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Pediatric Traumatic Brain Injury: Characteristic Features, Diagnosis, and Management

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Abstract

Traumatic brain injury (TBI) is the leading cause of death and disability in children. Pediatric TBI is associated with several distinctive characteristics that differ from adults and are attributable to age-related anatomical and physiological differences, pattern of injuries based on the physical ability of the child, and difficulty in neurological evaluation in children. Evidence suggests that children exhibit a specific pathological response to TBI with distinct accompanying neurological symptoms, and considerable efforts have been made to elucidate their pathophysiology. In addition, recent technical advances in diagnostic imaging of pediatric TBI has facilitated accurate diagnosis, appropriate treatment, prevention of complications, and helped predict long-term outcomes. Here a review of recent studies relevant to important issues in pediatric TBI is presented, and recent specific topics are also discussed. This review provides important updates on the pathophysiology, diagnosis, and age-appropriate acute management of pediatric TBI.

Key words: traumatic brain injury, pediatric, treatment, intensive care, intracranial pressure

Introduction

Traumatic brain injury (TBI) is the leading cause of death and disability in children. TBI in children result in a range of traumatic injuries to the scalp, skull, and brain that are comparable to those in adults but differ in both pathophysiology and management. The differences are attributable to age-related structural change, mechanism of injuries based on physical ability of the child, and the difficulty in neurological evaluation of pediatric populations. The scalp is highly vascularized and a potential cause of lethal blood loss. Even a small loss of blood volume can lead to hemorrhagic shock in a newborn, infant, and toddler, which may occur without apparent external bleeding. Therefore, children are considered to exhibit a specific pathological response to brain injury and accompanying neurological symptoms. Advances in diagnostic imaging have improved the quality of care by assisting healthcare providers to evaluate and diagnose children with TBI. In addition, magnetic resonance imaging (MRI) has facilitated accurate diagnosis, appropriate selection of treatment, prevention of further complications such as higher brain dysfunction as well as post-traumatic seizures.

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Epidemiology

Unintentional injuries are the leading cause of death in children. Of all the types of traumatic injuries, brain injuries are the most likely to result in death or permanent disability. A large amount of data has emerged from studies by the U.S. Centers for Disease Prevention and Control regarding pediatric TBI. An estimated 475,000 people in U.S. in the age group of 0–14 years sustain TBI annually, of which up to 90% return home with mild injuries, 37,000 are hospitalized, and 2,685 die because of their injuries. A study with respect to age in the same year revealed that emergency consultations were most common among children aged 0–4 years (1,035 per 100,000 children), and of these, 80 per 100,000 children were hospitalized. The annual death rate from traumatic injury in children younger than 4 years is 5 per 100,000. The death rate is higher for children younger than 4 years than for those 5–14 years of age. The higher traumatic injury death rate in younger children may reflect the number of abusive injuries in infants and young children.[1] Hospitalization for TBI was most commonly observed in adolescents (129 per 100,000). More boys were found to undergo emergency consultation and hospitalization than girls.[2] The most common mechanisms of pediatric TBI vary

according to age. Falls are the leading cause of TBI in children younger than 14 years of age.[3] Children younger than 4 years of age are injured mainly by falls but are also affected by abusive injuries and motor vehicle accidents. Children 4–8 years of age are injured in falls and motor vehicle accidents but also become more at risk for other transportation-related injuries such as bicycle-related incidents.[4] Abusive head trauma (AHT) is particularly common in young infants aged less than 2 years; approximately 30 of every 100,000 infants aged less than 1 year were hospitalized for AHT.[5]

Injury characteristics according to age and development

The clinical presentation of children with head injury is extremely variable depending on the severity of trauma. The Pediatric Glasgow Coma Scale (PGCS) is commonly used to assess consciousness and to define the severity of head injuries. Generally, neurological deficits are found at the time of injury, and newly appeared clinical signs may indicate further progression of pathological changes due to head injuries and should be carefully investigated. The evolving anatomy and age-specific properties of the skull, face, brain, and neck muscles make children susceptible for distinctive types of injuries that are not encountered in adults. (Table 1.)

