Received: 2 July 2023 | Revised: 28 October 2023 | Accepted: 1 November 2023

DOI: 10.1002/hsr2.1713

PERSPECTIVE

Health Science Reports Open Access WILEY

Posttraumatic hydrocephalus: Recent advances and new therapeutic strategies

Vivek Sanker[1,2] | Mrinmoy Kundu[1,3] | Sarah El Kassem[1,4] | Ahmad El Nouiri[1,4] | Mohamed Emara[1,5] | Zeina Al Maaz[1,4] | Abubakar Nazir[1] | Bezawit Kassahun Bekele[1,6,7] | Olivier Uwishema[1,8,9]

[1]Oli Health Magazine Organization, Research and Education, Kigali, Rwanda

[2]Society of Brain Mapping and Therapeutics, Los Angeles, California, USA

[3]Institute of Medical Sciences and SUM Hospital, Bhubaneswar, India

[4]Faculty of Medicine, Beirut Arab University, Beirut, Lebanon

[5]College of Medicine, University of Sharjah, Sharjah, United Arab Emirates

[6]School of Medicine, Addis Ababa University, Addis Ababa, Ethiopia

[7]Milken Institute of Public Health, George Washington University, Washington, District of Columbia, USA

[8]Department of medicine, Clinton Global Initiative University, New York, New York, USA

[9]Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey

Correspondence

Abubakar Nazir, Oli Health Magazine Organization, Research and Education, Kigali, Rwanda.
Email: abu07909@gmail.com

Abstract

Background: Hydrocephalus or ventriculomegaly is a condition brought on by an overabundance of cerebrospinal fluid (CSF) in the ventricular system. The major contributor to posttraumatic hydrocephalus (PTH) is traumatic brain injuries (TBIs), especially in individuals with occupations set in industrial settings. A variety of criteria have been employed for the diagnosis of PTH, including the combination of neurological symptoms like nerve deficits and headache, as well as an initial improvement followed by a worsened relapse of altered consciousness and neurological deterioration, which is detected by computed tomography-brain imaging that reveals gradual ventriculomegaly.

Aim: In this article, we discuss and summarize briefly the current understandings and advancements in the management of PTH.

Methods: The available literature for this review was searched on various bibliographic databases using an individually verified, prespecified approach. The level of evidence of the included studies was considered as per the Centre for Evidence-Based Medicine recommendations.

Results: The commonly practiced current treatment modality involves shunting CSF but is often associated with complications and recurrence. The lack of a definitive management strategy for PTH warrants the utilization of novel and innovative modalities such as stem cell transplantations and antioxidative stress therapies.

Conclusion: One of the worst complications of a TBI is PTH, which has a high morbidity and mortality rate. Even though there hasn't been a successful method in stopping PTH from happening, hemorrhage-derived blood, and its metabolic by-products, like iron, hemoglobin, free radicals, thrombin, and red blood cells, may be potential targets for PTH hindrance and management. Also, using stem cell transplantations in animal models and antioxidative stress therapies in future studies can lower PTH occurrence and improve its outcome. Moreover, the integration of

clinical trials and theoretical knowledge should be encouraged in future research projects to establish effective and updated management guidelines for PTH.

KEYWORDS

animal model, cerebrospinal fluid, posttraumatic hydrocephalus, stem cell therapy, traumatic brain injury, ventriculoperitoneal shunt

1 | INTRODUCTION

Hydrocephalus or ventriculomegaly is a condition caused by an overabundance of cerebrospinal fluid (CSF) in the ventricular system.[1] CSF is produced in the choroid plexus and is reabsorbed by arachnoid granulations that drain into venous sinuses as they travel down the ventricles.[1] Any barrier or gliosis can reduce CSF absorption, hinder bulk CSF flow, or lead to ventricular overfilling.[1] Hydrocephalus can develop with an underlying disease or can present alone.[2] To classify hydrocephalus, numerous intricate categorization schemes have been created.[2] Hydrocephalus may be characterized as obstructive, communicative, hypersecretory, or normal pressure.[1] One of the most common causes of communicating hydrocephalus is posthemorrhagic hydrocephalus (PHH).[1] Traumatic brain injuries (TBIs) are a major contributor to posttraumatic hydrocephalus (PTH), especially in individuals with occupations set in industrial settings.[1] Diffuse axonal injuries (DAIs), cerebral contusions, subarachnoid hemorrhage (SAH), and epidural hematomas (EDH), alongside other pathologies associated with TBIs, can contribute to PTH development.[3]

The precise etiology of PTH is still unknown despite its initial recognition in 1914.[4] The symptoms of PTH may vary considerably and are difficult to identify, although they range from mild to severe TBI, exhibiting signs of either high- or low-pressure hydrocephalus.[3,5] Hence, in addition to radiological evaluations, the clinical manifestation of hydrocephalus is utilized to diagnose PTH.[4] Uncertainty surrounds the prevalence of PTH, which is estimated to be between 0.7% and 45%.[5] Due to the wide array of diagnostic criteria and the lack of a gold standard diagnostic tool, the incidence varies greatly.[4,5] PTH is a progressive illness with an undefined timeline, which makes management exceedingly challenging.[3,6] Appropriate surgical intervention may be warranted initially if PTH manifests during the acute stages of a TBI; nevertheless, PTH may develop later and worsen during rehabilitation.[3]

PTH has been reported to carry complications in more than 65% of patients and carries the probability of frequent misdiagnosis and mistreatment.[6,7] Whether the outcome is positive or negative, PTH impairs the quality of life within the affected populace by lengthening hospital admissions and periods of rehabilitation.[6]

PTH remains a perplexing disease. There is a lack of gold-standard diagnostic criteria. The currently used criteria and investigations have limited sensitivity and specificity, and thus, clear epidemiological data is hard to obtain.[3] In addition, treatment options are quite limited, and outcomes remain poor.[6] This highlights the need for more accurate biomarkers and more effective therapies. This review comprehensively examines the pathophysiological mechanisms, clinical manifestations, epidemiological insights, risk factors, and contemporary management strategies. It also offers an extensive exploration of recent advancements and pioneering therapeutic modalities. Our aim is to guide future research endeavors and offer a contemporary update for practitioners.

2 | PATHOPHYSIOLOGY OF PTH

The mechanism of CSF generation is still not fully understood because of opposing views. It was once widely accepted that the choroid plexus was the main source of CSF. Following production, the CSF largely transits from the lateral ventricles to the third ventricle through the foramen of Monro. Once arrives at the third ventricle, CSF flows through the Aqueduct of Sylvius to the fourth ventricle, where it ultimately reaches the subarachnoid cisterns via passage through the foramina of Luschka and Magendie. The superior sagittal sinus would then reabsorb the CSF through the arachnoid granulations.[8] Primary injury, also known as direct physical damage to the brain from TBI, may be focal, like contusions, or widespread, like DAI.[9] Subsequent to the initial injury, secondary injuries may appear, which may be precipitated by excitotoxicity, mitochondrial malfunction, oxidative stress, or other factors.[9] Brain tissue may also experience intraparenchymal, acute subdural hemorrhage (ASH), or EDH, which may result in a variety of neurological sequelae.[10] Cerebral edema, ischemia, or gliosis are further pathological alterations that may develop following TBI.[11–13]

PTH may be caused by a variety of circumstances. Clot formation preceded by SAH or intraventricular hemorrhage (IVH) may obstruct the ventricular system, thus resulting in reduced CSF drainage, which then would lead to acute hydrocephalus.[6] Scarring of the arachnoid granulations may potentially have an impact on CSF drainage. This occurs when a decompressive craniectomy (DC) is not performed to manage an ASH precipitated by TBI. An increase in venous return or the development of subdural hygromas may cause ventriculomegaly and PTH in cases where ASH is refractory to standard treatment methods. Thus, DC is performed to prevent cerebral herniation.[6]

3 | CLINICAL PRESENTATION

The intersection of clinical manifestations exhibited from PTH, such as urinary incontinence, ataxia, gait difficulties, memory loss and amnesia, retarded psychomotor function, cognitive impairment, nausea, headache, and obtundation, alongside the presented clinical picture of

the initial injury, is a frequent obstacle in the diagnosis of PTH.[14] Yet, following a TBI, a poor recovery or stagnation in improvement is a common indicator of PTH. It is important to note that early identification is essential for the management of TBI patients.[15] The diagnosis of PTH may be confirmed by the existence of associated signs and symptoms alongside favorable radiological investigations. A variety of criteria have been employed, including the combination of neurological symptoms like nerve deficits and headache, as well as the gradual improvement of the clinical condition over time. This is followed by a worsened relapse of altered consciousness and neurological deterioration and computed tomography (CT)-brain imaging that reveals gradual ventriculomegaly.[16]

In addition to PTH, TBI may cause a variety of sequelae, including seizures, posttraumatic epilepsy, meningitis, stroke, vertigo, cranial nerve injury comprising facial nerve palsy, and symptoms like dizziness and nausea that should be contemplated when establishing the differential diagnosis of PTH.[16]

4 | EPIDEMIOLOGY AND RISK FACTORS

PTH is a well-known neurological sequela of TBI that may adversely affect patients. However, there isn't a unified diagnostic criterion for it to be adequately reported; its prevalence ranges from 0.7% to 45%.[5] Even though the exact etiology remains unknown, with little present information on its risk factors, it has been demonstrated that increasing age, displaying low Glasgow coma scale (GCS) scores, undergoing a DC, having meningitis with a positive CSF culture, and possessing an IVH or SAH are all thought to be potential risk factors.[17] However, in a specific study on 116 patients, it was elucidated that 60 out of 86 males and 17 out of 30 females had poor outcomes, respectively, and age was divided into three subgroups: less than 44, between 45 and 49, and exceeding 60 years old.[17] There were no conclusive statistics to conclude the development of such a complication based on either gender or age.

