure in the tissues surrounding the clot, thereby contributing to ionic influx of circulating fluid.[66,67] Perihematomal vasogenic edema is formed when the BBB becomes permeable to serum, but still excludes circulating erythrocytes. The BBB adopts a permeable phenotype through action of various factors found in the clot, including thrombin,[68] complement,[69] and leukocytes. These factors trigger reduced expression of tight junction proteins and BBB opening.[70] Delayed vasogenic edema, the third and final stage of perihematomal edema formation, forms due to accumulation of hemoglobin degradation products in the tissues surrounding the hematoma. The process of erythrocyte lysis and hemoglobin breakdown takes ~3 days to occur.[71] The toxic hemoglobin breakdown products then trigger a delayed form of vasogenic edema.[32]

Cerebral contusions are a common form of traumatic intracerebral hemorrhage resulting from direct trauma to the cortical surface. They frequently exhibit the rapid formation of massive edema in the contusional and peri-contusional core distinct from other pathological processes, which may only be partly explained by the toxicity of extravasate blood products.[30,72-75] Several studies suggest that mechanical injury leads to disintegration of cellular elements within the central area of cerebral contusion, creating a pathophysiological state in which tissue osmolality increases rapidly, driving water influx.[76] This mechanism is supported by Katayama et al., who suggested that the primary driving force of water accumulation into contused brain tissue is the elevated colloid osmotic potential of contusion necrosis.[31]

Alternatively, regional blood flow studies raise the question of an "ischemic" state within and around contused tissues, which has led to the concept of a "peri-contusional penumbra". Cunningham et al. suggests that contused regions harbor significantly lower CBF compared to non-lesion regions.[77] Additional studies show low CBF in peri-contusional hypodense grey matter regions with increased propensity

towards progression towards necrosis.[63,78] The pathophysiology of these metabolic derangements, however, may not be ischemic. *In vivo* studies using global CBF and arteriovenous differences in oxygen concentration have largely failed to detect appreciable ischemia in models of cerebral contusions.[79] Similarly, Coles et al. were unable to demonstrate focal, discrete areas of ischemia,[80] and Wu et al. found evidence of hypoperfusion without ischemia in peri-contusional tissues.[81]

6.4 Hyperemia

Hyperemia has long been considered a contributing cause of diffuse CE and raised ICP after severe head injury.[82] Histological studies by Evans and Schenker suggests that acute CE is produced by vascular engorgement.[83] Similarly, Langfitt et al. concluded that post-traumatic ICP elevation was caused by cerebrovascular dilatation and increased CBV due to injury related impaired vasoconstriction.[84] In children with severe head injuries, Bruce et al. performed CBF and CT density studies and suggested that the bilateral, diffuse swelling pattern frequently observed was due to cerebral hyperemia and increased blood volume.[85] Numerous additional studies also report abnormally elevated CBF parameters after TBI. [86-88] More recent studies, however, have shown little to no relationship between CBF, CE, and intracranial hypertension. Bouma et al. evaluated the responses of CBF and ICP to induce changes in blood pressure in comatose patients with severe closed head injury and found no association between cerebral perfusion pressure and ICP.[89] Similarly, Sakas et al. report that post-traumatic hyperemia may occur across a wide spectrum of head injuries and may even be associated with favorable outcomes.[90] In their analysis of 53 TBI patients using single-photon emission computerized tomography (SPECT) to map CBF, Sakas et al. found hyperemia predominantly localized to structurally normal grey and white matter. Interestingly, focal hyperemia was associated with lower rates of mortality and improved functional outcomes.[90] Importantly, although hyperemia may be common following TBI, OEF is highly variable and may allow for preservation of flow-metabolism coupling.[62]

7 Treatment

Currently, there are no specific therapies for traumatic CE. Rather, treatment today targets the downstream sequelae of raised ICP. This section reviews established treatments of intracranial hypertension frequently resulting from CE and briefly introduces potential anti-edema drugs. While an exhaustive description of all medical and surgical interventions for treatment of intracranial hypertension as well as a list of all drugs with potential anti-edema effects is beyond the scope of this review, the following section outlines the foundation for many interventions implemented in daily clinical practice, as supported by the Brain Trauma Foundation.[24] Ultimately, this highlights the need to further advance our understanding of post-traumatic CE to discover targeted treatments to prevent swelling.