There are unique biomechanical properties for pediatric brain injury due to a combination of higher plasticity and deformity, whereby external forces are absorbed in a different way compared to adults. The infant skull is less rigid, and open sutures function as joints, allowing for a small degree of movement in response to a mechanical stress.[6] However, intra and extracranial injuries are also associated with a normal delivery and even intracranial hemorrhages can be seen in vaginal deliveries because of compression and traction exerted on the fetal head during its passage through the birth canal with the use of obstetric instruments. Neonates are prone to have conditions such as cephalic hematoma and subgaleal hematoma. Since it has been well known that a low birth weight and hypoxemia are risk factors for intraventricular hemorrhage in this age group, those factors should be differentiated from AHT and coagulopathy.[7]

Shaking usually produces slight deformation of the skull, and high plasticity of the skull results in share forces between the skull and adjacent cortical vessels and brain. These share forces may result in stretching and sharing injuries of the vessels and brain parenchyma.[8] Children have larger heads than adults in relation to their body size. Consequently, the likelihood of the head being hit in pediatric trauma is higher than that in adults. The relation between head and body size continuously declines with increasing age. Furthermore, the head is relatively heavy compared to the rest of the body making the head more vulnerable to TBI and results in different dynamics of head acceleration due to the external forces.

The cerebral white matter contains little myelin, and its distribution is very different in newborns compared with that in adults. The neonatal brain is watery, while the myelinated brain has a much higher density due to the progressing myelination and progressively lowering of the water content. Temporal differences between myelination of various brain areas are pronounced during progressing development. Myelination follows programmed patterns with a caudo-cranial and posterior-anterior

Table 1 Injury characteristics according to age and development

Newborns	• Delivery head injury • Intracranial hemorrhages • Cephalic hematoma • Subgaleal hematoma	• Caused by head compression and traction through the birth canal (vaginal delivery) with obstetric instruments. • A low birth weight and hypoxemia are risk factors for intracranial hemorrhage.
Infants	• Accidental head injury • Abusive Head Trauma	• Caused by inappropriate childcare practices. • If mechanism of injury is not clear, careful consideration for diagnosis of child abuse is required. AHT is the most common cause of TBI-related hospitalization and death.
Toddlers and School children	• Accidental head injury	• Caused by accidents increase as children develop motor ability. • With increase in use of child safety seats, the severity of injury and the mortality has dropped. • Pedestrian injury also increases in this age group.
Adolescents	• Bicycle and motorcycle-related accidents • Sports-related head injuries	• Awareness of prevention must be raised. • Trainers and players those involved in contact sports (i.e., judo, rugby, American football) will require education about concussion.

predominance. The degree of myelination results in different absorption of traumatic forces, with increased susceptibility to TBI in the unmyelinated regions.[9]

During development, more energy can be absorbed by the sinuses, with less energy directly transmitted to the skull and brain; hence, brain damage is limited with facial development and progressive development of the paranasal sinuses. In addition, the protruding forehead in young children increases the possibility that a force directly impacts the frontal skull and underlying cerebral parenchyma. Facial growth occurs in a forward and downward direction, which increases the chances of midfacial fractures with increasing age.

Young children have weaker neck muscles, and the head is relatively heavy. The cranio-cervical stability is more dependent on the ligaments and soft tissues than on the vertebrae. In severe trauma cases, cranio-cervical junction lesions are sometimes detected. Cervical spinal fractures and cervical vascular lesions need to be ruled out in the presence of acute, focal neurological deficits that cannot be explained by the forces that directly impacted the brain (Table 2).

Table 2 Structural consideration in pediatric population

Skin	• Scalp • Epidermis / Dermis • Subcutaneous fat layer • Galea aponeurotica • Periosteum	• The younger a child is, the thinner and the poorer its ability to cushion against external forces. • Fragile and prone to blistering and tearing. • Easily retains water and microvascular breakdown causes subcutaneous hematoma. • Blood and exudate can accumulate beneath galea. • Cephalic hematoma can be calcified rarely.
Cranium	• Cranium	• The craniofacial ratio is at its greatest. Cranial sutures are loose and highly mobile. • Calvarium is soft and rich in bone marrow, connected with a periosteum, strongly attached to the bone cortex. Continuity of the skull tends to be well-maintained. Bone fragments are less likely to occur.
Brain and nerve fibers	• Nerve fibers • Brain/ Cortical veins	• Undeveloped myelin sheaths, the water content per unit volume of brain tissue is high. Fibers are pliable and less prone to rupture. • Cerebral contusion by direct external force is high because of its softness. Easily extended with accelerated-decelerated motion, and can cause of subdural hematoma with disruption.
Neck and cervical spine	• Neck • Vertebrae	• Undeveloped neck muscle and poor head support. The fulcrum of the vertebral body is located in the upper cervical spine. • Ligaments and soft tissues are flexible and facets are flat. Vertebral body is prone to dislocation.