The severity of TBI is determined by three factors: whether a patient has posttraumatic amnesia, how long the patient has been unconscious, and the severity of the patient's presenting GCS.[18]

5 | CURRENT MANAGEMENT STRATEGIES

Management strategies for PTH are determined by the severity of the symptoms as well as the underlying etiology of the hydrocephalus.

A. Medical management: Various pharmacological and nonpharmacological interventions are regularly administered in the treatment of PTH.

5.1 | Pharmacological agents

Pharmacological treatment of PTH aims at symptomatic relief of hydrocephalus by decreasing CSF production or increasing CSF absorption. PTH may be managed with any of the pharmacological agents mentioned below (Table 1):

1. Acetazolamide: This drug works by blocking the enzyme carbonic anhydrase, which lowers CSF production.[19] Both oral and intravenous administration methods are available. In PTH patients, it is usually administered to lower intracranial pressure (ICP).[19]
2. Osmotic diuretics: By removing excess fluid from brain tissue, osmotic diuretics, such as mannitol[20] or glycerol,[21] may be used to reduce ICP. Typically, these drugs are administered intravenously.
3. Anticonvulsants: Patients with PTH may be treated for seizures with anticonvulsants like phenytoin or levetiracetam.[22]
4. Furosemide: This diuretic drug stimulates the body to excrete salt and water. By preventing sodium uptake in the brain, it may also lower CSF production.[22] Acetazolamide and furosemide are commonly used in combination when managing PTH.[23]
5. Anti-inflammatory medications: Corticosteroids may be utilized in patients with PTH to reduce cerebral edema, swelling, and inflammation.[24] Additionally, these medications may be taken either orally or intravenously.

5.2 | Nonpharmacological interventions

While there are several pharmacological treatments for PTH, nonpharmacological interventions may also help reduce symptoms and improve overall quality of life.

TABLE 1 Pharmacological treatment of PTH.

Medication	Mechanism of action	Route of administration
Acetazolamide	Inhibits carbonic anhydrase and reduces CSF production	Oral or intravenous
Osmotic diuretics	Lowers ICP by drawing excess fluid	Intravenous usually
Anticonvulsants	Treats seizures in PTH patients	Oral or intravenous
Furosemide	Encourages excretion of water and salt and reduces CSF production by inhibiting sodium absorption in the brain	Oral or intravenous
Anti-inflammatory	Reduces brain swelling and inflammation	Oral or intravenous

Abbreviations: CSF, cerebrospinal fluid; ICP, intracranial pressure; PTH, posttraumatic hydrocephalus.

1. Physiotherapy: Physiotherapy may aid with muscle strength, flexibility, balance, and coordination. This is especially beneficial for those who have suffered TBI as it can assist in regaining individual physical function and independence.[25]
2. Speech therapy: Individuals with PTH who have communication difficulties, such as difficulty finding the right words or speaking clearly, may benefit from speech therapy. Cognitive rehabilitation and memory training may also benefit from speech therapy.
3. Cognitive rehabilitation: This entails a variety of techniques aimed at improving cognitive function, such as attention, memory, and problem-solving abilities. This may be especially beneficial for individuals with PTH who have cognitive deficits because of TBI. Apps such as CogniFit, Peak, and Lumosity have made home-based cognitive rehabilitation more accessible, aiding in addressing these deficits.[26–28]
4. Lifestyle modifications: There is mounting evidence that lifestyle choices, including sleep, exercise, and eating habits, may contribute to either neuroprotective or pathogenic processes that affect how severe TBI-related neurocognitive impairments are, and further investigations are needed.[29] Although no class I evidence supporting nutritional supplementation is available, zinc and magnesium proved most effective in improving TBI outcomes in class III studies.[30] In addition, endogenous showed improvement in cognition in class IIC studies.[30]

B. Surgical management: PTH is surgically managed with either an endoscopic third ventriculostomy (ETV) or a ventriculoperitoneal shunt (VPS). A VPS is a device that is implanted to transfer excess CSF from the brain to another area of the body, usually the abdomen.[31] Relieving excessive ICP brought on by hydrocephalus is the goal of VP shunting.[32,33] Although it is linked to a favorable clinical outcome, complications can arise. These include mechanical malfunction, placement failure, infection, CSF leak, and, in rare cases, intracerebral hemorrhage.[33,34] Peritoneal catheter complications can also arise, including ileus, pseudocyst formation, and bowel perforation that leads to shunt failure.[35,36] Within the first month of a pediatric surgical series, 14% of children experienced shunt failure, and 4%–50% of shunts fail within the first year.[34] Within the first year, adults also have a rather high (29%) shunt failure rate. Regardless of age, long-term studies indicate that 45%–59% of patients will need a shunt revision. Infections and multiple shunt failures are frequent, and 48% of shunt-related surgeries involve modifications.[37,38]

   Infection should always be suspected in patients exhibiting symptoms of shunt malfunction since shunt infection is a dangerous complication that carries a high risk of major morbidity and death.[39,40] Selecting the right particular antibiotic medication and isolating the pathogenic organisms depend on the CSF culture.[41] The conventional approach to treating shunt infections usually entails removing the contaminated hardware and starting intravenous antibiotic treatment. According to research by Shurtleff et al., patients who got systemic antibiotics alone had a 9% cure rate, compared to 100% for those who received total shunt removal along with treatment.[42] According to a meta-analysis by Schreffler et al., replacing the infected shunt with a new one right away or using antibiotics alone is not nearly as effective as completely removing it with EVD implantation and antibiotic therapy.[43] To save expenses and lower morbidity, it is crucial to develop strategies for preventing shunt infections, such as the use of catheters impregnated with antibiotics[44] perioperative antibiotics,[45] improving sterile procedures, and shortening procedure times.[46]

   By far, the most frequent cause of shunt malfunction is shunt catheter occlusion, yet the exact causes of this issue are still unknown. The proximal catheter is the most often found location of obstruction in most investigations. However, obstruction can also occur within the valve or the distal catheter.[47,48] Shunt blockage is often diagnosed by a combination of lumbar puncture, shunt tapping, and CT scans. Although this isn't always the case, and these studies may produce conflicting data, in cases with shunt obstruction, CT is likely to reveal an increase in the size of the ventricles, and LP is likely to show a higher opening pressure. It is beneficial to diagnose the site of shunt obstruction before surgery, as the blocked portion of the shunt (proximal catheter, valve, or distal catheter) can be removed and replaced separately, keeping the other hardware intact.[41]

   Subdural collections and SDHs may develop during shunting procedures due to CSF over drainage.[49,50] Patients with low-pressure hydrocephalus may be more likely to develop SDH as a result of bridging veins stretching when the brain depressurizes following shunting, causing the brain to recede from the skull.[51] Additionally, patients with higher ICPs and NPH may be more susceptible to increased CSF leakage, increasing their risk of developing SDHs.[52] While the invention of programmable shunt valves has greatly aided in the treatment of symptoms, surgical drainage was necessary in certain situations.[53]

   Another treatment option for hydrocephalus involves a slightly invasive surgical procedure called ETV. ETV entails making a small hole in the floor of the third ventricle, where an endoscope is introduced into the ventricular system.[54] Through this opening, CSF may move from the ventricles and into the subarachnoid space encircling the brain, where it is reabsorbed back into the body.

C. Neurostimulation techniques: A study has suggested that through diminishing cephaledema and anti-inflammatory pathways, vagus nerve stimulation efficiently, and significantly protects the brain.[55] In addition, another study has concluded the safety and feasibility of transcutaneous vagus nerve stimulation in patients suffering from TBI. However, further studies are still needed.[56]

6 | TRAUMATIC BRAIN INJURY VERSUS PTH MANAGEMENT

The management of TBI is dependent on the severity of the injury. Patients might be monitored in the intensive care unit (ICU) and given the previously discussed medications to maintain an adequate ICP.

They may also have to undergo surgeries such as craniotomy only or DC and rehabilitation therapy for neurological deficits.

In addition to these therapies, however, patients with PTH might require the surgical placement of VPS.

7 | TECHNOLOGICAL ADVANCEMENTS IN WEARABLE DEVICES USED TO MONITOR AND MANAGE PTH

The technological advancements of the 21st century have changed our daily lives. These breakthroughs are revolutionizing medicine to better patient outcomes, and this case is no exception.

Patients now have access to smart monitors such as Raumedic Neurovent that enable them to continuously monitor their ICP and transmit it to their healthcare providers.[57] The device uses a telemetric catheter that is capable of measuring pressure (ICP), temperature (ICT), and partial pressure of oxygen (ptiO2).[57] Another monitor is the Miethke Sensor Reservoir, which allows for noninvasive ICP measurements and subsequent CSF drainage through VPS.[58]

A common complication of VPS is failure. As a matter of fact, 15%–23% of shunts in adults fail within 6 months, and that rate goes up to 50% in high-risk populations.[59] This is being tackled by Rhaieos's Flowsense noninvasive, wireless, wearable monitor. The device comes in the form of a skin patch that subdermally detects CSF flow in the body and allows early detection of shunt failure and, subsequently, early intervention.[60]

Certain monitors, such as Embrace2, are capable of detecting seizures that can happen in patients with PTH. These devices can alert caregivers and healthcare professionals of abnormal electrical brain activity.[61]

Other wearable sensors such as the Apple Watch, Fitbit, and Garmin can monitor vital signs, sleep patterns, and activity levels.[62–64] Although not directly developed for cases of PTH, these devices can definitely help with monitoring symptoms related to the condition.

8 | ADVANCES IN THE UNDERSTANDING AND TREATMENT OF PTH

Advancements in understanding the pathophysiology of PTH have helped to devise specific management modalities targeting the intermediates of the pathway and hence enhance the treatment efficacy and improve patient prognosis. The role of retinoic acid receptors in PHH is currently being investigated and can be a potential target for its treatment (Figure 1).

