PEDIATRIC TBI - CURRENT STATE OF THE ART AND FUTURE PERSPECTIVE

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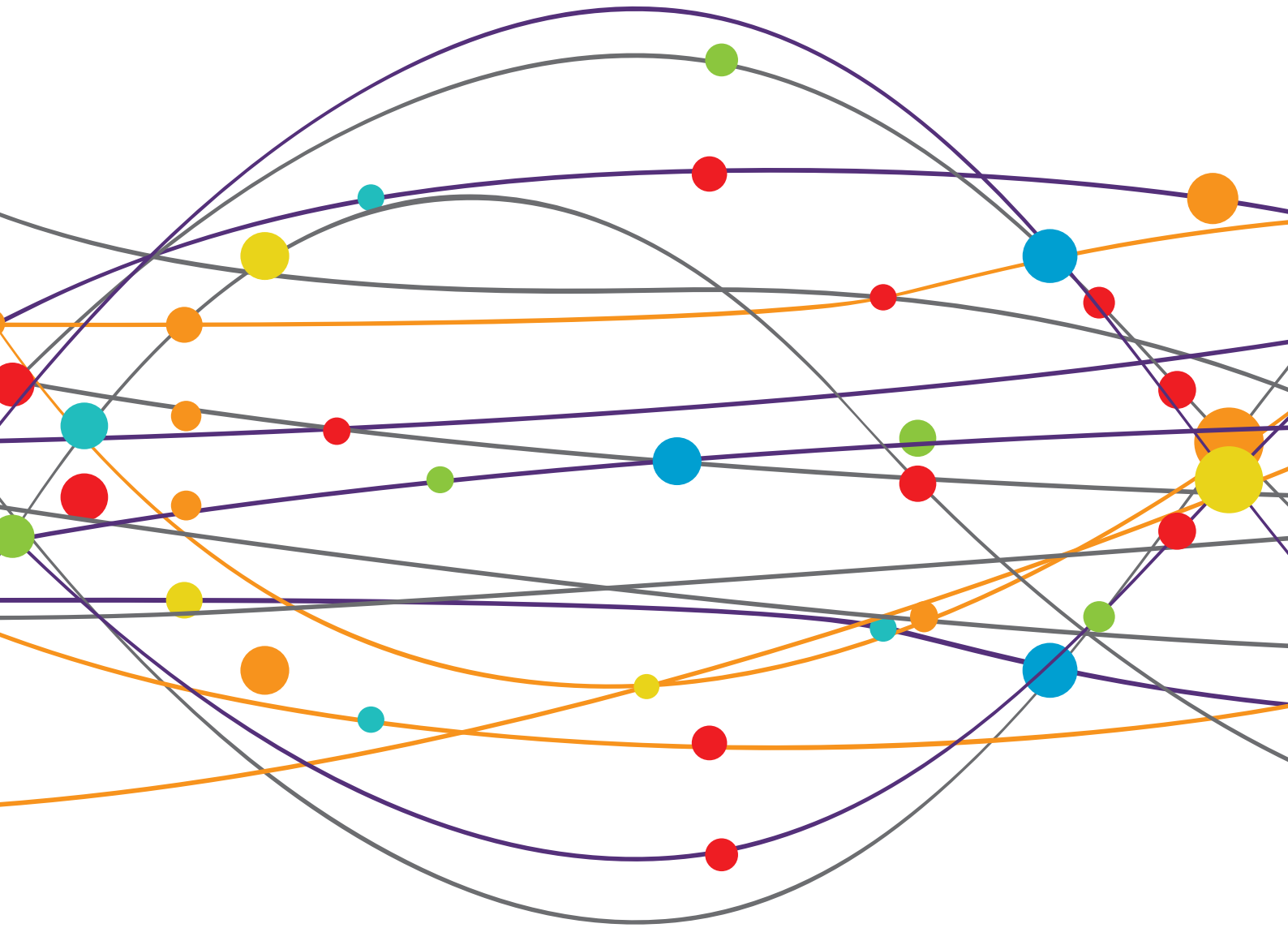

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PEDIATRIC TBI - CURRENT STATE OF THE ART AND FUTURE PERSPECTIVE

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EDITORIAL
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Editorial: Pediatric TBI - Current State of the Art and Future Perspective

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Keywords: traumatic brain injury, pediatric brain injury, neuromonitoring, ICP, CBF

Editorial on the Research Topic

Pediatric TBI - Current State of the Art and Future Perspective

Traumatic Brain Injury (TBI) remains a leading cause of death and disability in children worldwide and those who survive may suffer long-term cognitive and physical disabilities, The mechanism of injury often differs between high income and low- and middle-income countries, where road traffic accidents and interpersonal violence are comparatively more common. In the publication of Riemann et al. using data collected through CENTER-TBI which is a multicenter study conducted in Europe and Israel, they found that road-traffic incidents were the most common cause of injury overall and those admitted to ICU, while incidental falls were most common in patients admitted to the hospital wards. The overall mortality rate was 3% and the rate of unfavorable outcome 10%, where Glasgow Coma Score (GCS) and the occurrence of secondary insults were identified as independent predictors for an unfavorable outcome. Monitoring the injured brain is crucial in the management of TBI in order to prevent and detect secondary insults. Brain imaging and multimodal neuromonitoring in adults with TBI have improved diagnostics and management of these patients but there is limited experience in the pediatric population. As Appavu et al. describe in their paper methods of monitoring real-time cerebral physiology are also needed in the pediatric population to better understand when secondary brain injury develops and what treatment strategies may alleviate or prevent such injury. They discuss several different emerging technologies to better understand intracranial pressure (ICP), cerebral blood flow, metabolism, oxygenation, and electrical activity. While recent guidelines recommend ICP monitoring and a treatment threshold of 20 mmHg for 5 min, Hornshoj Pedersen et al. highlight the lack of data on normal ICP in healthy children to understand and guide treatment of TBI. Although age-differentiated ICP thresholds in pediatric TBI are needed, only one study reported this and it did not correlate with outcome. The issue with age-differentiated thresholds is also discussed by Rostami et al. regarding CBF. Monitoring of CBF and autoregulation following TBI is crucial. However, there is still lack of fundamental knowledge about normal physiology in children for both across the age spectrum and between genders. Few studies available report on differences across the age range. Following TBI, low initial CBF correlates with poor outcome, as does impaired cerebral pressure autoregulation, but the relationship between the two still needs clarification. Current studies are few and mainly based on small number of patients between the broad age span of 0–18 years. Larger studies across narrower age ranges are needed. The age range affects physiology, mechanism of injury, and outcome. For example, TBI outcome is age dependant: children under the age of 4–5 years have the worse outcome and the rates of TBI-related emergency department visits in this group have increased by more than 50% in US during recent years. Children under the age

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of 4 years are also the group mostly at risk of abusive head trauma (AHT). O'Meara et al. highlight the difficulty in early identification of AHT and how its incidence is underestimated. Pediatric TBI studies often exclude AHT, which limits the generalization of research to this population. Emerging imaging modalities and biomarkers may improve the diagnostic workup, but these must also be applied to the acute phase of AHT. Use of TBI models may improve our understanding of the underlying pathology. Martin et al. showed in a transgenic mouse model that genes important in age-related neurodegenerative diseases in humans have significant impact on mortality and morbidity after early-life brain injury and may influence adult-onset neurodegenerative disease during aging.