Diagnosis and Clinical Features

In general, primary TBI includes extra-parenchymal injury (epidural hematoma, subdural hematoma, subarachnoid hemorrhage, and intraventricular hemorrhage), intra-parenchymal injury (intracerebral hemorrhage, diffuse axonal injury [DAI], and intracerebral hematoma) and vascular injury such as vascular dissection, carotid artery-cavernous sinus fistula, dural arteriovenous fistula, and pseudo-aneurysm.[10]

Primary TBI

1. Skull fracture

The majority of pediatric skull fractures can be managed conservatively. Frontal bone fractures are more likely to require repair, and cases of TBI associated with fracture are more likely to involve two or three bones. Linear fractures most commonly occur in the parietal bone, followed by the occipital, frontal, and temporal bones, in that order.[11] Those fractures can be distinguished from normal sutures by their anatomical configuration, signs of ossification along sutures, and the presence of complex serrations. Extracranial subcutaneous swelling is an important clinical feature to indirectly diagnose skull fractures. In a recent report, 2D+3D computed tomography (CT) in combination were shown to have high sensitivity in the diagnosis of linear skull fractures in all children and increased specificity in children less than 2 years of age, with concurrent intracranial lesions being detected in 15%–30% of these cases.[12] Hospitalization is not necessary for many children with non-displaced skull fractures but patients with mental status changes, additional injuries, or those suspected to be cases of AHT may require hospitalization.[13]

Among depressed fractures, simple type is more common in children and results from localized external force. Compound type accounts for 42%–66% of all fractures in children, and 9% of all fractures in children aged less than 1 year. Dural injury can be observed underneath fractures; approximately 11% of pediatric depressed fractures are accompanied by dural injuries that resulted in intracranial lesions.[14,15] When fractures were seen above dural sinuses, children needed to be observed in the intensive care unit (ICU) for progression of epidural hematoma and posttraumatic venous sinus thrombosis. The ping-pong ball fractures in newborns rarely damage the dura. Spontaneous reduction can be expected in cases of simple depressed fracture in newborns, but older children may require cranioplasty. The current guidelines for surgical management of TBI recommends surgical repair in the following cases: (1) Cerebrospinal fluid (CSF) leak is clearly recognized, (2) detection of foreign body, (3) debridement of the local wound is deemed necessary, (4) infected wounds, (5) evacuation of hematoma is required, and (6) for cosmetic reasons.[16] Depressed skull fracture was claimed to be an independent risk factor for post-traumatic seizures; however, several case reports appear to refute the reported correlation between the two.[17] Postoperative improvement of neurological function in cases of depressed fracture that overlie the superior sagittal sinus have been reported and may possibly be related to improvement in venous circulation.[18,19]

Basal skull fracture (BSF) is rarely seen in children. In age groups where facial bones are still developing, BSF can result in cranial nerve and vascular injuries.[20] Fractures may present as tardive meningitis. Careful evaluation of clinical signs and symptoms is mandated in all cases.[21] Alhelali et al. reported that BSFs occurred in 26% of their patients. The temporal bone was fractured in two thirds of the patients with BSFs, and cerebrospinal fluid leaks were observed in one-third of these patients. They concluded that BSFs are indicative of a significant linear blunt force and are independent predictors of mortality.[22]

1-1. Growing skull fracture

In developing infants or young children, a leptomeningeal cyst or herniated brain tissue through dura mater can result in enlargement of the fracture line. This is due to localized pulsatile pressure via lesions that are adhered to the inner table of the skull. Such pathological changes on the skull bone will facilitate nutritional deficiencies, especially at the bone edges. In most cases, cosmetic issues such as cranial depression or pulsatile swelling are diagnostic factors, whereas headache and seizures may be observed in some cases. Reconstructed CT images are quite useful for cranioplasty. Nowadays, more radical treatment for GSF is recommended based on better understanding of the lesion pathology with the use of advanced radiographic techniques, although spontaneous resolution of GSF has also been reported.[23]