The occurrence of PTH is attributed to varied aetiologies in both pediatric and adult populations.[65] TBI in the pediatric population can have fatal and long-lasting effects on the developing brain. Understanding the pathogenesis (Figure 2) and the associated effects of TBI in this population is thus vital in devising a comprehensive treatment plan to address the complications of it as well. In neonates, the commonest subtype of IVH causing hydrocephalus is germinal matrix hemorrhage.[66,67] This may lead to fatal ICP elevation, neuronal tissue

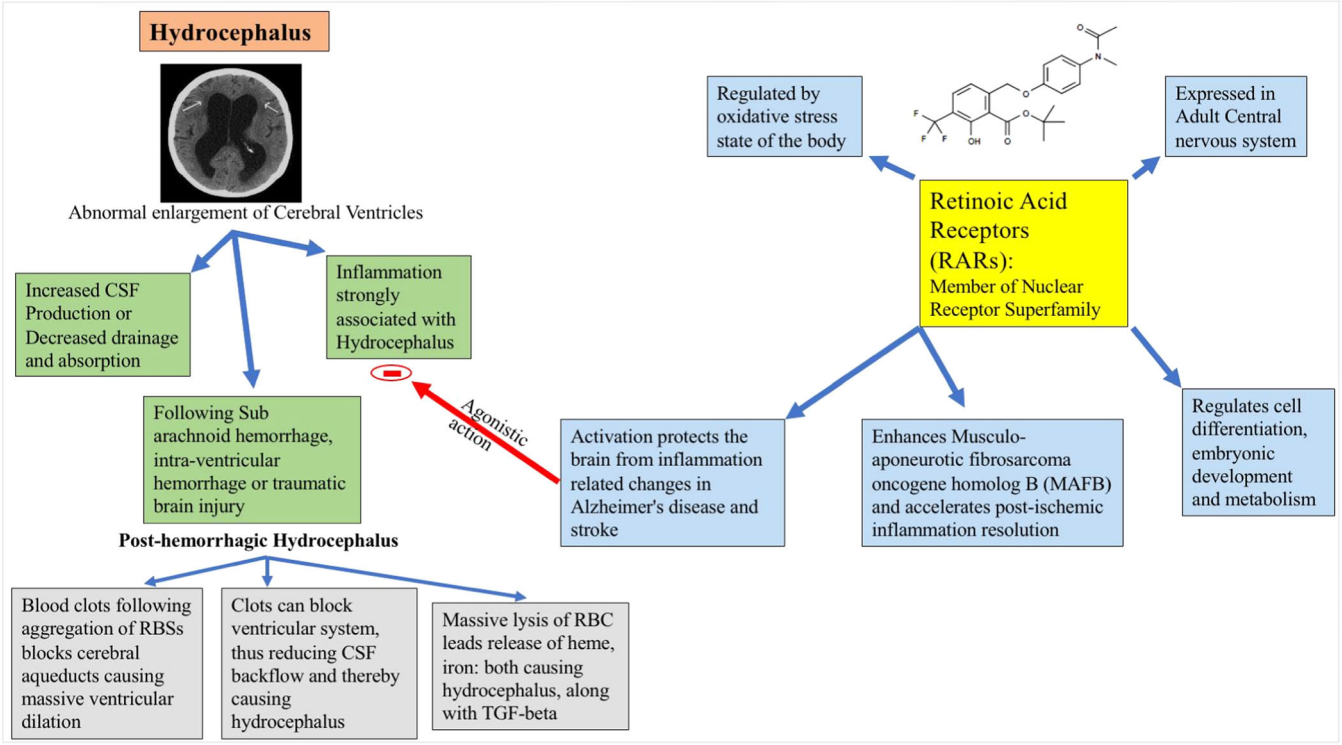

FIGURE 1 Role of retinoic acid receptors (RARs) in the pathogenesis of posthemorrhagic hydrocephalus (PHH) and associated manifestations.

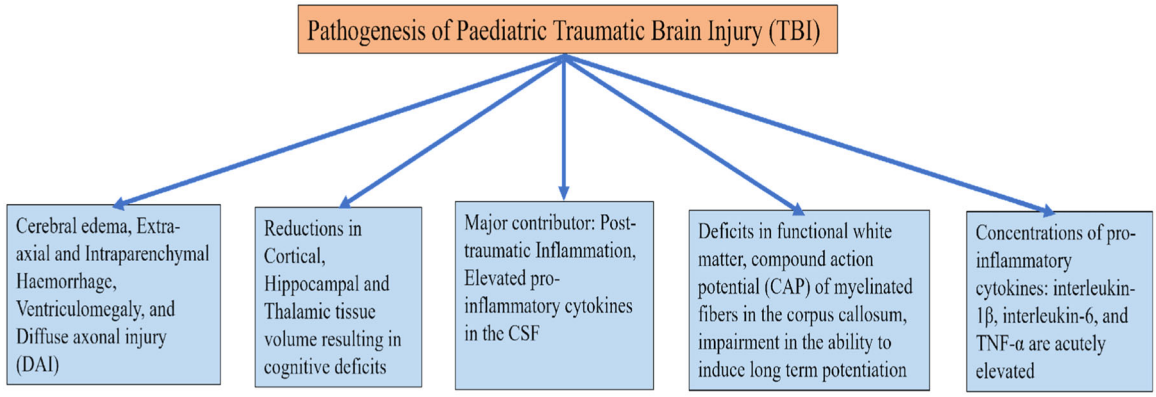

FIGURE 2 Pathogenesis of pediatric traumatic brain injury (TBI). CSF, cerebrospinal fluid.

damage, and hydrocephalus.[68,69] Currently, VPS is the first line of management for CSF permanent diversion[70] (Figure 2).

Conventional management methods include[71,72]:

1. External ventricular drainage (EVD)
2. CSF shunting
3. Endoscopic surgery

These techniques have been used for some time, but they are also prone to issues, including infection and drainage tube occlusion.[73,74] At this point, newer therapeutic approaches are necessary to lessen the probability of said issues.

1. Clot lysis: It has been proposed to remove ventricular clots and thereby halt hydrocephalus progression and formation.[75] A clinical trial involving a series of intra-ventricular thrombolysis, named CLEAR-IVH, is being conducted by injecting recombinant tissue plasminogen activator (rt-PA). Early phases showed promising results with faster clot dissolution.[76–78] For further understanding of the potential of this option, a phase-3 trial is currently being performed.[79]
2. A combination of drainage, fibrinolytic therapy, and irrigation, collectively termed "Brain-washing," targeted to remove blood and associated metabolic products, was conducted in the clinical trials by Whitelaw et al. to find its efficacy.[80] The results were, though, not in favor of reducing the incidence of PHH.
3. Medical management, ETV, catheterization of choroid plexus, and ventricular shunting procedures have been attempted for the management of hydrocephalus following IVH.[81–83]

In cases of hydrocephalus secondary to SAH, the current treatment protocol consists of a combined approach involving blood pressure maintenance, ICU care, and complication prevention. The surgical care comprises a permanent ventricular shunt, CSF drainage, and repeated lumbar punctures and is dependent on the radiological results and the patient's level of cognition.

Even though EVD has been traditionally used to manage acute cases of hydrocephalus, it is associated with the complication of ventriculitis if placed for more than 3 days.[84] Recent clinical trials have indicated lumbar drainage as an effective alternative for managing elevated ICP, draining CSF, and preventing cerebral vasospasm.[85,86]

PTH in adults is mostly associated with TBI.[87,88] First-line management options include CSF shunting and placement of EVD.[89–91] Elevated ICP following PTH is managed by DC, where some concerns regarding the size of the craniectomy have been expressed in the literature.[92] But on the contrary, few studies suggest that it may not be a risk factor for PTH.[93,94]

8.1 | Newer therapeutic alternatives for PTH are proposed below

1. Blood clots: The extravasated blood in the ventricular system or subarachnoid space, during the initial stages of evolution of hydrocephalus, forms blood clots, disrupting normal CSF flow and hence resulting in hydrocephalus.[95–99]

   The efficacy of fibrinolytic for the first time was shown in a dog model of IVH by Pang et al. in 1986, which showed an effective attenuation of ventriculomegaly following intra-ventricular administration.[100] Subsequently, several studies have been performed to determine the efficacy of fibrinolysis. Studies conducted in porcine and cat models showed alleviation of ventricular dilation following hemorrhage.[99,101] Conversely, it was seen that patients receiving intra-ventricular tPA infusion developed severe inflammatory responses, as shown by a recent clinical trial.[102] They also made an interesting observation that the severity of this response was associated with the extent of fibrinolysis. It is also worth noting the significance of an older thrombolytic drug, Urokinase-tissue plasminogen activator (uPA),[103,104] which has shown similar effects in clot resolution but significant outcome improvement when compared to tPA.[105,106]
2. Thrombin: Many studies have shown the involvement of thrombin in the early phase of brain injury following hemorrhage and the formation of hydrocephalus following IVH.[107–109] Significant

ventricular damage and severe ependymal ciliary damage were seen in a rat model following intra-ventricular thrombin infusion. The resolution of this injury by the administration of a protease-activated receptor 1 (PAR-1), SCH79797, shows that PAR-1 may have a role in hydrocephalus formation.[110]

Also, studies in rat models showed that thrombin caused an upregulation of TGF-beta1 expression and severe fibrosis of the subarachnoid membrane, which, on the administration of a TGF-beta1 inhibitor, was reversed completely.[111] This finding points to the fact that thrombin-induced TGF-beta1 may have a role to play in the formation of hydrocephalus following SAH.