Pediatric TBI also has long-lasting social, cognitive, physiological, and neurological impairments that can be hard to predict. Lindsey et al. highlight the importance of MRI in the acute management of pediatric TBI but most importantly its particular relevance for the sequential assessment of long-term consequences from injuries sustained to the developing brain. Different MRI modalities can reveal different aspects of the injury such as morphological changes in gray matter volume and cortical thickness, microstructural integrity of white matter, metabolic and neurochemical alterations in the brain, functional changes that occur as a result of structural damage, and typical developmental processes. There are few studies published in this field, and these demonstrate considerable heterogeneity in post-injury outcome. Larger sample sizes and multi-center future studies may identify key predictors of outcome following TBI.

One common neurological complication of severe TBI in children is spasticity, which may develop in up to 38% of patients within the first 12 months post injury. Enslin et al. discuss the importance of early identification, because late intervention has limited effect and major corrective surgery may then be needed. Most of the current data originates from stroke research. The review covers underlying pathophysiology as well as available prevention and management of spasticity.

Endocrinopathies (endocrine system disorders) may be caused by injury to the hypothalamic-pituitary axis/region. This is often overlooked and rarely reported but if left untreated, it may lead to subsequent health issues, hence the importance of early detection in pediatric TBI survivors.

Ortiz et al. found that children with a TBI diagnosis had 3.22 times greater risk of a central endocrine diagnosis compared with the general population ($\pm$0.28). This was also more common in females compared to males (64.1 vs. 35.9%). They suggest physicians managing pediatric TBI follow-up care should include preventive screening for endocrine disorders.

In this Research Topic we highlight the current knowledge in several key areas of pediatric TBI as well as gaps that can be the focus of future research.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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ORIGINAL RESEARCH
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Neonatal Brain Injury and Genetic Causes of Adult-Onset Neurodegenerative Disease in Mice Interact With Effects on Acute and Late Outcomes

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Neonatal brain damage and age-related neurodegenerative disease share many common mechanisms of injury involving mitochondriopathy, oxidative stress, excitotoxicity, inflammation, and neuronal cell death. We hypothesized that genes causing adult-onset neurodegeneration can influence acute outcome after CNS injury at immaturity and on the subsequent development of chronic disability after early-life brain injury. In two different transgenic (Tg) mouse models of adult-onset neurodegenerative disease, a human A53T-α-synuclein (hαSyn) model of Parkinson's disease (PD) and a human G93A-superoxide dismutase-1(hSOD1) model of amyotrophic lateral sclerosis (ALS), mortality and survivor morbidity were significantly greater than non-Tg mice and a Tg mouse model of Alzheimer's disease after neonatal traumatic brain injury (TBI). Acutely after brain injury, hαSyn neonatal mice showed a marked enhancement of protein oxidative damage in forebrain, brain regional mitochondrial oxidative metabolism, and mitochondriopathy. Extreme protein oxidative damage was also observed in neonatal mutant SOD1 mice after TBI. At 1 month of age, neuropathology in forebrain, midbrain, and brainstem of hαSyn mice with neonatal TBI was greater compared to sham hαSyn mice. Surviving hαSyn mice with TBI showed increased hαSyn aggregation and nitration and developed adult-onset disease months sooner and died earlier than non-injured hαSyn mice. Surviving hSOD1 mice with TBI also developed adult-onset disease and died sooner than non-injured hSOD1 mice. We conclude that mutant genes causing PD and ALS in humans have significant impact on mortality and morbidity after early-life brain injury and on age-related disease onset and proteinopathy in mice. This study provides novel insight into genetic determinants of poor outcomes after acute injury to the neonatal brain and how early-life brain injury can influence adult-onset neurodegenerative disease during aging.

Keywords: neonatal brain damage, traumatic brain injury, ALS, synuclein oligomerization, Parkinson's disease

INTRODUCTION

Epidemiological and molecular genetics studies have identified definitive genetic, environmental, and lifestyle risk factors for age-related neurodegenerative diseases (1–3). Most forms of Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) are sporadic (idiopathic) with no known inheritance pattern or genetic associations and are respectively the 1st, 2nd, and 3rd most common adult-onset neurodegenerative diseases (1, 4). Some familial forms of AD, PD, and ALS link to gene mutations (1, 5, 6). Along the lifelong spectrum, individuals can suffer from brain and spinal cord traumatic and ischemic injuries. Traumatic brain injury (TBI) at all ages is an enormous public health concern that embraces sports-, vehicular crash-, and warfare-related incidents, events linked to neurobehavioral, cognitive and motor deficits (7). About 5.3 million people in the US are living with some form of TBI-related disability (7). There is a connection between acute brain injury and chronic age-related neurodegenerative disease. For example, a history of head trauma is associated with AD (8), PD (9–11), and ALS (12, 13). A recent study of 7,130 participants identified a strong association of TBI with risk of PD in late-life (9). A greater than expected prevalence of ALS is found in Italian professional soccer players (13). Studies confirmed that risk for ALS is higher than expected in professional soccer players and extend the result to university athletes (14, 15). Other studies suggest associations between chronic traumatic encephalopathy in US athletes and motor neuron disease (12) and associations between TBI and ALS in the general population (16, 17). Importantly, TBI can promote proteinopathies involving human transactive DNA-binding protein 43 (hTDP43) and α-synuclein (hαSyn) (18). However, generally, these associations are for mature brain neuropathology. It is not known whether neonatal, pediatric, or juvenile CNS injury affects the aging brain and age-related neurodegenerative diseases and, inversely, if genetic variations linked to age-related neurodegenerative disease influence outcomes from acute CNS injury in early life. Poor outcome after hypoxia-ischemia in piglet newborns is associated with a variety of physiological abnormalities during early recovery (19), but the possibility of underlying genetic risk factors that might drive poor outcomes in acute injury settings in infants and children is unclear. Emerging data support this possibility. Single nucleotide polymorphisms in genes related to dopamine neurotransmission have roles in short- and long-term neurobehavioral recovery after early childhood TBI (20). *Catalase* gene (21) and *interleukin-6* gene (22–24) polymorphisms are associated with higher susceptibility to cerebral palsy after neonatal hypoxia-ischemia. Glial glutamate transporter gene *EAAT2* polymorphisms associate with cerebral palsy in preterm infants (25). Indeed, mitochondriopathy, oxidative stress, excitotoxicity, intracellular calcium stress, inflammation, and neuronal cell death are all putative mechanisms in neonatal brain damage (4, 26) and age-related neurodegenerative disease (4). We hypothesized that the genetics of AD, PD, and ALS can influence acute outcome after brain injury at immaturity and the subsequent development of adult-onset chronic neurodegenerative disease by aggravating proteinopathy.