2. Intracranial injury

2-1. Acute epidural hematoma

Acute epidural hematoma (AEDH) is relatively rare in young infants as the dura mater is strongly adhered to the inner surface of the skull, especially in the vicinity of the suture lines. In neonates, the middle meningeal artery is not contained within the skull, and the groove of arteries originating from extra-carotid artery is shallow and not likely to be damaged in TBI.[24,25] AEDH in infants is basically venous and often caused by injuries that overlie the dural venous sinus or by rupture of emissary veins in the vicinity of the fracture. Posterior fossa AEDH is commonly associated with occipital fracture overlying the region from the transverse to the sigmoid sinus. Other common sites of AEDH include the middle fossa, the parasagittal area, and the calvarium. However, the possibility of an arterial AEDH, which can rapidly grow and lead to cerebral herniation and death, should not be ignored. AEDH in neonates also commonly occurs in the posterior fossa as a type of birth-related head injury. It has been demonstrated that AEDH generally does not exceed the suture line. However, hematoma from venous sinus injury can extend beyond it and even to the opposite side; therefore, intensive care is required in such cases.[26] Recently, several groups have reported successful conservative management of pediatric AEDH attributed to absorption of blood through the fracture line to the adjacent subcutaneous layer.

2-2. Acute subdural hematoma

Acute subdural hematoma (ASDH) originates between the arachnoid membrane and dura mater and is thought to result not only from vascular rupture caused by direct external force but also due to the collision of a moving skull with a stationary object. A shearing force and rotational acceleration is inflicted due to the sudden deceleration thus causing vascular and cerebral parenchymal injury.[27] In particular, AHT is a relatively common cause of acute ASDH in children less than 2 years of age. Coexistence of multiple hematomas apparently sustained at different times (chronic and acute)

in the absence of coagulopathy should be strongly suspected as a case of AHT.

Wide subdural space makes the bridging vein susceptible to traction and prone to rupture.[28] In patients with a history of cerebral atrophy, hydrocephalus following shunt placement, benign external hydrocephalus, and subdural effusion, the bridging vein can be easily extended and is eventually liable to rupture.[29] Compared to AEDH, there is a higher rate of concurrent cerebral contusions in such cases. Bilateral ASDHs are common, and hematomas are typically located on the tentorium, along the calvarium, interhemispheric fissure, falx cerebri, and tentorium cerebelli. ASDH is more likely to be thinner in pediatric population. Especially, in AHT, the extensive hypoxic-ischemic encephalopathy is usually present underneath the ASDH and may result in intracranial hypertension. In such cases, urgent craniotomy for evacuation of ASDH may sometimes lead to hypovolemic shock resulting in intraoperative cardiac arrest. Therefore, careful consideration of craniotomy is required to avoid unexpected operative complications.

2-2-1. Abusive head trauma

AHT has come to occupy an important place in severe pediatric TBI. The estimated incidence of AHT in children aged less than 1 year is between 14 and 40 in 100,000, which is comparable to that of neonatal meningitis (25–32 per 100,000 births)[30] and acute lymphocytic leukemia (28.7–36.6 per 100,000 children < 1 year of age). AHT has previously been referred to as inflicted TBI (ITBI), non-accidental head injury (NAHI), and shaken-impact syndrome. AHT is a generic term for head trauma including injury to the cranium, cerebral parenchyma, and cervical spinal cord. The mechanism of injury can be shaken, direct impact, or a combination of these, secondary brain injury due to hypoxia and/or hypotension, which is broader than syndromes such as shaken baby syndrome (SBS) that have a specific mechanism of injury. The diagnosis of SBS is contingent on observation of abnormal shaking behavior as the mechanism of injury and mandates close attention.[31] AHT is the most common cause of TBI in children less than 2 years of age; therefore, it is important to consider AHT in the differential diagnosis of children with traumatic injuries, including head injury. Clinical findings of AHT include impaired consciousness, seizures, vomiting, and delayed developmental milestones. On diagnostic imaging, ASDH is the most common finding (up to 77%–89% of all cases).[32,33] Up to 83%–90% of AHT cases have signs of ASDH on autopsy.[34,35] Other characteristic imaging findings include subarachnoid hemorrhage (SAH), Intracerebral hemorrhage (ICH), and cerebral contusion. AEDH, however, are rarely associated with AHT. Among physical findings, only "apnea" is specific to AHT, with a positive predictive value of 93%.[36] Rib fractures and retinal hemorrhage are important findings that have positive predictive values of 73% and 71%, respectively. Seizures are commonly observed in AHT. However, long bone fractures, skull fractures, and scalp injuries showed no significant association with AHT. Among ophthalmologic findings, retinal hemorrhage is observed in 74% of diagnosed AHT cases and 82% of autopsy cases. Retinal hemorrhages are often multilaminar and bilateral.[37] The absence of any superficial findings of trauma in cases of serious intracranial injury is suggestive of AHT.