3. Iron, hemoglobin, and free radicals: Several studies have shown the role of iron and hemoglobin in the evolution of PTH.[112] According to a recent study, an intraventricular administration of hemoglobin caused ventricular enlargement and the overexpression of the iron-handling protein lipocalin 2 (LCN2).[113]

   Intra-ventricular administration of hemoglobin was shown to cause significant ventricular enlargement at 24 h in rat models, which also indicates the involvement of hemoglobin causing hydrocephalus following IVH.[114]

   A possible role of iron in the development of hydrocephalus was originally suggested by the iron chelator deferoxamine (DFO), which reduced IVH-induced hydrocephalus.[115] According to a study done on adult rats, lysed red blood cells (RBCs) but not packed RBCs were found to cause ventricular dilatation when injected intravenously.[116] It has also been demonstrated that iron infusion alone causes ventricular enlargement. Moreover, coinjection of DFO dramatically reduced the swelling of the ventricles brought on by lysed RBCs. These findings suggest that iron is a critical factor in IVH-induced hydrocephalus.

   Earlier research has shown that iron, through the Haber –Weiss reaction, causes oxidative brain damage following ICH.[117] Following that, generating reactive oxygen species, like harmful hydroxyl radicals, may cause DNA damage and lipid peroxidation. In vitro, brain exposure to hydrogen peroxide (3% w/v) destroys the ependymal structure and alters normal ependymal ciliary beat frequency, according to research by Hirst et al. published in 2009.[118]

4. RBCs: According to several research, hemoglobin contributes to the development of PTH, and encouraging anti-RBC lysis or RBC phagocytosis may be a potential strategy for preventing PTH.[114] Earlier studies have shown that ICH-induced brain edema and neurological impairment in mice are dramatically decreased by complement C3 deletion and that MAC-mediated RBC rupture is a parallel damage mechanism after ICH.[119]

The potential effectiveness of complement inhibition in avoiding PTH has not, however, been extensively assessed so far. The likelihood that brain phagocytic cells, such as macrophages and microglia, are to blame for RBC phagocytosis before lysis and the consequent release of harmful substances is growing.[120–122] Hence, by boosting RBC clearance in the early stages of IVH, SAH, and TBI, PTH could be prevented from progressing.

8.2 | Anti-oxidative stress treatment for PTH

Oxidative stress, which is triggered by hypoxia/ischemia and involves lipid peroxidation, oxidative, and nitrosylation processes, is one of the possible mechanisms of brain damage in hydrocephalus. These processes may continue to be active even after ventricular expansion has stopped.[123] Antioxidants can be used to alleviate damage that is followed by oxidative stress in hydrocephalus. Melatonin, a hormone secreted by the pineal gland, has proven to have protective effects by scavenging free radicals.

Rats who had hydrocephalus precipitated by kaolin injection were administered melatonin. The findings showed that melatonin could delay the loss of glutathione, an antioxidant and free radical scavenger, as well as delay rises in nitric oxide levels in choroid plexus tissue.[124]

Angiogenesis is a defensive mechanism under the settings of ischemia and hypoxia.[125] In preterm infants with PTH or patients with adult hydrocephalus, vascular endothelial growth factor (VEGF), which has a mitogenic action and increases the vascular permeability effect on endothelial cells, is said to be substantially elevated in the CSF.[126] Hypoxia-inducible factor-1 alpha accumulated quickly in rats exposed to prolonged hypoxia and increased the expression of VEGF.[127] An anti-VEGF antibody called bevacizumab can be used to treat the symptoms precipitated via VEGF injection.[128] According to reports, VEGF injection causes ependymal cell denudation, cilia loss, and ventriculomegaly in rats. As a result, controlling VEGF and its receptors should be investigated as a therapeutic option for hydrocephalus.

8.3 | Stem cell transplantation in pediatric TBI

While neural stem cells (Figure 3) have the potential to promote regeneration and neurogenesis in the injured brain due to their capacity to self-renew and inherent potential to differentiate into neurons and glial cells,[129] mesenchymal stromal cells (MSCs) are useful because they can cross the blood-brain barrier, migrate to the site of injury, and secrete trophic and anti-inflammatory factors that prevent cell death.[130]

Premature birth is frequently associated with severe IVH and the PHH that follows, which increases mortality and neurological morbidities. Following a biventricular injection of 80 µL of fresh maternal whole blood at P7, Cherian et al. reported ventriculomegaly in 65% of Wistar rat pups, with a death rate of 20%.[131] In a different study, PHH was produced following severe IVH, and P4 rats—rather than P7 rats—had a death rate of 17%. It was demonstrated that the newborn rat pup model is appropriate and suitable for studying preterm IVH and the accompanying PHH.[132] Furthermore, observed are the following: decreased corpus callosum thickness and MBP; aberrant histological features such as increased astrocytic gliosis and TUNEL-positive cells; impaired behavioral function on the negative geotaxis and rotarod tests; and significantly attenuated PHH following severe IVH following intraventricular transplantation of

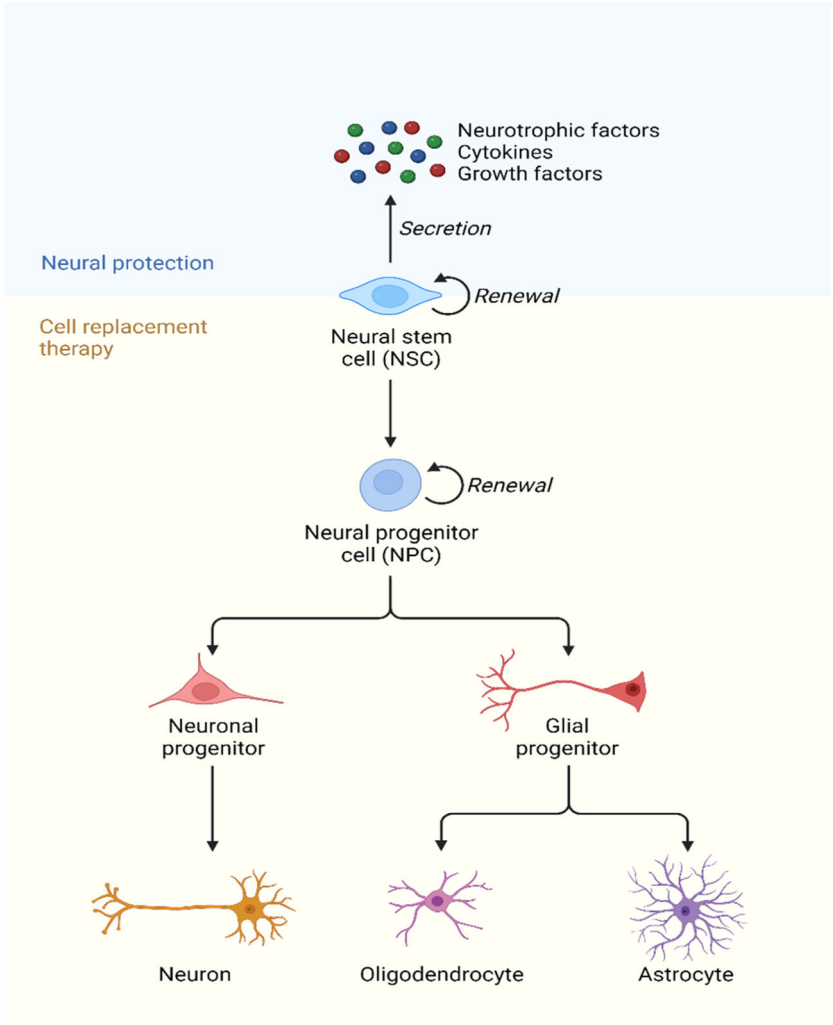

FIGURE 3 Role of NSCs in cell replacement therapy. NSC, neural stem cells.

human umbilical cord blood (UCB)-derived MSCs, but not fibroblasts.[132] Thus, it lends credence to the possible application of human UCB-derived MSCs as a cutting-edge therapeutic approach for severe IVH, for which no proven cures exist.

It is also hypothesized that rather than their capacity for regeneration, the anti-inflammatory properties of human UCB-derived MSCs may be the primary mechanism mediating or linked to their protection against PHH and brain injury following severe IVH.[133,134] After causing experimentally produced IVH in a rabbit model, USSC injection decreased cell infiltration and denudation of ependymal cells from the choroid plexus and lateral ventricle walls, as well as the diameters of the ventricular cross-sectional area at postnatal ages 7 and 14 days. It lends credence to the theory that USSCs aid in the regeneration and anti-inflammatory processes that follow damage.[135]

Local intraventricular transplantation using either low-dose (5 × 106 cells/kg) or high-dose (1 × 107 cells/kg) of allogeneic human UCB-derived MSCs did not result in any acute adverse effects or mortality in a clinical investigation including nine extremely preterm infants with grade 4 IVH. These results imply that it would be safe and possible to transplant human UCB-derived MSCs into preterm newborns suffering from severe IVH.[136] Proving the safety of MSC transplantation requires a long-term follow-up safety evaluation because serious brain injury caused by IVH can last throughout childhood and increase the risk of cognitive disability, cerebral palsy, and developmental delays.[137–139] As a result, a 2-year assessment of the nine preterm children in this research who received MSC treatment is presently being conducted (NCT02673788).

These methods have demonstrated the effectiveness of stem cell therapy in lowering neuronal cell death and inflammatory cascades following TBI, resulting in improved recovery of cognitive and motor functions.[130,140] UCB stem cells have been shown to reduce neurovascular damage following newborn brain injury.[141] By analyzing the effects of stem cell therapies in these neonatal brain damage models, future research on developing focused and effective stem cell treatments for pediatric TBI will considerably benefit (Figure 4).

8.4 | Ethical and safety considerations associated with stem-cell-based therapy

Due to their origins, elevated threat of tumorigenicity, and other factors, embryonic/fetal stem cells raise significant ethical and safety concerns.