MATERIALS AND METHODS

Mice

We used transgenic (Tg) mice expressing human mutant A53T-α-synuclein (hαSyn) (27), human mutant G93A-superoxide dismutase-1(hSOD1) (28), and human mutant amyloid precursor protein-presenilin 1 (hAPP-PS1) (29). Colonies of these mouse lines and their genotyping have been used by us before (27, 30–32). Non-transgenic (non-Tg) littermates were controls. The institutional Animal Care and Use Committee approved the animal protocols. Because each mutant mouse line has its own background strain, non-trangenic controls were strain specific for each mutant line.

Unilateral Closed Skull Cortical Contusion Injury Model (CCI) in Neonatal Mice

CCI (**Figure 1A**) was produced in postnatal day 7 (p7) mice using a protocol adapted from our earlier model of neonatal mouse open skull cortical trauma (33) and excitotoxic injury (34), except that the injury was induced by non-penetrating, closed-head, weight-drop. Mice were deeply anesthetized using isoflurane as described (33, 34). The contusion device consists of a pivotable hollow plastic cylinder 20 cm in length and a 5 mm diameter opening allowing for loading of 1 or 5 g weights. The angle of the skull impact was ∼80°. Sham Tg and sham non-Tg mice were anesthetized and the weight-drop guide barrel and weight were placed gently on the skull without drop impact. Only male mice, identified by their external genitalia, were used. Each group initially had 40 mice.

Clinical Outcome and Neurological Measurements

Acute spontaneous deaths occurring over the initial 48 h after injury were recorded. Morbidity was assessed by testing survivors on a voluntary running wheel at 30 days of age as described (27, 35, 36). Predetermined mouse survivals were 3 h, 24 h, 30 days, 3 months and endstage disease for lifespan determination. Animal attrition from the study was also noted over longer-term follow-up. For the 24 h time point, moribund mouse pups were excluded; pups with a milk spot were used. Onset of clinical disease of A53T-hαSyn mice was designated as the day the mouse shows slow ataxic and awkward jerking/spastic movements while walking (27). Endstage disease for A53T-hαSyn mice was defined as severe rigidity and bradykinesia that impairs movement to feed (27). Onset of clinical disease of G93A-hSOD1 mice was designated as the day the mouse shows hind-leg tremor (31, 32). Endstage disease for G93A-hSOD1 mice was defined as paralysis that impairs movement to feed (32).

Brain Harvesting and Processing for Biochemistry and Histology

Naïve, sham, and CCI mice were killed at 3 and 24 h after the procedure, at 1 day, 30 days, and 3 and 6 months of age, or were euthanized at endstage disease. For the A53T-hαSyn cohort, mice at 24 h after CCI and 30 days of age were used for histology ($n = 10$/group) and biochemistry ($n = 6$/group), and mice at 3 months of age were used for biochemistry

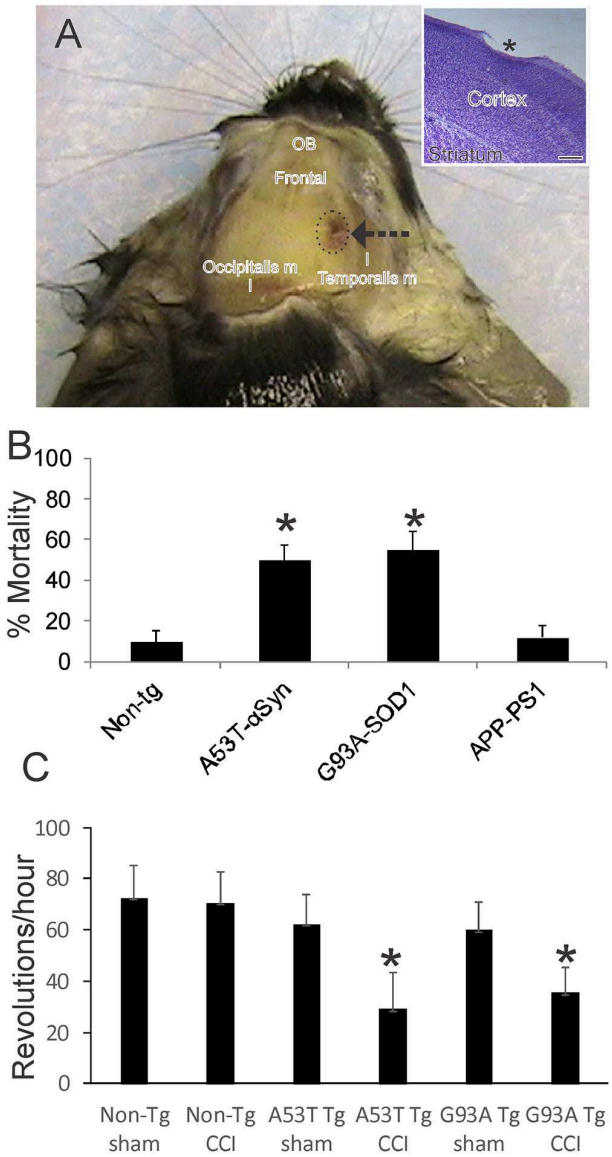

FIGURE 1 | Mouse model of mild closed skull cortical contusion injury (CCI) and clinical outcomes. **(A)** Head of a postnatal day 30 mouse that received a right side CCI (arrow) on postnatal day 7. Surrounding skull muscles and some underlying brain structures, olfactory bulbs (OB) and frontal cortex (frontal), are identified for orientation. Inset shows mild injury to frontal cortex (asterisk) in a cresyl violet-stained section. Scale bar = 238 μm. **(B)** Acute 48 h mortality of non-transgenic (non-tg) and tg neonatal mouse lines expressing human mutant genes causing human neurodegeneration such as Parkinson's disease (A53T-αSyn), amyotrophic lateral sclerosis (G93A-SOD1), and Alzheimer's disease (APP-PS1). Values shown are mean ± standard deviation ($n = 40$ mice/group). Asterisks denote significant difference ($p < 0.001$) compared to non-tg. **(C)** Motor performance (on running wheel) of 30-day-old mice subjected to sham procedure or CCI at postnatal day 7. Tg A53T-αSyn and G93A-SOD1 mice with CCI had significant deficits in running activity. Values are means ± standard deviation ($n = 10$/group). Asterisks denote ($p < 0.01$) compared to sham.