2-2-2. Subdural fluid accumulation

Subdural fluid accumulation is a major subject of research linked to pediatric TBI. The accumulated fluid can vary from hematoma to a highly concentrated protein or a mixture of these. Most fluid accumulations are bilateral, and the symptoms are hard to differentiate from those generally seen in pediatric patients such as dysphoria, poor appetite, lethargy, excitability, and an enlarged head circumference. The subdural fluid collection is sometimes incidentally diagnosed on imaging. The treatment and natural course largely depend on the site of fluid accumulation (subdural or subarachnoid).[38,39] This is of interest considering its relevance to the applicability of subdural-peritoneal shunts. Y-shunt technique often successfully reduces the amount of subdural fluid collection over a period of 2–3 months.[40] Good prognosis can be expected in such cases. However, in cases of AHT, delayed enlargement of subdural space is more likely to involve the bifrontal area, but may also reflect compensated subdural fluid collection alongside extensive bilateral atrophic change in the cerebral hemispheres, an injury condition referred to as enceplalomalacia.

2-3. Traumatic subarachnoid hemorrhage

Traumatic SAH (tSAH) is caused by microvascular ruptures in the subarachnoid space or on the brain surface, circulation and redistribution of intraventricular hemorrhage, penetrated from intracranial hematomas and cerebral contusions and in the subarachnoid space. Hochstadter et al. retrospectively analyzed 171 severe TBI patients (pre-sedation Glasgow Coma Scale (GCS) ≤ 8 and head Maximum Abbreviated Injury Scale (MAIS) ≥ 4) who underwent CT head imaging within the first 24 h of hospital admission. tSAH was present in almost half of pediatric severe

TBI patients, and it was indicative of TBI severity and a higher level of care required at discharge. tSAH in pediatric patients was not independently associated with increased risk of mortality.[41]

2-4. Intraventricular hemorrhage

Intraventricular hemorrhage (IVH) is often caused by intraventricular perforations of intracerebral hematomas located next to the cerebral ventricles. In addition, IVH can be observed in the event of subependymal vascular ruptures and damage to the paraventricular structures including the fornix, transparent septum, and corpus callosum. In some instances, tSAH flows back into the ventricle systems. In diffuse axonal injuries, shear and rotational forces can rupture subependymal and ventral corpus callosum blood vessels, causing IVH. In pediatric IVH, intensive care is required to monitor for signs of secondary hydrocephalus. Post-traumatic hydrocephalus is usually caused by either obstruction of the aqueduct or malabsorption of CSF due to subarachnoid granular obstruction. In addition, degradation products of red blood cells can cause chemical ependymitis.[42]

Evidence for treatment of IVH is rather deficient. Further research is required into the specific trauma-related phenomenon associated with IVH.

2-5. Cerebral contusions

Cerebral contusions are relatively common in pediatric TBI and tend to occur just below the site of impact of external force (coup injury). Contusions are seen usually on the gray matter, while the white matter is often relatively well preserved. Lesions tend to occur in the both frontal and temporal lobes because of the irregular surface of the cranial base, and the anatomical contiguity of the crista galli and the petrous bone to the cortex.[43] Lesions on the opposite site of the impacted area (contrecoup injury) are rarely seen in infants. However, cerebral swelling caused by primary contusion may quickly develop into extensive hypoxic lesion surrounding the original lesions. The progression of each focal hypoxic lesion may induce extensive secondary brain injury and influence the focal cerebral blood circulation as well. This may in turn aggravate cerebral ischemia at the site of primary lesion. Rapid increase in focal cerebral pressure in the limited compartments such as middle or posterior fossa can quickly progress to cerebral herniation and death.