7.1 Medical Optimization and Patient Positioning

Aggressive management of CE and optimization of ICP benefits from normalization of derangements affecting metabolism and respiratory mechanics. Normalization of carbon dioxide (CO_2) tension, careful prevention of hyperglycemia, manipulation of patient head position, and adequate analgesia are immediate measures that can be taken to combat the sequelae of post-traumatic CE and resulting ICP crisis.

Many patients with severe TBI suffer additional polytraumatic injuries, with as many as 20–25% exhibiting acute lung injury and perturbations in blood CO_2 tension. CO_2 is a potent vasoregulator, and thus hypercapnia accompanying severe lung injury can worsen an ICP crisis. Importantly, the development of acute lung injury is a critical independent factor affecting mortality in TBI patients and is associated with worse long-term neurologic outcomes. Holland et al. evaluated the incidence and impact of acute lung injury in severe TBI patients.[91] In their series, 31% of patients with severe TBI developed acute lung injury, which increased mortality to 38% compared to 15% in those without acute lung injury. In practice, optimization of pulmonary mechanics in obtunded patients with Glasgow Coma Scale (GCS) <8 or in patients with respiratory compromise must be an immediate focus, both for systemic stabilization and, in part, for ICP management.

Metabolic derangement, particularly hyperglycemia, is another important consideration. Hyperglycemia is an independent predictor of worsened outcome and occurs in roughly 12% of patients with severe brain injury.[92] Salim et al. retrospectively reviewed 834 patients with severe TBI and found that those with blood glucose above 150 mg/dL on all days in the first week of admission had higher odds of mortality.[92] Importantly, the causal relationship between hyperglycemia and poor clinical outcome in TBI patients is likely multifactorial derived from a combination of metabolic and electrolyte derangements and neuroinflammation.[93] While the relationship between glucose control and CE in TBI is not established, hyperglycemia is associated with intracellular acidosis, endothelial dysfunction, BBB impairment, edema, and necrosis.[93] Current practice stresses the normalization of blood glucose to >80 mg/dL within the first 24 hours after TBI.

Patient positioning can have a profound impact on ICP, specifically through optimization of cerebral venous outflow. Neutral head positioning in the midline can reduce ICP by up to 7 cm H_2O, and elevation of a patient's head to 30 degrees can reduce ICP by as much as 10 cm H_2O.[94-96] For patients with severe TBI, CE and ICP crisis, every 10 degrees of head elevation can potentially decrease ICP by 1.3 cm H_2O.[97]

7.2 Hyperventilation and Hyperosmolar Therapy

Therapeutic hyperventilation is an effective strategy to temporize patients with an acute ICP crisis following TBI. Therapeutic

hyperventilation capitalizes on the potent vasoregulatory effects of CO_2 to reduce CBF and ICP. Targeting an end tidal pCO_2 of 30–32 mm Hg can rapidly reduce ICP by up to 47% within 8 minutes.[98] Importantly, hyperventilation is recommended only as a temporizing measure, since prolonged hyperventilation can promote cerebral ischemia.

Hyperosmolar agents are frequently administered to TBI patients who continue to suffer ICP elevations despite optimization of patient position, analgesia, metabolic parameters, and CSF diversion. Hypertonic saline and/or mannitol are frequently used in clinical practice, which increase plasma oncotic pressure favoring water movement out of the brain parenchyma. James et al. prospectively evaluated the effects of mannitol in 48 patients suffering ICP crisis resulting from a variety of pathologies, and reported a mean 52% reduction in ICP.[98] Hypertonic saline similarly demonstrates marked reductions in ICP in those suffering acute ICP crisis.[99] Numerous studies support equivocal mortality rates when comparing mannitol versus hypertonic saline.[100] However, additional clinical factors predominantly based upon side-effect profile, patient comorbidities, volume status, and renal function may influence choice of hyperosmolar agents in clinical practice.

7.3 Sedatives, Neuromuscular Blockade, and Hypothermia

Sedatives and analgesics reduce ICP by suppressing cerebral metabolism, reducing oxygen consumption and CBF, and improving metabolic coupling.[101] Reduced pain and agitation also improves tolerance of endotracheal intubation and prevents Valsalva maneuvers (e.g., cough) to help maintain normal ICP values. The addition of neuromuscular blocking agents may further facilitate mechanical ventilation, prevent coughing or shivering, and further decrease energy expenditure to control ICP.[102,103] In the presence of elevated ICP, propofol, fentanyl, and rocuronium are used in more than 80% of cases, with midazolam and ketamine reported less frequently.[104] Importantly, sedatives can result in myocardial depression, peripheral vasodilation, and decreased mean arterial pressure (MAP), and hemodynamic side effects should be carefully monitored to avoid secondary ischemia particularly in those with impaired cerebral autoregulation.[105]