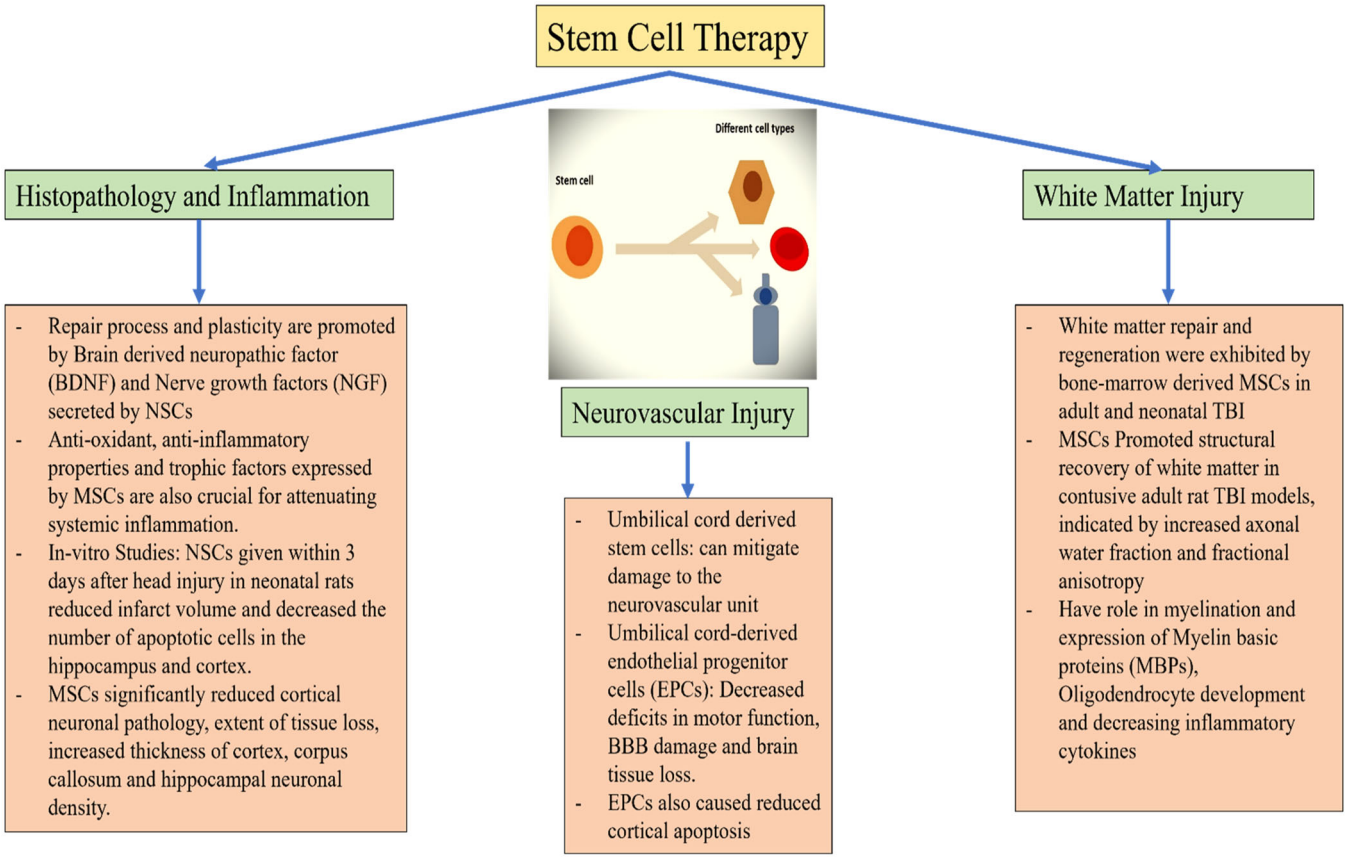

FIGURE 4 Role of stem cell therapy in the management of posttraumatic hydrocephalus (PTH). MSC, mesenchymal stromal cells; TBI, traumatic brain injuries.

Therefore, emphasis has turned to alternative cell types because of these logistical issues, particularly adult tissue-derived cells.[142]

9 | CHALLENGES IN THE MANAGEMENT OF PTH

PTH management can be challenging for a few reasons. PTH administration presents several challenges, including:

Diagnoses are challenging because PTH symptoms can resemble those of a TBI or other neurological conditions.[14] It is essential to separate PTH from other disorders to ensure optimal treatment.

Surgery schedule: Early intervention enhances results. Therefore, PTH surgery scheduling is crucial. Determining the ideal period, however, can be challenging because some individuals may not exhibit symptoms until their illness has progressed.[14]

Options for surgical therapy of PTH include ETV and shunt implantation. Because each surgical procedure has a unique set of advantages and dangers, choosing the ideal one can be challenging.[143]

Complication management: PTH patients run the risk of consequences, including infections, shunt problems, and seizures.[14] It can be challenging to manage these side effects, and more surgeries or medical procedures might be required. To improve their cognitive and physical function, PTH sufferers may need long-term therapy. Because it requires a multidisciplinary strategy and a customized treatment plan for each patient, rehabilitation can be challenging.[144] Neurosurgeons, neurologists, rehabilitation specialists, and other medical professionals must all work together to treat PTH. Close observation and prompt action can help to improve outcomes and lessen the burden of this condition's sequelae.[144]

9.1 | The importance of a multidisciplinary approach involving neurosurgeons, neurologists, and rehabilitation specialists in providing comprehensive care for patients

PTH is a complex condition that requires a multidisciplinary approach and strong interprofessional collaboration between neurologists, neurosurgeons, and rehabilitation specialists. Neurologists are vital in diagnosing and monitoring these patients. They have an important role in treatment plans alongside neurosurgeons who perform procedures such as VP shunt placements, endoscopic third ventriculostomies, and craniotomies. Rehabilitation specialists such as physical, occupational, and speech therapists are an essential part of these patients' care. They form the backbone of postacute care, improving quality of life and allowing patients to maximize their recovery potential. With that said, the collaborative efforts of these

medical professionals are crucial in achieving the best possible outcomes for patients with PTH.

10 | CONCLUSION

PTH is a severe complication with a high mortality and morbidity rate after TBI. Recent preclinical research has made some significant strides in our knowledge of PTH's pathogenesis and treatment options. Although there is currently no effective way of preventing PTH from occurring, hemorrhage-derived blood and its metabolic by-products, such as iron, hemoglobin, free radicals, thrombin, and RBCs, may be possible targets for PTH prevention and treatment. Other therapeutic approaches, like antioxidative stress therapy and stem cell transplantation in animal models, offer great promise for further study and improved therapeutic results. Multimodal interventions could culminate in even more benefits for PTH prevention.[145] Facilitating the application of basic science in the clinical context should be emphasized in future research to develop an effective management strategy for this clinical entity.

AUTHOR CONTRIBUTIONS

Vivek Sanker: Writing—original draft; writing—review and editing. **Mrinmoy Kundu**: Writing—original draft; writing—review and editing. **Sarah El Kassem**: Writing—original draft; writing—review and editing. **Ahmad El Nouiri**: Writing—original draft; writing—review and editing. **Mohamed Emara**: Writing—original draft; writing—review and editing. **Zeina Al Maaz**: Writing—original draft; writing—review and editing. **Abubakar Nazir**: Writing—original draft; writing—review and editing. **Bezawit Kassahun Bekele**: Writing—original draft; writing—review and editing. **Olivier Uwishema**: Writing—original draft; writing—review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The authors have nothing to report.

TRANSPARENCY STATEMENT

The lead author Abubakar Nazir affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

ORCID

Vivek Sanker http://orcid.org/0000-0003-0615-8397
Sarah El Kassem http://orcid.org/0000-0002-6290-5804
Ahmad El Nouiri http://orcid.org/0000-0003-1221-6629
Mohamed Emara http://orcid.org/0000-0003-1331-6365
Zeina Al Maaz https://orcid.org/0000-0001-7095-7842
Abubakar Nazir http://orcid.org/0000-0002-6650-6982
Bezawit Kassahun Bekele http://orcid.org/0000-0002-2926-235X
Olivier Uwishema http://orcid.org/0000-0002-0692-9027

REFERENCES

1. Koleva M, De Jesus O. Hydrocephalus. *StatPearls*. StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC; 2022.
2. Oi S. Hydrocephalus research update—controversies in definition and classification of hydrocephalus. *Neurol Med Chir*. 2010;50(9):859-869. doi:10.2176/nmc.50.859
3. Yoon JE, Lee CY, Sin EG, Song J, Kim HW. Clinical feature and outcomes of secondary hydrocephalus caused by head trauma. *Korean J Neurotrauma*. 2018;14(2):86-92.
4. Guyot LL, Michael DB. Posttraumatic hydrocephalus. *Neurol Res*. 2000;22(1):25-28.
5. Svedung Wettervik T, Lewén A, Enblad P. Posttraumatic hydrocephalus—incidence, risk factors, treatment, and clinical outcome. *Br J Neurosurg*. 2022;36(3):400-406.
6. Rufus P, Moorthy R, Joseph M, Rajshekhar V. Post traumatic hydrocephalus: incidence, pathophysiology and outcomes. *Neurol India*. 2021;69(8):420-428.
7. Lalou AD, Levrini V, Czosnyka M, et al. Cerebrospinal fluid dynamics in non-acute posttraumatic ventriculomegaly. *Fluids Barriers CNS*. 2020;17(1):24.
8. Khasawneh A, Garling R, Harris C. Cerebrospinal fluid circulation: what do we know and how do we know it? *Brain circulation*. 2018;4(1):14-18. doi:10.4103/bc.bc_3_18
9. Ng SY, Lee AYW. Traumatic brain injuries: pathophysiology and potential therapeutic targets. *Front Cell Neurosci*. 2019;13. doi:10.3389/fncel.2019.00528
10. Tenny S, Thorell W. Intracranial hemorrhage. In: *StatPearls [Internet]*. StatPearls Publishing; 2022.
11. Konar SK, Shukla D, Agrawal A. Posttraumatic brain edema: pathophysiology, management, and current concept. 2019. Apollo Med [serial online].
12. DeSai C, Hays Shapshak A. Cerebral ischemia. In: *StatPearls [Internet]*. StatPearls Publishing; 2022.
13. Karthikeyan A, Dhivya CR, Kavitha, Bevin S, Kannan PP. Post traumatic brain injury—organic personality change with fronto-temporal gliosis—case report. *Indian J Psychiatry*. 2022;64(Suppl 3):S670.
14. Beyerl B, Black PM. Posttraumatic hydrocephalus. *Neurosurgery*. 1984;15(2):257-261.
15. Heinonen A, Rauhala M, Isokuortti H, et al. Incidence of surgically treated post-traumatic hydrocephalus 6 months following head injury in patients undergoing acute head computed tomography. *Acta Neurochir*. 2022;164(9):2357-2365.
16. Zhuo J, Zhang W, Xu Y, et al. Nomogram for predicting posttraumatic hydrocephalus after decompressive craniectomy for traumatic brain injury. *Rev Assoc Med Bras*. 2022;68(1):37-43.
17. Sun S, Zhou H, Ding Z-Z, Shi H. Risk factors associated with the outcome of posttraumatic hydrocephalus. *Scandinavian J Surg*. 2018;108(3):265-270.
18. Graham DI, Adams JH, Nicoll JAR, Maxwell WL, Gennarelli TA. The nature, distribution and causes of traumatic brain injury. *Brain Pathol*. 1995;5(4):397-406.
19. Del Bigio MR, Di Curzio DL. Nonsurgical therapy for hydrocephalus: a comprehensive and critical review. *Fluids Barriers CNS*. 2016;13:3. doi:10.1186/s12987-016-0025-2
20. Miller JD, Leech P. Effects of mannitol and steroid therapy on intracranial volume-pressure relationships in patients. *J Neurosurg*. 1975;42(3):274-281. doi:10.3171/jns.1975.42.3.0274
21. Cantore G, Guidetti B, Virno M. Oral glycerol for the reduction of intracranial pressure. *J Neurosurg*. 1964;21:278-283. doi:10.3171/jns.1964.21.4.0278