($n = 6$/group). For the G93A-hSOD1 cohort, mice at 3 and 24 h after CCI were used for biochemistry ($n = 6$/group). For the hAPP-PS1 cohort, mice at 6 months of age after CCI were used for histology ($n = 6$/group). Mice were killed by an overdose of sodium pentobarbital. For biochemistry, the brains were removed rapidly from the skull after decapitation, divided into contralateral and ipsilateral hemispheres, and snap frozen in isopentane made cold (−78°C) by dry ice. For histology the mice were perfused through the heart with cold (4°C) phosphate buffer-saline (PBS, 100 mM, pH 7.4) followed by ice-chilled 4% paraformaldehyde. After perfusion-fixation, the brain was removed after 2 h, postfixed overnight in 4% paraformaldehyde (4°C), and cryoprotected 24 h in 20% glycerol-PBS (4°C). The fixed brains for A53T-hαSyn cohort were frozen under dry ice and were sectioned serially from frontal pole to posterior cerebellum in the coronal plane at 40 μm on a sliding microtome. The fixed brains for hAPP-PS1 cohort were frozen under dry ice and were sectioned serially from the lateral neocortical convexity to the midline in the sagittal plane at 40 μm on a sliding microtome. Every section was saved individually in 96-well plates containing antifreeze buffer. The sections were stored at −20°C. For histological analyses of A53T-hαSyn, brain sections were selected systematically and stained using cresyl violet (CV) for Nissl substance staining, cell morphology, and counting (27, 31), FD-silver (FD Neurotechnologies Inc., Baltimore, MD) for neurodegeneration (37), cytochrome c oxidase (COX) enzyme histochemistry for mitochondrial complex IV activity (38), and immunohistochemistry for mitochondrial morphology (31, 32). For histological analyses of hAPP-PS1 mice, brain sections were selected systematically and stained using immunoperoxidase immunohistochemistry for APP/amyloid β protein (Aβ).

Electron Microscopy

Electron microscopy (EM) was used for ultrastructural assessments to confirm mitochondrial pathology in PD mice with neonatal CCI. From some brains from A53T-hαSyn mice ($n = 3$ sham, $n = 3$ CCI), neocortical samples were taken after perfusion-fixation and post-fixed in 2% glutaraldehyde. The samples were used to identify unequivocally mitochondrial swelling by EM as described (31, 32).

Regional Forebrain Measurements and Cell Counting

Neocortical gray mantle and subcortical white matter thicknesses in A53T-hαSyn mice were measured by ocular filar micrometry in Nissl-stained brain sections at a level of bregma −0.58. Somatosensory (S1) cortex and corpus callosum were analyzed in five different sections in each mouse. Dorsal septal diameters were measured in the same anterior-posterior level in the same mice. Profile counting of Nissl-stained sections was done to estimate the numbers of neurons in the substantia nigra pars compacta (SNc) and pedunculopontine tegmental nucleus (PPN). Neurons in these regions were counted in anatomical level-matched sections (2–3 sections/region) at 1,000x magnification. Corresponding to a standard mouse brain stereotaxic atlas, SNc neurons were counted at bregma −292, −3.16, and −3.52; PPN neurons were counted at bregma −4.48 and −4.60. Strict morphological criteria were applied when classifying normal appearing neurons, including

a round, open, euchromatic nucleus (not condensed and darkly stained), globular Nissl staining of the cytoplasm, clear vacuole-free cytoplasm, and a cell body diameter of ∼10–20 μm. With these criteria, degenerating neurons with necrotic, apoptotic, and necrotic-apoptotic hybrids as well as astrocytes, oligodendrocytes, and microglia were excluded from the counts.

Immunohistochemistry

We used superoxide dismutase-2 (SOD2) as an *in situ* mitochondrial marker (31, 32). SOD2 immunoreactive cytoplasmic particles have been used for assessing mitochondrial morphology such as mitochondrial diameters (31, 32, 39). Immunoperoxidase histochemistry with diaminobenzidine (DAB) as chromogen was used as described (31, 32, 39) to detect SOD2 protein with a highly specific rabbit polyclonal antibody (SOD-111, Stressgen). Mitochondrial diameters were measured in A53T-hαSyn mice by ocular filar micrometry in somatosensoty cortex and hippocampus CA1 in anatomical level-matched sections (2–3 sections/region) at 1,000x magnification. Immunoperoxidase histochemistry with DAB was used to detect Aβ-positive parenchymal deposits in hAPP-PS1 mouse neocortex with monoclonal antibody 6E10 (Covance) and CV-counterstaining. In mid-sagittal sections, all Aβ plaques were counted from frontal pole to posterior cingulate cortex.

COX Activity

We used COX (complex IV) enzyme histochemistry as an *in situ* mitochondrial oxidative metabolism assay (40). This non-antibody based histological biochemical method is a functional assay that detects complex IV enxyme activity in tissue sections (40). The enzymatic reaction method has been described (31, 38, 41, 42). Brain regional enzyme activity was quantified by densitometry (31, 42, 43).

Protein Oxidation Assay

Carbonylated proteins were detected with the OxyBlot Protein Oxidation Detection Kit (Millipore, Burlington, MA, USA) as described (44). Negative controls were prepared on paired brain homogenates by adding hydrazine derivatization solution or derivatization control solution (non-derivatized). Protein loading was measured by Ponceau S staining of the membrane used to detect carbonylated proteins. To quantify protein immunoreactivity, films were scanned and densitometry was performed as described (45). We used ImageJ to analyze the immunoreactive band intensities normalized to (divided by) the total protein in Ponceau S-stained gels. Protein levels were expressed as relative optical density measurements.

Western Blotting

Western blotting was done to detect hαSyn and nitrated hαSyn (27). Crude tissue extracts were prepared from ipsilateral hemisphere forebrain. Protein fractions were subjected to SDS-PAGE and immunoblotting using enhanced chemilumesence detection as described (27, 32, 45). The reliability of sample loading and electroblotting in each experiment was evaluated by staining nitrocellulose membranes with Ponceau S before immunoblotting and by reprobing the blot for synaptophysin using a highly specific rabbit polyclonal antibody (Dako). If transfer was not uniform based on the Ponceau S, blots were discarded and gels were run again. Mouse monoclonal antibody clone Syn211 (46) was used to detect hαSyn. Mouse monoclonal antibody clone Syn12 (46) was used to detect nitrated synuclein. The antibodies were used at concentrations for visualizing protein immunoreactivity within the linear range.

Statistical Analyses

All outcomes were assessed in a manner blind to treatment. After the procedure, all animals were coded so that subsequent experimenters were aware only of animal number. For histological and western blot measurements, group means, and variances were evaluated statistically by one-way ANOVA followed by a Newman-Keuls *post-hoc* test.

Photography and Figure Construction

Marker comparisons between sham and CCI mice were made from sections that were imaged under identical conditions and analyzed using identical parameters. Original images used for figure construction were generated using digital photography. Digital images were captured as TiF files using a SPOT digital camera and SPOT Advanced software (Diagnostic Instruments) or a Nikon digital camera (DXM1200) and ACT-1 software. Images were altered slightly for brightness and contrast using ArcSoft PhotoStudio 2,000 or Adobe Photoshop software without changing the content and actual result. Figure composition was done using CorelDraw software with final figures being converted to TiF files. Files of composite figures were adjusted for brightness and contrast in Adobe Photoshop.