2-6. Diffuse axonal injury

Classically, symptoms of DAI include coma with decorticate and decerebrate posturing. With recent advances in imaging technology and the development of new MRI sequences, the association between mild TBI and high cognitive function, especially in the pediatric population, has attracted much attention. Therefore, radiological evidence of DAI based on MRI findings may enable a more definitive diagnosis of DAI rather than relying only on clinical symptoms.[44] Recently, a case of axonal injury in the cervical spine was documented in an infant with AHT. Such patients tend to present complex pathological features due to repeated instances of external force applied throughout the brain from various motions. In DAI, blood vessels and nerve fibers are liable to be injured by shear force. Furthermore, changes are observed in the axons of the subcortical white matter of the frontal and parietal lobes as well as in the ampulla, basal ganglia, internal capsule, and the central corpus callosum. The diagnosis of DAI in pediatric TBI requires careful consideration as in the adult cases.[43]

2-7. Intracerebral hemorrhage

The intrinsic causes of intracerebral hemorrhage (ICH) may be difficult to determine, especially in children with congenital vascular abnormalities such as arterio-venous malformations. Traumatic ICH is commonly observed in the frontal and temporal white matter but may also be seen in the basal ganglia and the cerebellum due to disruption of perforators. Delayed traumatic intracerebral hemorrhage (DTICH) typically occurs in geriatric TBI patients who have multiple intraparenchymal contusions with possible coagulopathy. However, it should be considered in the differential diagnosis of children who develop sudden neurological deterioration and the condition requires urgent intervention.[45–47]

Secondary TBI

1. Diffuse cerebral swelling

Diffuse cerebral swelling (DCS) is among the most life-threatening complications of TBI and commonly noted on CT of AHT patients. Based on a retrospective study of a series of 118 patients with DCS, Lang et al. reported that CT findings of DCS tend to develop more readily in children because of the relative lack of cerebrospinal fluid available for displacement. They also observed a relatively benign disease course in children as compared to that in adults, except in cases with severe primary injury or secondary hypotensive insult.[48] Due to an underdeveloped auto-regulatory mechanism for cerebral blood flow (CBF), children are particularly vulnerable to cerebral hyperemia, which can result in serious intracranial hypertension.[49] In preclinical studies, excessive exposure of immature brain tissue

to excitatory neuro-transmitters was shown to enhance inflammatory response, vascular permeability, and accelerated pathological changes. In addition, infants have a low mean arterial pressure with little reserve capacity to counter low blood pressure and hypoxia, which renders them liable to develop a fatal decrease in CBF.[50] These mechanisms appear to play a key role in the pathogenesis of DCS. The typical CT findings of DCS include hemispheric extensive low density lesion with effacement of cerebral sulci and cisterns as well as ventricular system (Big Black Brain).[51,52]

Management of Severe Pediatric TBI

1. Intracranial Pressure monitoring

Use of intraparenchymal intracranial pressure (ICP) sensor is an invasive method but is the only scientifically proven method for early detection of increased ICP in children with severe TBI. In a recent report, use of ICP monitoring for this purpose was associated with reduced in-hospital deaths of children with severe TBI.[53] On the other hand, Alkhoury et al. analyzed patients' data from the National Trauma Data Bank to determine the effect of ICP monitoring on survival in pediatric patients with severe TBI. They suggested that there is a survival advantage in patients who have ICP monitors and a GCS score of 3 with a longer hospital length of stay, longer ICU stay, and more ventilator days compared with those without ICP monitors.[54] The contribution of variable ICP monitoring rates to interhospital variation in pediatric TBI mortality was modest.