22. Libenson MH, Kaye EM, Rosman NP, Gilmore HE. Acetazolamide and furosemide for posthemorrhagic hydrocephalus of the newborn. *Pediatr Neurol*. 1999;20(3):185-191. doi:10.1016/s0887-8994(98)00127-1
23. Shinnar S, Gammon K, Bergman Jr., EW, Epstein M, Freeman JM. Management of hydrocephalus in infancy: use of acetazolamide and furosemide to avoid cerebrospinal fluid shunts. *J Pediatr*. 1985;107(1):31-37. doi:10.1016/s0022-3476(85)80609-0
24. Gualberto IJN, Medeiros GA, Santos MV, da Silva Lopes L, Machado HR, Sbragia L. Is there a role in the central nervous system development for using corticosteroids to treat meningomyelocele and hydrocephalus? *Childs Nerv Syst*. 2022;38(10):1849-1854. doi:10.1007/s00381-022-05615-3
25. Lendraitienė E, Kriščiūnas A. Trauminį galvos smegenų sužalojimą patyrusių asmenų kineziterapija. *Medicina*. 2010;46(10):712-719.
26. Cognifit. The science behind CogniFit and their brain games—scientific validated articles. (n.d.). https://www.cognifit.com/neuroscience
27. About peak. About peak brain training. (n.d.). https://www.peak.net/about/
28. Scientists L. (2018, November 21). Lumosity brain training: learn about our research. https://www.lumosity.com/en/science/
29. Markovic SJ, Fitzgerald M, Peiffer JJ, et al. The impact of exercise, sleep, and diet on neurocognitive recovery from mild traumatic brain injury in older adults: a narrative review. *Ageing Res Rev*. 2021;68:101322.
30. Lucke-Wold BP, Logsdon AF, Nguyen L, et al. Supplements, nutrition, and alternative therapies for the treatment of traumatic brain injury. *Nutr Neurosci*. 2018;21(2):79-91. doi:10.1080/1028415X.2016.1236174
31. Pillai S. Techniques and nuances in ventriculoperitoneal shunt surgery. *Neurol India*. 2021;69(supplment):471. doi:10.4103/0028-3886.332261
32. Pan P. Outcome analysis of ventriculoperitoneal shunt surgery in pediatric hydrocephalus. *J Pediatr Neurosci*. 2018;13:176-181. doi:10.4103/jpn.JPN_29_18
33. Chung JJ, Yu JS, Kim JH, Nam SJ, Kim MJ. Intraabdominal complications secondary to ventriculoperitoneal shunts: CT findings and review of the literature. *Am J Roentgenol*. 2009;193:1311-1317. doi:10.2214/AJR.09.2463
34. Wu Y, Green NL, Wrensch MR, Zhao S, Gupta N. Ventriculoperitoneal shunt complications in California: 1990 to 2000. *Neurosurgery*. 2007;61:557-563. doi:10.1227/01.neu.0000290903.07943.af
35. Misaki K, Uchiyama N, Hayashi Y, Hamada J. Intracerebral hemorrhage secondary to ventriculoperitoneal shunt insertion. *Neurol Med Chir*. 2010;50:76-79. doi:10.2176/nmc.50.76
36. Kingsly EN, Kanumba ES, Lemeri L, Shabbhay Z. Outcome of ventriculo-peritoneal shunts inserted at the parieto-occipital area: a one-year experience at muhimbili orthopaedic institute, Dar es Salaam. *Inter J Neurosurg*. 2012;1:117-121.
37. Athanasakis E, Ermidou D. Post-operative complications of ventriculoperitoneal shunt in hydrocephalic pediatric patients-nursing care. *Inter J Caring Sci*. 2011;4:66-71.
38. Braga MHV, Carvalho GTC, Brandão RACS, Lima FBF, Costa BS. Early shunt complications in 46 children with hydrocephalus. *Arq Neuropsiquiatr*. 2009;67:273-277.
39. Wang KW, Chang WN, Shih TY, et al. Infection of cerebrospinal fluid shunts: causative pathogens, clinical features, and outcomes. *Jpn J Infect Dis*. 2004;57(2):44-48.
40. Forward KR, Fewer HD, Stiver HG. Cerebrospinal fluid shunt infections: a review of 35 infections in 32 patients. *J Neurosurg*. 1983;59(3):389-394.
41. Miller JP, Fulop SC, Dashti SR, Robinson S, Cohen AR. Rethinking the indications for the ventriculoperitoneal shunt tap. *J Neurosurg Pediatrics*. 2008;1(6):435-438.
42. Shurtleff DB, Foltz EL, Weeks RD, Loeser J. Therapy of *Staphylococcus epidermidis*: infections associated with cerebrospinal fluid shunts. *Pediatrics*. 1974;53(1):55-62.
43. Schreffler RT, Schreffler AJ, Wittler RR. Treatment of cerebrospinal fluid shunt infections: a decision analysis. *Pediatr Infect Dis J*. 2002;21(7):632-636.
44. Raffa G, Marseglia L, Gitto E, Germanò A. Antibiotic-impregnated catheters reduce ventriculoperitoneal shunt infection rate in high-risk newborns and infants. *Childs Nerv Syst*. 2015;31:1129-1138.
45. Ratilal BO, Costa J, Sampaio C. Antibiotic prophylaxis for surgical introduction of intracranial ventricular shunts. *Cochrane Database Syst Rev*. 2006;(3).
46. Rotim K, Miklic P, Paladino J, Melada A, Marcikic M, Scap M. Reducing the incidence of infection in pediatric cerebrospinal fluid shunt operations. *Childs Nerv Syst*. 1997;13:584-587.
47. McGirt MJ, Buck DW, Sciubba D, et al. Adjustable vs set-pressure valves decrease the risk of proximal shunt obstruction in the treatment of pediatric hydrocephalus. *Childs Nerv Syst*. 2007;23:289-295.
48. Dickerman RD, McConathy WJ, Morgan J, et al. Failure rate of frontal versus parietal approaches for proximal catheter placement in ventriculoperitoneal shunts: revisited. *J Clin Neurosci*. 2005;12(7):781-783.
49. Becker DP, Nulsen FE. Control of hydrocephalus by valve-regulated venous shunt: avoidance of complications in prolonged shunt maintenance. *J Neurosurg*. 1968;28(3):215-226.
50. Illingworth RD. Subdural haematoma after the treatment of chronic hydrocephalus by ventriculocaval shunts. *J Neurol, Neurosurg Psychiatr*. 1970;33(1):95-99.
51. Samuelson S, Long DM, Chou SN. Subdural hematoma as a complication of shunting procedures for normal pressure hydrocephalus. *J Neurosurg*. 1972;37(5):548-551.
52. Khan QA, Wharen RE, Grewal SS, et al. Overdrainage shunt complications in idiopathic normal-pressure hydrocephalus and lumbar puncture opening pressure. *J Neurosurg*. 2013;119(6):1498-1502.
53. Carmel PW, Albright AL, Adelson PD, et al. Incidence and management of subdural hematoma/hygroma with variable-and fixed-pressure differential valves: a randomized, controlled study of programmable compared with conventional valves. *Neurosurg Focus*. 1999;7(4):E8.
54. Yadav YR, Parihar V, Pande S, Namdev H, Agarwal M. Endoscopic third ventriculostomy. *J Neurosci Rural Pract*. 2012;03(2):163-173. doi:10.4103/0976-3147.98222
55. Zhou L, Lin J, Lin J, Kui G, Zhang J, Yu Y. Neuroprotective effects of vagus nerve stimulation on traumatic brain injury. *Neural Regen Res*. 2014;9(17):1585.
56. Hakon J, Moghiseh M, Poulsen I, Øland CML, Hansen CP, Sabers A. Transcutaneous vagus nerve stimulation in patients with severe traumatic brain injury: a feasibility trial. *Neuromodulation: Technol Neural Interface*. 2020;23(6):859-864.
57. Catheters measuring intracranial pressure in the brain. RAUMEDIC. (n.d.). https://www.raumedic.com/us/application-areas/neuromonitoring/neuro-icu/icp-measurement
58. Bjornson A, Henderson D, Lawrence E, McMullan J, Ushewokunze S. The sensor reservoir-does it change management? *Acta Neurochir*. 2021;163(4):1087-1095. doi:10.1007/s00701-021-04729-y
59. Isaacs AM, Ball CG, Sader N, et al. Reducing the risks of proximal and distal shunt failure in adult hydrocephalus: a shunt outcomes quality improvement study. *J Neurosurg*. 2022;136(3):877-886. doi:10.3171/2021.2.JNS202970
60. Publications. Rhaeos. 2023. https://www.rhaeos.com/publications/
61. Embrace2 seizure monitoring: Smarter epilepsy management: embrace watch. Empatica. (n.d.). https://www.empatica.com/embrace2/