Hypothermia decreases cerebral metabolic rate, alters the release of post-trauma excitatory neurotransmitters, and reduces BBB disruption and is frequently used in management of ICP crisis.[106,107] While hypothermia may reduce ICP, its effect on functional outcome is unclear. A randomized control trial evaluating hypothermia versus standard care for treatment of adult TBI patients with ICP > 20 mmHg despite tier 1 treatments found that therapeutic hypothermia plus standard care did not result in outcomes better than those with standard care alone.[25]

7.4 Decompressive Craniectomy

Decompressive craniectomy (DC) increases intracranial compliance and

decreases ICP and is frequently employed for patients with medically refractory intracranial hypertension following TBI. The DECRA trial[26] and RESCUE-ICP trial[28] examined the utility of DC in TBI. DECRA compared decompression to standard care in patients with ICP > 20 mmHg refractory to first-tier therapies. DECRA showed early bifronto-temporo-parietal decompressive craniectomy decreased ICP and length of ICU stay but did not significantly alter rates of death at 6 months and resulted in worse extended Glasgow outcome scores (GOS) compared to those receiving standard care.[26] Importantly, DECRA had several limitations including more severe primary TBI injuries in the surgical arm, questionable application to DC performed unilaterally, and high crossover rate from standard care arm to the surgical arm.[108] RESCUE-ICP included more commonly encountered patient types and refined the definition of refractory intracranial hypertension. In the RESCUE-ICP trial, patients with refractory elevated ICP (>25 mmHg for 1–12 hours) were randomized to undergo DC or receive ongoing medical care.[28] At 6 months, DC was associated with lower mortality but higher rates of vegetative state.[28] Importantly, bifrontal approaches were used in 63% of cases and unilateral approaches in only 37%, opposite the practice pattern in the United States, potentially limiting generalizability. A significant portion of patients in the medical group (37%) also underwent DC due to medical treatment failure and clinical deterioration, whereas only 9% of patients in the surgical arm suffered ongoing ICP crisis. Taken together, these studies suggest that DC may reduce mortality in TBI patients with refractory ICP crisis but at the cost of increased rates of long-term morbidity. More investigation into nuances of patient selection and development of refined clinical decision-making tools are needed.[109]

7.5 Anti-Edema Drugs

Evidence suggests that ICP-directed therapies may reduce mortality, but the lack of improvement in functional outcome presents ongoing opportunities to improve management of TBI related CE and the downstream deleterious consequences. It is possible that targeted treatments addressing important contributors to TBI edema pathways may alter key pathophysiological mechanisms not addressed with current ICP-targeted therapies. Several new anti-edema drugs are currently being investigated and have recently been reviewed.[2,7,110] While few have progressed to human TBI studies, many are supported by promising preclinical results as well as favorable findings in clinical trials treating CE related to other CNS pathologies. Common molecular pathways underlying CE development across multiple CNS injury models may suggest potential cross-over therapeutics. These promising agents include vaptans, inhibitors of arginine vasopressin;[111] fingolimod, a functional inhibitor of spingosine-1-phosphate signaling;[112,113] celecoxib, a cyclooxygenase-2 inhibitors;[114] and glyburide, an SUR1-TRPM4 channel inhibitor.[115-117] Several of these anti-edema drugs are reviewed in detail by Stokum et al., 2020.[110] Of note, an intravenous formulation

of glyburide (BIIB093) is currently being evaluated in a phase-II study of contusional TBI.[118]

Conclusions

Despite numerous advances in neurosurgical and neurocritical care, CE remains a substantial burden and a major source of morbidity and mortality following severe head injury. Despite significant progress in our pathophysiological understanding of CE following TBI, the complexity remains daunting. This review discusses several known and proposed contributors to TBI induced CE and reviews standard practices for treating downstream effects of intracranial hypertension with the aim of providing a contemporary overview specific to TBI. The lack of approved anti-edema drugs and current long-term morbidity seen with ICP-directed treatments presents an opportunity for further research to improve our understanding and treatment of this challenging disease process. Future improvements in TBI care will likely come from advances in our molecular understanding of CE, radiographic markers, biological markers, and multimodal monitoring. Such advancements may ultimately allow targeted treatments to be instituted prophylactically to prevent CE instead of non-specifically addressing the downstream effects on ICP and tissue perfusion that constitute current practices.

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Conflict of Interest Statement

RMJ and JMS are paid consultants and on the advisory board of Biogen.

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