2. Cerebral perfusion pressure

The effect of ICP and cerebral perfusion pressure (CPP) on outcomes of TBI in adults is well acknowledged.[55,56] In adults, common practice is to augment arterial blood pressure in instances of raised ICP. However, not only marked elevations of CPP accelerate edema leading to secondary intracranial hypertension,[57,58] but they can frequently contribute to systemic insult.[59] This is more frequently observed in patients who present with a reduced GCS.[60] Although there is insufficient level I & II evidence to support the notion that uncontrolled ICP and CPP affects outcomes, joint management of ICP and CPP is considered a standard practice for management of children with severe TBI.[61] In some cohorts, strong association of high ICP with morbidity was well-demonstrated. However, Brady et al.[62] found a significant correlation between outcomes and CPP, especially the deviation from optimal CPP. The concept of individualized CPP in the adult population has been around for over a decade[63] and has recently been proposed as an optional strategy in the current TBI guidelines.[64] While there have been no large studies to determine CPP in children, Chambers et al.[59] proposed age-stratified critical levels of CPP. Specifically, in the age groups 2–6, 7–10, and 11–16 years, CPP values of 43, 54, and 58 mmHg, respectively, were associated with good outcomes.[58] Using ΔCPP values, it was observed that deviation of values of CPP from optimum levels affected the association between pressure and outcomes. In particular, those who spent more time with CPP lower than optimal CPP appeared to have relatively poorer outcomes.

3. Treatment[61]

3-1. Therapeutic uses of sedatives, analgesics, and neuromuscular blockade

Sedatives and analgesics are required for general care of all TBI children to achieve a level of anesthesia needed for invasive procedures, such as airway management, ICP control, to synchronize respiratory efforts with the ventilator, and anxiety relief during diagnostic imaging. Mostly, combination of opioids and benzodiazepines for pain control and sedation are used in children with severe TBI. Continuous infusion of Propofol is prohibited to use for children due to propofol infusion syndrome. However, neuromuscular blockade is utilized in children with severe TBI to improve compliance with mechanical ventilation, reduce metabolic demand, and eliminate shivering. Sanfilippo et al. confirmed the lack of evidence on the effect of neuromuscular blockade on ICP and related outcomes in his recent systematic review.[65]

3-2. Hyperosmolar therapy

Intravenous mannitol and hypertonic saline are routinely used to control intracranial hypertension in children with severe TBI. Those osmotic agents are used after or concurrently with sedation, mild hyperventilation, and CSF drainage. Mannitol has been the traditional agent to use and a 20% of mannitol dose of 0.25–1.0 g/kg is often repeatedly administered. Treatment should be titrated to maintain plasma osmolality at ≤ 310 mOsm/L. Prevention of hypovolemia is another component of management of TBI. Recently, hypertonic saline has become one of the most popular options to treat intracranial hypertension in the North America. In a pediatric double-blind study, 3% saline resulted in a more significant reduction in ICP than 0.9% saline. Similarly, in a randomized controlled trial, 1.7% saline was superior to lactated Ringer's solution in ICP reduction. Hypertonic saline may warrant consideration as the first-line drug for treating increased ICP, as it was associated with the most favorite cerebral hemodynamics and fastest

resolution of intracranial hypertension in children with severe TBI.[66]

3-3. Cerebrospinal fluid drainage

Cerebrospinal fluid drainage is used to reduce the volume of the contents of the intracranial vault for the management of increased ICP. An external ventricular drain is commonly used to drain off the CSF. The addition of a lumbar drain may be considered in the case of refractory intracranial hypertension with a functioning external ventricular drainage (EVD), open basal cisterns, and no evidence of a mass lesion or shift on imaging studies. Therapy may be associated with an increased risk of complications from hemorrhage and infection.

3-4. Hyperventilation

Hyperventilation reduces ICP by lowering CBF by cerebral vasoconstriction of arterioles. A significant decrease in CBF is expected to occur within 48 h of injury, and hyperventilation may lead to subclinical cerebral ischemia and a reduction in cerebral oxygenation. Therefore, severe hyperventilation should be avoided. Mild hyperventilation ($PaCO_2$, 30–35 mmHg) is recommended in patients who have refractory intracranial hypertension. Under such circumstances, arterial blood gas analysis or end-tidal carbon dioxide ($ETCO_2$) monitoring will be beneficial to monitor and prevent further reducing CBF.

3-5. Barbiturates

Barbiturates have been considered for the control of refractory intracranial hypertension after other medical therapies have failed. Pentobarbital has been found to be effective in lowering ICP in children with severe TBI. Concurrently, systemic hemodynamic parameters should be maintained stable with continuous monitoring, preferably in an ICU setting due to the potential risk of myocardial depression and hypotension.