62. iOS-Health. Apple. (n.d.). https://www.apple.com/ios/health/
63. Smart technology to help you transform your health. Fitbit Technology. (n.d.). https://www.fitbit.com/global/us/technology
64. Health science: Garmin technology. Health Science. Garmin Technology. (n.d.). https://www.garmin.com/en-US/garmin-technology/health-science/
65. Das A, Bhadran B, Sanker V, Suresh V, Agarwal P, Dave T. Pediatric primary intraventricular hemorrhage: a case report of isolated fourth ventricle hemorrhage in a 10-year-old boy. *Clin Case Rep*. 2023;11(9):e7952. doi:10.1002/ccr3.7952
66. du Plessis AJ. The role of systemic hemodynamic disturbances in prematurity-related brain injury. *J Child Neurol*. 2009;24(9):1127-1140.
67. Kazan S, Güra A, Uçar T, Korkmaz E, Ongun H, Akyuz M. Hydrocephalus after intraventricular hemorrhage in preterm and low-birth weight infants: analysis of associated risk factors for ventriculoperitoneal shunting. *Surg Neurol*. 2005;64(64 suppl):S77-S81; Discussion S81.
68. Ahn SY, Shim SY, Sung IK. Intraventricular hemorrhage and post hemorrhagic hydrocephalus among very-low-birth-weight infants in Korea. *J Korean Med Sci*. 2015;30(suppl 1):S52-S58.
69. Murphy BP. Posthaemorrhagic ventricular dilatation in the premature infant: natural history and predictors of outcome. *Archiv Dis Childhood-Fetal Neonatal Edition*. 2002;87(1):37F-41F.
70. Schmitz T, Heep A, Groenendaal F, et al. Interleukin-1β, interleukin-18, and interferon-γ expression in the cerebrospinal fluid of premature infants with posthemorrhagic hydrocephalus—markers of white matter damage? *Pediatr Res*. 2007;61(6):722-726.
71. Di Rocco C, Massimi L, Tamburrini G. Shunts vs endoscopic third ventriculostomy in infants: are there different types and/or rates of complications? a review. *Childs Nerv Syst*. 2006;22(12):1573-1589.
72. Robinson S. Neonatal posthemorrhagic hydrocephalus from prematurity: pathophysiology and current treatment concepts. *J Neurosurg: Pediatr*. 2012;9(3):242-258.
73. Drake JM, Kestle JR, Tuli S. CSF shunts 50 years on—past, present and future. *Child's Nervous System: ChNS*. 2000;16(10-11):800-804.
74. Di Rocco C, Marchese E, Velardi F. A survey of the first complication of newly implanted CSF shunt devices for the treatment of nontumoral hydrocephalus. Cooperative survey of the 1991–1992 Education Committee of the ISPN. *Childs Nerv Syst*. 1994;10(5):321-327.
75. Hinson HE, Hanley DF, Ziai WC. Management of intraventricular hemorrhage. *Curr Neurol Neurosci Rep*. 2010;10(2):73-82.
76. Morgan T, Awad I, Keyl P, Lane K, Hanley D. Preliminary report of the clot lysis evaluating accelerated resolution of intraventricular hemorrhage (CLEAR-IVH) clinical trial. *Acta Neurochir Suppl*. 2008;105:217-220.
77. Webb AJS, Ullman NL, Mann S, Muschelli J, Awad IA, Hanley DF. Resolution of intraventricular hemorrhage varies by ventricular region and dose of intraventricular thrombolytic: the clot lysis: evaluating accelerated resolution of IVH (CLEAR IVH) program. *Stroke*. 2012;43(6):1666-1668.
78. Naff N, Williams MA, Keyl PM, et al. Low-dose recombinant tissue-type plasminogen activator enhances clot resolution in brain hemorrhage: the intraventricular hemorrhage thrombolysis trial. *Stroke*. 2011;42(11):3009-3016.
79. Ziai WC, Tuhrim S, Lane K, et al. A multicenter, randomized, double-blinded, placebo-controlled phase III study of Clot Lysis Evaluation of Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III). *Int J Stroke*. 2014;9(4):536-542.
80. Whitelaw A, Evans D, Carter M, et al. Randomized clinical trial of prevention of hydrocephalus after intraventricular hemorrhage in preterm infants: brain-washing versus tapping fluid. *Pediatrics*. 2007;119(5):e1071-e1078.
81. Drake JM. The surgical management of pediatric hydrocephalus. *Neurosurgery*. 2008;62(suppl 2):633-640; Discussion 640-642.
82. Horinek D, Cihar M, Tichy M. Current methods in the treatment of posthemorrhagic hydrocephalus in infants. *Bratisl Lek Listy*. 2003;104(11):347-351.
83. Roland EH, Hill A. Intraventricular hemorrhage and posthemorrhagic hydrocephalus. *Clin Perinatol*. 1997;24(3):589-605.
84. Hasan D, Vermeulen M, Wijdicks EF, Hijdra A, van Gijn J. Management problems in acute hydrocephalus after subarachnoid hemorrhage. *Stroke*. 1989;20(6):747-753.
85. Hoekema D, Schmidt RH, Ross I. Lumbar drainage for subarachnoid hemorrhage: technical considerations and safety analysis. *Neurocrit Care*. 2007;7(1):3-9.
86. Murad A, Ghostine S, Colohan ART. Role of controlled lumbar CSF drainage for ICP control in aneurysmal SAH. *Acta Neurochir Suppl*. 2011;110(2):183-187.
87. Souminen P, Kivioja A, Öhman J, Korpela R, Rintala R, Olkkola KT. Severe and fatal childhood trauma. *Injury*. 1998;29(6):425-430.
88. Jennett B. Epidemiology of head injury. *Arch Dis Child*. 1998;78(5):403-406.
89. De Bonis P, Tamburrini G, Mangiola A, et al. Posttraumatic hydrocephalus is a contraindication for endoscopic third ventriculostomy: isn't it? *Clin Neurol Neurosurg*. 2013;115(1):9-12.
90. Oder GW. Outcome after shunt implantation in severe head injury with posttraumatic hydrocephalus. *Brain Inj*. 2000;14(4):345-354.
91. Silver BV, Chinarian J. Neurologic improvement following shunt placement for post-traumatic hydrocephalus in a child. *Pediatr Rehabil*. 1997;1(2):123-126.
92. Honeybul S, Ho KM. Incidence and risk factors for posttraumatic hydrocephalus following decompressive craniectomy for intractable intracranial hypertension and evacuation of mass lesions. *J Neurotrauma*. 2012;29(10):1872-1878.
93. Wang QP, Ma JP, Zhou ZM, You C. Impact of operation details on hydrocephalus after decompressive craniectomy. *Neurosciences*. 2016;21(1):10-16.
94. Ding J, Guo Y, Tian H. The influence of decompressive craniectomy on the development of hydrocephalus: a review. *Arq Neuropsiquiatr*. 2014;72(9):715-720.
95. Hanley DF. Intraventricular hemorrhage: severity factor and treatment target in spontaneous intracerebral hemorrhage. *Stroke*. 2009;40(4):1533-1538.
96. Graff-Radford NR. Factors associated with hydrocephalus after subarachnoid hemorrhage. A report of the Cooperative Aneurysm Study. *Arch Neurol*. 1989;46(7):744-752.
97. Cordobés F, de la Fuente M, Lobato RD, et al. Intraventricular hemorrhage in severe head injury. *J Neurosurg*. 1983;58(2):217-222.
98. Pang D, Sclabassi RJ, Horton JA. Lysis of intraventricular blood clot with urokinase in a canine model: part 1. Canine intraventricular blood cast model. *Neurosurgery*. 1986;19(4):540-546.
99. Mayfrank L, Kissler J, Raoofi R, et al. Ventricular dilatation in experimental intraventricular hemorrhage in pigs. *Stroke*. 1997;28(1):141-148.
100. Pang D, Sclabassi RJ, Horton JA. Lysis of intraventricular blood clot with urokinase in a canine model: part 3. Effects of intraventricular urokinase on clot lysis and posthemorrhagic hydrocephalus. *Neurosurgery*. 1986;19(4):553-572.
101. Brinker T, Seifert V, Dietz H. Subacute hydrocephalus after experimental subarachnoid hemorrhage. *Neurosurgery*. 1992;31(2):306-312; Discussion 311-312.
102. Kramer AH, Jenne CN, Zygun DA, et al. Intraventricular fibrinolysis with tissue plasminogen activator is associated with transient cerebrospinal fluid inflammation: a randomized controlled trial. *J Cereb Blood Flow Metab*. 2015;35(8):1241-1248.