RESULTS

Adult-Onset Neurodegenerative Disease Gene Mutations Can Worsen Acute and Delayed Clinical Outcome in Mice After Neonatal Traumatic Cortical Injury

This TBI model produces a frontal-parietal-occipital cortical lesion depending on the intended placement of the weight-guide cylinder (**Figure 1A**, arrow). The mice in this study had frontal-parietal injury. In non-tg mice, the acute insult is maximally mild as evidenced by the ∼90% survival (**Figure 1B**). CCI on neonatal mutant A53T-hαSyn and mutant G93A-hSOD1 tg mice causes significantly greater mortality ($p < 0.01$) than in injured non-tg mice (**Figure 1B**, $n = 40$ males/genotype). Similar CCI on a mouse model of AD (APP/PS1ΔE9 line) did not cause significant effects on acute mortality (**Figure 1B**) nor was there any mouse attrition over longer periods. Morbidity after neonatal CCI was manifested in juveniles as evidenced by the significant deficit in motor activity in mutant A53T-hαSyn tg mice and mutant G93A-hSOD1 tg mice compared to respective age-matched sham mutant mice (**Figure 1C**).

Parkinson's Disease Causing Mutant α-Synuclein Exacerbates Brain Damage After Neonatal TBI

Nissl staining (**Figure 2**) was used to characterize forebrain neuropathology in this model. We focused on the mutant hαSyn mouse because of the significant acute neonatal mortality and because head trauma is a known risk factor for developing PD in human (9, 10). In neonatal rodent brain injury models, sham surgical procedures are essential because of the potential of anesthesia toxicity (47), and even making a skull bone window with the utmost care can cause damage (33). Here, sham surgeries on p7 mice involved anesthesia and placement of the weight and guide barrel on the head without drop impact. The brain damage seen at p30 after p7 CCI is reproducible. In non-tg mice, the insult causes maximally mild injury as reveal by the ∼10–20% reduction in sensorimotor cortical thickness (**Figure 1A**, inset, **Figures 2C,D,G**), but apparent small cell inflammatory changes are persistent (**Figure 2D**, arrows). The cerebral cortex of sham A53T-hαSyn mice was unremarkable at this age (**Figures 2A,B,G**) consistent with other work (27). Cortical atrophy in p30 A53T-hαSyn mice with p7 CCI was severe compared to non-tg mice with CCI and sham A53T-hαSyn mice (**Figures 2E,G**), and foci of attenuated cell density were evident (**Figure 2F**). Severe forebrain pathology was also evident in A53T-hαSyn mice with CCI by significant reductions in corpus callosum thickness (**Figure 2H**) and septal atrophy (**Figure 2I**).

Nissl and silver staining revealed ventral midbrain and brainstem neuropathology in this neonatal CCI model at 1 month of age. Neuronal loss (∼30%, $p < 0.01$) was found in the ipsilateral substantia nigra pars compacta (SNc) in A53T-hαSyn mice with CCI but not in age-matched sham A53T-hαSyn mice or in non-Tg mice with CCI (**Figures 3A–D**).