3-6. Temperature control

It is recommended to at least avoid hyperthermia which increases metabolic demands, lipid peroxidation, inflammation, excitotoxicity, and lowering seizure thresholds. Those reactions can cause of extensive secondary brain injury. For the use of hypothermia (HT) to treat of refractory intracranial hypertension, the guidelines provide level II evidence for recommending moderate HT to treat severe TBI in children for duration of up to 48 h, followed by rewarming slowly prevent rebound intracranial hypertension over 12–24 h.[67] HT is effective in decreasing ICP as an adjunct to standard treatment but, so far, conveyed no functional outcome or increased mortality benefit at 6-months post-TBI.

3-7. Decompressive craniectomy

In pediatric cases, it has been reported that decompressive craniectomy (DC) is performed for controlling intracranial hypertension due to any causes such as TBI, hypoxic-ischemic encephalopathy, metabolic disease, CNS infection, or others, and was effective at ICP reduction.[68] Bifrontal craniotomy is more likely to be selected in children compared to adults.[69] In addition to the mortality, long-term outcome studies are required including the evaluation of various high cognitive functions.[70] The effectiveness of DC on AHT was also investigated, and it clearly reduced mortality; however, no answer has been obtained regarding functional outcomes.[71]

3-8. Corticosteroids

The routine use of corticosteroids to treat children with severe TBI is not recommended because the lack of evidence for benefit in children and potential harm from infectious complications. Significant suppression of endogenous cortisol levels was documented with dexamethasone treatment and trends toward increased incidence of pneumonia were observed. Steroid treatment is not associated with improved functional outcome, decreased mortality, reduced ICP.

3-9. Nutritional management

Nutritional support is very important for children with severe TBI. It is recommended that full nutritional replacement be instituted by day 7 post-injury because TBI patients lose sufficient nitrogen to reduce weight by 15% per week and support administration of 130-160% replacement of energy expenditure, which may reduce nitrogen loss.

3-10. Anticonvulsants

Children, particularly infants, have lower seizure thresholds and are at high risk for early seizures. Immediate prophylactic administration of anticonvulsant is recommended in children with severe TBI. There is a widespread opinion that prophylactic administration of anticonvulsant is ineffective to prevent the development of epilepsy. Risk factors for early onset of seizures in infants aged less than 2 years include concomitant hypotension, history of child abuse, and Glasgow Coma Scale score of ≤ 8. In such cases, prophylactic anticonvulsant is recommended.[72] No specific guidelines exist for the discontinuation of prophylactic anticonvulsant. If no further seizures occur more than 2 years after the last seizure, imaging studies, electroencephalogram (EEG),

and CBF studies are recommended to decide potential reduction in dosage by half.

Outcomes[73,74]

Long-term follow-up is often required to evaluate both physical and intellectual disability outcomes. Kurihara et al. suggested a comprehensive, multidisciplinary rehabilitation protocol to promote recovery and facilitate a smooth transition to home and school activities. The importance of early and regular communication between rehabilitation specialists, family members, and educators is strongly recommended. Such collaboration permits a clear identification of functional abilities and increases the child's potential for positive long-term outcomes.

In a cohort of TBI children who presented with GCS score of 3 or 4, 56.6% died within 1 year. However, approximately 15% of patients had good outcomes at 10 or more years. Pupillary response at admission, occurrence of hypothermia, and mechanism of injury were associated with survival and outcomes.[75]

Neuroimaging has an indispensable role in the management of pediatric TBI. Newer MRI-modalities such as diffusion weighted and diffusion tensor imaging, susceptibility weighted imaging, and (1) H-magnetic resonance spectroscopy allow for determination of several sensitive parameters that predict chronic function and possibly neuropsychological function.[76] They may also allow earlier identification of chronic sequelae of TBI in an individual child and, thereby, help tailor the rehabilitation services.[77]

Conclusion

The optimal care of an infant or child with TBI requires a multidisciplinary approach in each phase of management. After the initial evaluation, prompt diagnosis, multimodal monitoring, and titrated management of intracranial hypertension are necessary to minimize pathophysiological damage to the developing brain. Management of pediatric TBI provides challenges due to differences in the basic mechanisms of injury. Further additional medical evidences will be available on the aspects of the evolution of neuronal damage and repair in pediatric TBI near in the future.

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Conflicts of Interest Disclosure

The authors declare that they have no conflict of interest.

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