103. King NKK, Lai JL, Tan LB, et al. A randomized, placebo-controlled pilot study of patients with spontaneous intraventricular haemorrhage treated with intraventricular thrombolysis. *J Clin Neurosci*. 2012;19(7):961-964.
104. Naff NJ, Carhuapoma JR, Williams MA, et al. Treatment of intraventricular hemorrhage with urokinase: effects on 30-day survival. *Stroke*. 2000;31(4):841-847.
105. Gaberel T, Magheru C, Parienti JJ, Huttner HB, Vivien D, Emery E. Intraventricular fibrinolysis versus external ventricular drainage alone in intraventricular hemorrhage: a meta-analysis. *Stroke*. 2011;42(10):2776-2781.
106. Tan Q, Chen Q, Niu Y, et al. Urokinase, a promising candidate for fibrinolytic therapy for intracerebral hemorrhage. *J Neurosurg*. 2016:1-10.
107. Hua Y, Keep RF, Hoff JT, Xi G. Brain injury after intracerebral hemorrhage: the role of thrombin and iron. *Stroke*. 2007;38 (2 suppl):759-762.
108. Matsuoka H, Hamada R. Role of thrombin in CNS damage associated with intracerebral haemorrhage: opportunity for pharmacological intervention? *CNS Drugs*. 2002;16(8):509-516.
109. Li L, Tao Y, Tang J, et al. A cannabinoid receptor 2 agonist prevents thrombin-induced blood-brain barrier damage via the inhibition of microglial activation and matrix metalloproteinase expression in rats. *Transl Stroke Res*. 2015;6(6):467-477.
110. Gao F, Liu F, Chen Z, Hua Y, Keep RF, Xi G. Hydrocephalus after intraventricular hemorrhage: the role of thrombin. *J Cereb Blood Flow Metab*. 2014;34(3):489-494.
111. Li T, Zhang P, Yuan B, Zhao D, Chen Y, Zhang X. Thrombin-induced TGF-β1 pathway: A cause of communicating hydrocephalus post subarachnoid hemorrhage. *Int J Mol Med*. 2013;31(3):660-666.
112. Bu Y, Chen M, Gao T, Wang X, Li X, Gao F. Mechanisms of hydrocephalus after intraventricular haemorrhage in adults. *BMJ*. 2016;1(1):23-27.
113. Shishido H, Toyota Y, Hua Y, Keep RF, Xi G. Role of lipocalin 2 in intraventricular hemoglobin-induced brain injury. *Stroke Vascular Neurol*. 2016.
114. Strahle JM, Garton T, Bazzi AA, et al. Role of hemoglobin and iron in hydrocephalus after neonatal intraventricular hemorrhage. *Neurosurgery*. 2014;75(6):696-706; Discussion 706.
115. Meng H, Li F, Hu R, et al. Deferoxamine alleviates chronic hydrocephalus after intraventricular hemorrhage through iron chelation and Wnt1/Wnt3a inhibition. *Brain Res*. 2015;1602:44-52.
116. Gao C, Du H, Hua Y, Keep RF, Strahle J, Xi G. Hydrocephalus after intraventricular hemorrhage: the role of thrombin. *J Cerebral Blood Flow Metabolism*. 2014;34(3):489-494.
117. Xiong XY, Wang J, Qian ZM, Yang QW. Iron and intracerebral hemorrhage: from mechanism to translation. *Transl Stroke Res*. 2014;5(4):429-441.
118. Hirst RA, Rutman A, O'Callaghan C. Hydrogen peroxide at a concentration used during neurosurgery disrupts ciliary function and causes extensive damage to the ciliated ependyma of the brain. *Childs Nerv Syst*. 2009;25(5):559-561.
119. Yang S, Nakamura T, Hua Y, et al. The role of complement C3 in intracerebral hemorrhage-induced brain injury. *J Cereb Blood Flow Metab*. 2006;26(12):1490-1495.
120. Zhao X, Sun G, Zhang J, et al. Hematoma resolution as a target for intracerebral hemorrhage treatment: role for peroxisome proliferator-activated receptor γ in microglia/macrophages. *Ann Neurol*. 2007; 61(4):352-362.
121. Zhao X, Grotta J, Gonzales N, Aronowski J. Hematoma resolution as a therapeutic target: the role of microglia/macrophages. *Stroke*. 2009;40(3 suppl):S92-S94.
122. Zhao H, Garton T, Keep RF, Hua Y, Xi G. Microglia/macrophage polarization after experimental intracerebral hemorrhage. *Transl Stroke Res*. 2015;6(6):407-409.
123. Del Bigio MR. Neuropathology and structural changes in hydrocephalus. *Develop Disabilities Res Rev*. 2010;16(1):16-22.
124. Turgut M, Erdogan S, Ergin K, Serter M. Melatonin ameliorates blood-brain barrier permeability, glutathione, and nitric oxide levels in the choroid plexus of the infantile rats with kaolin-induced hydrocephalus. *Brain Res*. 2007;1175:117-125.
125. Luciano MG, Skarupa DJ, Booth AM, Wood AS, Brant CL, Gdowski MJ. Cerebrovascular adaptation in chronic hydrocephalus. *J Cereb Blood Flow Metab*. 2001;21(3):285-294.
126. Heep A, Stoffel-Wagner B, Bartmann P, et al. Vascular endothelial growth factor and transforming growth factor-β1 are highly expressed in the cerebrospinal fluid of premature infants with posthemorrhagic hydrocephalus. *Pediatr Res*. 2004;56(5): 768-774.
127. Chávez JC, Agani F, Pichiule P, LaManna JC. Expression of hypoxiainducible factor-1alpha in the brain of rats during chronic hypoxia. *J Appl Physiol*. 2000;89(5):1937-1942.
128. Shim JW, Sandlund J, Han CH, et al. VEGF, which is elevated in the CSF of patients with hydrocephalus, causes ventriculomegaly and ependymal changes in rats. *Exp Neurol*. 2013;247:703-709.
129. Gao J, Grill RJ, Dunn TJ, et al. Human neural stem cell transplantation-mediated alteration of microglial/macrophage phenotypes after traumatic brain injury. *Cell Transplant*. 2016;25: 1863-1877.
130. Borlongan CV, Glover LE, Tajiri N, Kaneko Y, Freeman TB. The great migration of bone marrow-derived stem cells toward the ischemic brain: therapeutic implications for stroke and other neurological disorders. *Prog Neurobiol*. 2011;95:213-228. doi:10.1016/j.pneurobio.2011.08.005
131. Cherian SS, Love S, Silver IA, Porter HJ, Whitelaw AGL, Thoresen M. Posthemorrhagic ventricular dilation in the neonate: development and characterization of a rat model. *J Neuropathol Exp Neurol*. 2003;62:292-303.
132. Ahn SY, Chang YS, Sung DK, et al. Mesenchymal stem cells prevent hydrocephalus after severe intraventricular hemorrhage. *Stroke*. 2013;44(2):497-504. doi:10.1161/STROKEAHA.112.679092
133. Chang YS, Choi SJ, Sung DK, et al. Intratracheal transplantation of human umbilical cord blood-derived mesenchymal stem cells dose-dependently attenuates hyperoxia-induced lung injury in neonatal rats. *Cell Transplant*. 2011;20:1843-1854.
134. Chang YS, Oh W, Choi SJ, et al. Human umbilical cord blood-derived mesenchymal stem cells attenuate hyperoxia-induced lung injury in neonatal rats. *Cell Transplant*. 2009;18:869-886.
135. Purohit D, Finkel DA, Malfa A, et al. Human cord blood derived unrestricted somatic stem cells restore aquaporin channel expression, reduce inflammation and inhibit the development of hydrocephalus after experimentally induced perinatal intraventricular hemorrhage. *Front Cell Neurosci*. 2021;15:633185. doi:10.3389/fncel.2021.633185
136. Ahn SY, Chang YS, Sung SI, Park WS. Mesenchymal stem cells for severe intraventricular hemorrhage in preterm infants: phase I dose-escalation clinical trial. *Stem Cells Transl Med*. 2018;7(12): 847-856. doi:10.1002/sctm.17-0219
137. Sutsko RP, Young KC, Ribeiro A, et al. Long-term reparative effects of mesenchymal stem cell therapy following neonatal hyperoxia-induced lung injury. *Pediatr Res*. 2013;73:46-53.
138. Can A, Celikkan FT, Cinar O. Umbilical cord mesenchymal stromal cell transplantations: a systemic analysis of clinical trials. *Cytotherapy*. 2017;19:1351-1382.
139. Wildrick D. Intraventricular hemorrhage and long-term outcome in the premature infant. *J Neurosci Nurs*. 1997;29:281-289.
140. Mashkouri S, Crowley M, Liska M, Corey S, Borlongan C. Utilizing pharmacotherapy and mesenchymal stem cell therapy to reduce inflammation following traumatic brain injury. *Neural Regen Res*. 2016;11:1379-1384. doi:10.4103/1673-5374.191197

141. Disdier C, Stonestreet BS. Hypoxic-ischemic-related cerebrovascular changes and potential therapeutic strategies in the neonatal brain. *J Neurosci Res*. 2020;98:1468-1484. doi:10.1002/jnr.24590
142. Bonsack B, Corey S, Shear A, et al. Mesenchymal stem cell therapy alleviates the neuroinflammation associated with acquired brain injury. *CNS Neurosci Ther*. 2020;26(6):603-615.
143. Jiang L, Gao G, Zhou Y. Endoscopic third ventriculostomy and ventriculoperitoneal shunt for patients with noncommunicating hydrocephalus. *Medicine*. 2018;97(42):e12139.
144. Gross BA, Jankowitz BT, Friedlander RM. Cerebral intraparenchymal hemorrhage: a review. *JAMA*. 2019;321(13):1295-1303. doi:10.1001/jama.2019.2413
145. Clarfield AM. Normal-pressure hydrocephalus-reply. *JAMA: J Am Med Associa*. 1990;264(3):336-337. doi:10.1001/jama.1990.03450030052025

How to cite this article: Sanker V, Kundu M, El Kassem S, et al. Posttraumatic hydrocephalus: recent advances and new therapeutic strategies. *Health Sci Rep*. 2023;6:e1713. doi:10.1002/hsr2.1713