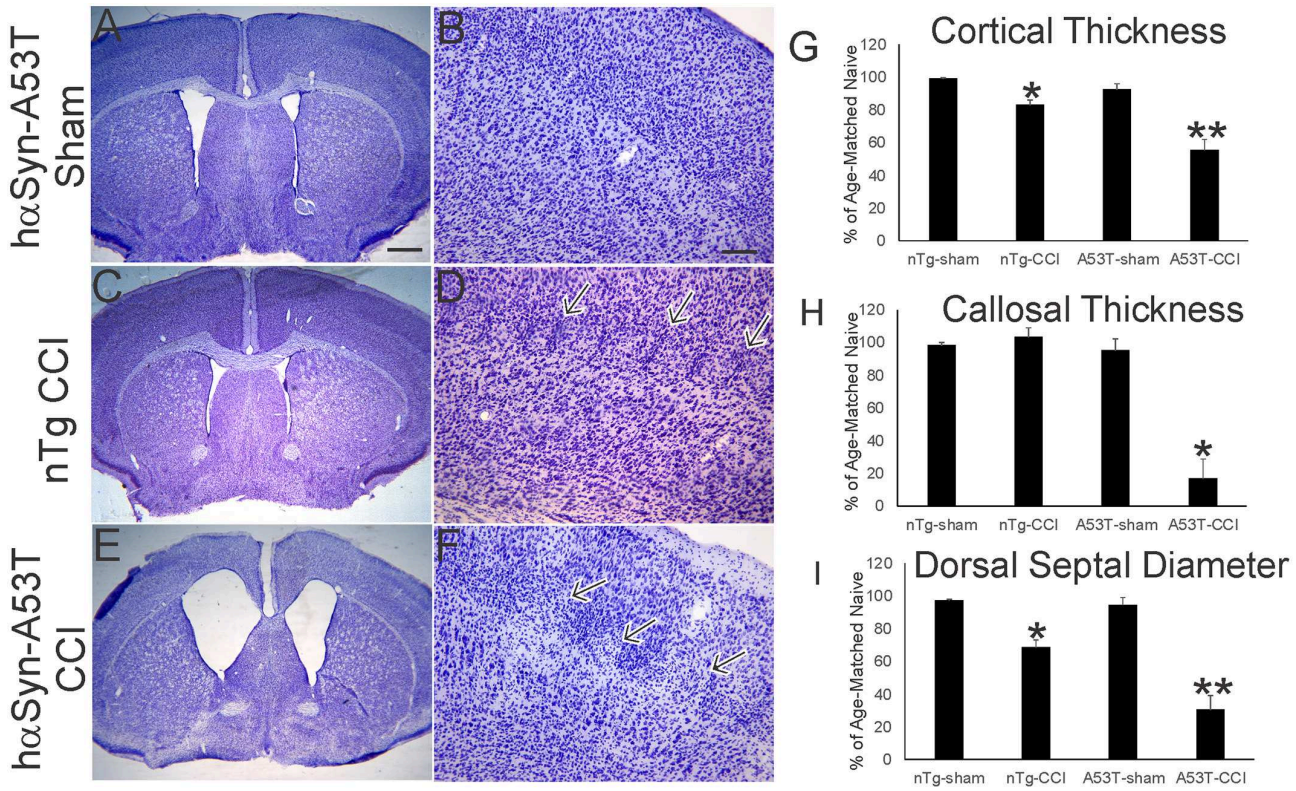

FIGURE 2 | Mutant A53T-hαSyn exacerbates forebrain injury in a neonatal mouse model of closed skull cortical contusion injury (CCI). Mice received CCI on postnatal day 7 and then killed at postnatal day 30 to show forebrain histology by cresyl violet staining. Shown are anatomically-matched levels of forebrain from Tg A53T-hαSyn mice with sham procedure **(A,B)**, non-Tg (nTg) mice with CCI **(C,D)**, and Tg A53T-hαSyn mice with CCI **(D,E)**. **(A,B)** Thirty-day-old sham Tg A53T-hαSyn mice have histologically normal cerebral cortex, septum, and striatum. No abnormalities in cortical lamination and cytology are apparent **(B)**. **(C,D)** Thirty-day-old nTg mice with CCI have slightly smaller forebrains with a modest reduction in cerebral cortical thickness **(G)**, and septal atrophy **(I)**, but no thinning of corpus callosum **(H)**. In the middle layers of cerebral cortex, some foci of small cell accumulation were present (**D**, arrows). **(E,F)** Thirty-day-old Tg A53T-hαSyn mice with CCI have grossly atrophic forebrains **(E)** as evident by the dilation of the lateral ventricles, marked cerebral cortical and corpus callosum thinning **(G,H)**, and prominent atrophy of septum **(I)**. In the middle and superficial layers of cortex, discontinuous patchy pale zones of apparent cell loss are present (**F**, arrows). **(G)** Cortical thickness (vertical depth, surface of cortex to start of corpus callosum) in sham and CCI mice at postnatal day 30. Measurements were made in somatosensory cortex. Values are mean ± SD ($n = 10$ mice/group). *$p < 0.01$ compared to non-Tg sham; **$p < 0.005$ compared to A53T-sham. **(H)** Corpus callosum thickness (vertical depth, inferior cortical layer 6 end to striatum) in sham and CCI mice at postnatal day 30. Measurements were made deep to somatosensory cortex. Values are mean ± SD ($n = 10$ mice/group). *$p < 0.001$ compared to A53T-sham. **(I)** Diameter of the dorsal septum in sham and CCI mice at postnatal day 30. Measurements were made precisely inferior to the decussation of the corpus callosum. Values are mean ± SD ($n = 10$ mice/group). *$p < 0.01$ compared to non-Tg sham; **$p < 0.005$ compared to A53T-sham. Scale bars: A (same for **C,E**) = 476 μm; **B** (same for **D,F**) = 83 μm.

Some remaining ipsilateral SNc neurons showed chromatolytic reaction, consistent with axonopathy (33, 41, 48), or cytoplasmic palor and cell nucleus abnormalities (**Figure 3E**) compared to the contralateral SNc neurons seen as normal large multipolar, Nissl-rich profiles (**Figure 3F**). Apoptotic profiles were also observed in the ipsilateral SNc in A53T-hαSyn mice with CCI (**Figure 3E** inset) but not contralaterally. Silver staining delineated degenerating neuronal cell bodies, axons, and terminals in the ipsilateral SNc of A53T-hαSyn mice with CCI (**Figure 3G**) but not in the contralateral SNc (**Figure 3H**) or in 1-month-old sham A53T-hαSyn mice or non-Tg mice with CCI. In the brainstem tegmentum, the pedunculopontine tegmental nucleus (PPN) of A53T-hαSyn mice with CCI had ∼50% loss of neurons ipsilaterally compared to the contralateral PPN (**Figures 4A–C,F**). No loss of PPN neurons was detected in age-matched sham A53T-hαSyn mice or in non-Tg mice with CCI (**Figure 4F**). Silver staining identified axonal and neuritic pathology in the ipsilateral PPN (**Figure 4E**) but not in the contralateral PPN (**Figure 4D**) or in the PPN of age-matched sham A53T-hαSyn mice or non-Tg mice with CCI. In contrast to the SNc and PPN, the red nucleus, raphae nucleus, and bulbar cranial nerve motor neuron groups were all unremarkable (data not shown).

Mutant α-Synuclein Exacerbates Protein Oxidative Damage in Forebrain After Neonatal TBI

Protein oxidative damage in mouse cerebrum at 24 h after CCI was assessed by the levels of carbonyl-modified proteins after derivatization and western blotting. Carbonylated proteins were detected at 15–250 kD throughout the length of the gels (**Figure 5A**). Negative controls without protein derivatization but with exposure to dinitrophenylhydrazone antibody were blank (**Figure 5A**). Non-tg CCI mice and A53T-hαSyn mice sham mice differed modestly but significantly ($p < 0.05$) from non-tg shams (**Figure 5B**). In contrast, protein carbonyl levels were dramatically elevated in A53T-hαSyn mice with CCI compared to non-tg sham ($p < 0.001$) as well as non-tg CCI and sham A53T-hαSyn mice ($p < 0.01$). Interestingly, the basal pattern of oxidized proteins appeared preserved rather than sets of apparently different proteins emerging with carbonylation after injury.

Mutant α-Synuclein Mice Have Elevated Mitochondrial Oxidative Activity Acutely After Neonatal TBI

We used COX enzyme histochemistry to detect mitochondrial metabolic activity *in situ*. The specificity of this histochemical reaction for COX has been established (40, 42). As shown before (40, 43), the brain regional distribution of COX activity varies widely at baseline (**Figure 6**, contralateral side). The thalamic ventrobasal nuclear complex and subthalamic nucleus show high activity, while other areas of diencephalon have lower activity (**Figure 6A**). The distinct layers of hippocampus show differential activity, with the CA1 stratum lacunosum-moleculare showing the highest activity and the stratum radiatum and stratum pyramidale with lower activity (**Figure 6A**). At 1 day after CCI, the ipsilateral hemisphere in non-tg mice had

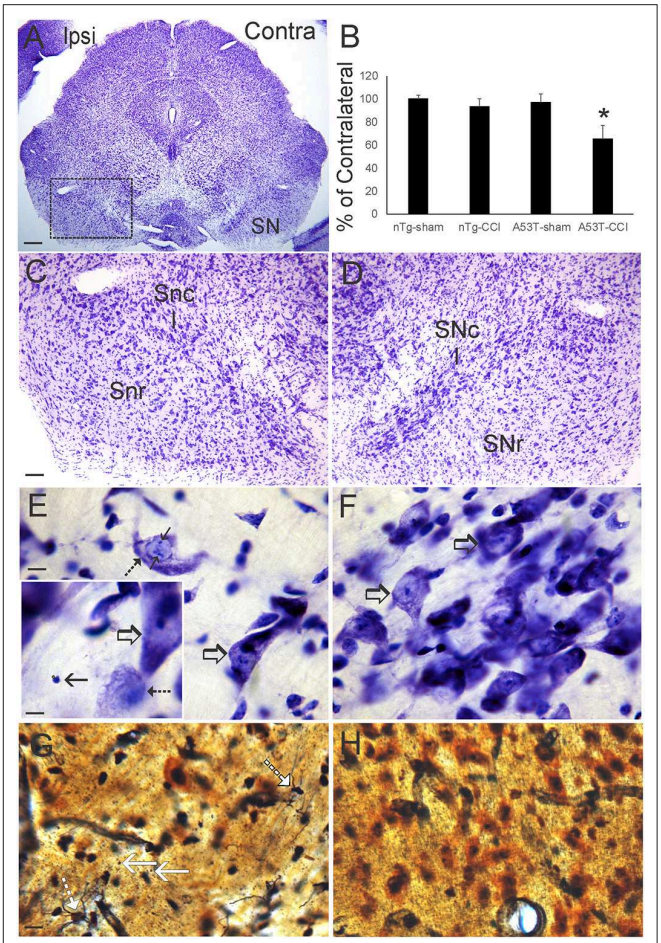

FIGURE 3 | Neonatal cortical contusion injury (CCI) causes early degeneration of the substantia nigra. **(A)** Cresyl violet-stained section of midbrain from a 30-day-old mutant A53T-hα Syn mouse with CCI on postnatal day 7. Ipsilateral (ipsi) is the side with the CCI, and contralateral (contra) is the side without the CCI. Box delineates part of the substantia nigra (SN) shown at higher magnification in **(C,D)**. **(B)** Counts of large Nissl-stained neurons in the substantia pars compacta (SNc) at 1 month of age after CCI at postnatal day 7. Values are mean ± SD ($n = 10$ mice/group). *$p <$ 0.01 compared to all other groups. **(C,D)** Nissl staining of the SN in ipsi **(C)** and contra **(D)** sides of the ventral midbrain after CCI. On the control Contra side **(D)** the SNc is clearly divisible from the substantia nigra reticulata (SNr). In the Ipsi SNc **(C)**, cell loss is apparent particularly in the central SNc. (**E,F)** High magnification of the central SNc on Ipsi **(E)** and Contra **(F)** sides. Cell loss is apparent ipsilaterally **(E)** compared to the contralateral SNc **(F)** that is populated by large healthy-appearing multipolar neurons (**F**, open arrows). Ongoing neuron degeneration is present in the ipsilateral SNc as demonstrated by a large neuron with chromatolytic features (**F**, hatched arrow) and nuclear inclusions (**F**, solid arrow). A nearby neuron appears normal (**E**, open arrow). Inset in **(F)** shows an endstage apoptotic profile (solid arrow), a degenerating neuron with chromatolytic features and condensed nucleus (hatched arrow), and a normal neuron (open arrow). **(G,H)** Silver staining in the SNc shows degenerating axons with neuritic abnormalities/degenerating cell bodies (**G**, hatched white arrows) and degenerating axon terminals (**G**, solid white arrows). Degenerating profiles were not seen in the contralateral SNc **(H)** in the same sections. Scale bars: **(A)**, 250 μm; **(C)** (same for **D**) 100 μm; **(E)** (same for **F**) 10 μm; **(E)** (inset) 8 μm; **(G)** (same for **H**) 12.5 μm.

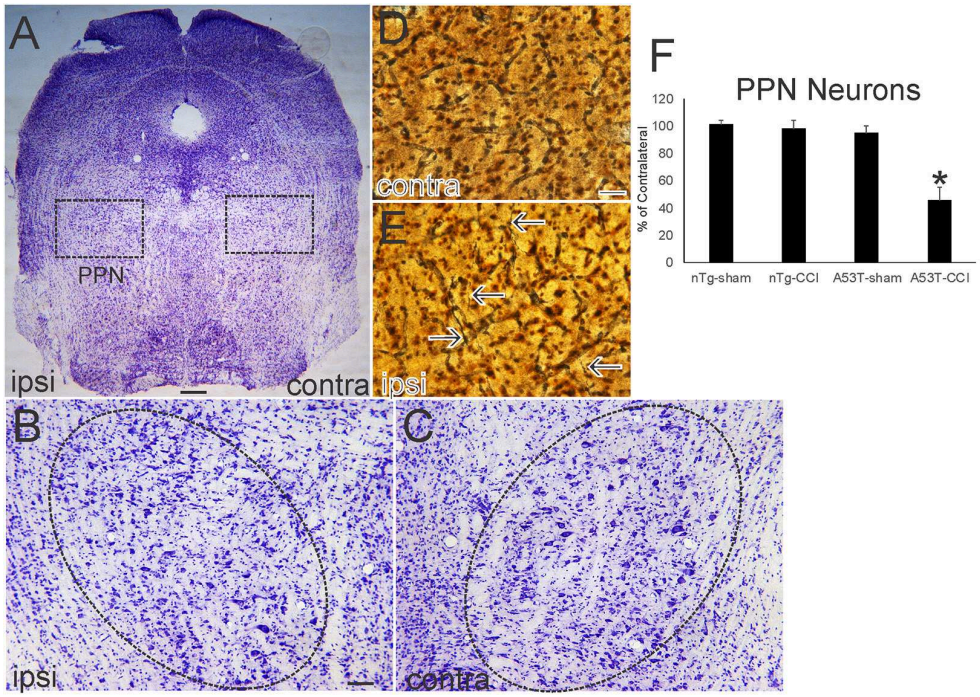

FIGURE 4 | Neonatal cortical contusion injury (CCI) causes early degeneration in brainstem. **(A)** Cresyl violet-stained section of near-pontine brainstem from a 30-day-old mutant A53T-hαSyn mouse with CCI on postnatal day 7. Ipsilateral (ipsi) is the side with the CCI, and contralateral (contra) is the side without the CCI. Boxes delineate bilaterally the pedunculopontine tegmental nucleus (PPN) shown at higher magnification in **(B,C)**. **(B,C)** The ipsi **(B)** and contra **(C)** PPN are delineated by the hatched oval. The ipsi PPN shows apparent loss of large neurons. (**D,E)** Silver staining in the ipsi PPN **(E)** shows degenerating axons with neuritic abnormalities (**E**, arrows). Degenerating profiles were not seen in the contra PPN **(D)**. **(F)** Counts of large Nissl-stained neurons in the PPN at 1 month of age after CCI at postnatal day 7. Values are mean ± SD ($n = 10$ mice/group). *$p < 0.01$ compared to all other groups. Scale bars: **(A),** 322 μm; **(B)** (same for **C**), 100 μm; **(D)** (same for **E**) 12.5 μm.

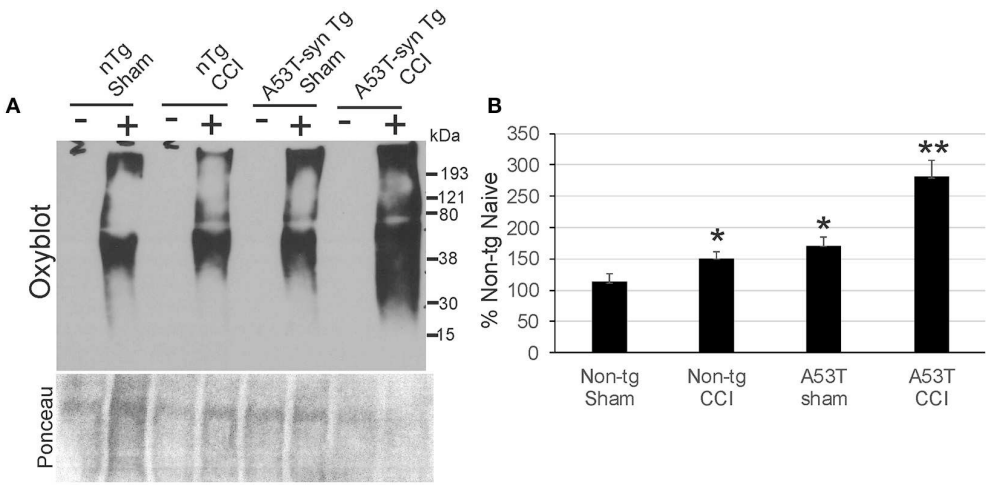

FIGURE 5 | Protein oxidation is exacerbated acutely in mutant A53T-αSyn after neonatal CCI. **(A)** Oxyblot showing protein carbonyls in forebrain of sham and cortical contusion injury (CCI) mice 24 h after injury at postnatal day 7. Plus (+) and minus (–) lane designations are same samples with and without (negative control) chemical derivatization. Ponceau S-stained membrane shows protein loading for each lane. **(B)** Densitometry measurements of total-lane protein carbonyl immunoreactivities in sham and CCI mice. Values are mean ± SD ($n = 6$ mice/group). *$p < 0.01$ compared to non-Tg sham; **$p < 0.001$ compared to A53T-sham.

modest, but significant, elevations in mitochondrial activity in cerebral cortex and the thalamic lateral geniculate nucleus. In A53T-hαSyn mice with CCI, the enhancement of mitochondrial oxidative metabolism was exacerbated in magnitude and regional

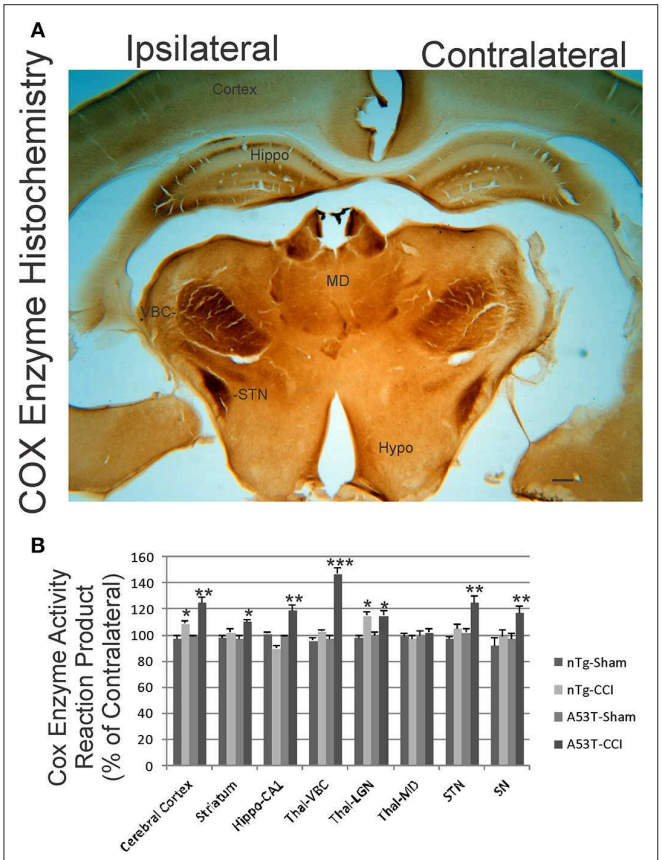

FIGURE 6 | Mitochondrial oxidative metabolism is amplified acutely in mutant A53T-αSyn after neonatal cortical contusion injury (CCI). **(A)** Cytochrome c oxidase (COX) enzyme histochemistry showing the *in situ* enzyme activity of COX in neonatal mouse brain at 24 h after injury at postnatal day 7. The ventrobasal complex of thalamus (VBC), subthalamic nucleus (STN), and hippocampus (Hippo) show intense mitochondrial activation ipsilaterally after CCI. The mediodorsal thalamic nucleus (MD) and hypothalamus (Hypo) are unchanged and similar on both hemispheres. Scale bar = 255 μm. **(B)** Densitometry measurements of COX enzyme activity reaction product in sham and CCI mice. Values are mean ± SD ($n = 10$ mice/group). *$p < 0.05$ compared to non-Tg sham; **$p < 0.01$, or ***$p < 0.001$ compared to A53T-sham.

distribution with the thalamic ventrobasal complex showing the greatest activation (**Figures 6A,B**). The pyramidal cell layer of hippocampus also had a marked increase in COX activity in A53T-hαSyn mice with CCI at 1 day recovery (**Figures 6A,B**).

Mutant α-Synuclein Mice Accumulate Swollen Mitochondria Acutely After Neonatal TBI

Immunohistochemistry for SOD2 (**Figures 7A–F**) was used as an additional assay to study mitochondria and was used to measure mitochondrial diameters as an index of their swelling directly in neurons (31, 32, 39). In naïve wildtype mice, mitochrondrial diameter in various neurons is about 0.5 μm (**Figures 7A,D,G**). Both sham groups were no different from naïve mice (**Figure 7G**). In contrast, mitochondrial diameters in cortical and hippocampal neurons were modestly increased in non-Tg mice with CCI at 1 day recovery (**Figures 7B,E,G**). Mitochondrial swelling at 24 h after CCI was markedly exacerbated in A53T-hαSyn mice (**Figures 7C,F,G**). Mitochondrial swelling in cortical neurons was confimed by EM (**Figure 7H**).

Acute Brain Injury in Early Life Accelerates Later Development of PD in hαSyn tg Mice

Neonatal hαSyn-A53T tg mice with p7 CCI developed motor deficits at a juvenile age compared to age-matched non-injured sham hαSyn tg-A53T mice (**Figure 1C**). Disease onset, defined by the presence of jerky/spastic movements [(27), see videos], was accelerated in hαSyn-A53T tg mice with CCI (**Figure 8A**). Furthermore, hαSyn-A53T tg mice with neonatal CCI had a shortened lifespan compared to age-matched non-injured sham hαSyn tg-A53T mice (**Figure 8B**). The early disease onset at about 3 months of age in hαSyn-A53T tg mice with neonatal CCI was associated with prominent accumulation of nitrated hαSyn and hαSyn oligomers in brain (**Figures 8C,D**).

Mutant hSOD1 Causes Severe Protein Oxidative Damage in Forebrain After Neonatal TBI

We examined acute oxidative stress after neonatal CCI in our ALS mouse model. Protein oxidative damage in mouse cerebrum at 3 and 24 h after CCI was assessed by the levels of carbonyl-modified proteins after derivatization and western blotting. At baseline, carbonylated proteins were detected at the high molecular weight range 150–250 kD (**Figure 9A**), and non-tg sham and G93A-hSOD1 sham mice had similar patterns. Baseline protein carbonyl patterns were very different in hαSyn-A53T tg mice and their non-tg sham controls compared to G93A-hSOD1 tg mice and their non-tg sham controls probably because these mouse lines have completely different genetic background strains. After CCI, protein carbonyl levels were dramatically elevated in G93A-hSOD1 compared to non-tg sham at 3 h (**Figure 9A**). At 24 h after CCI the accumulation of protein carbonlys was greater compared to 3 h with very distinct bands of damaged protein bands resolving in the lower- to mid-molecular weight ranges (**Figure 9A**).

Acute Brain Injury in Early Life Accelerates Later Development of ALS in G93A-hSOD1 tg Mice

Neonatal G93A-hSOD1 tg mice with p7 CCI developed motor deficits at a juvenile age compared to age-matched non-injured sham hαSyn tg-A53T mice (**Figure 1C**). Disease onset, defined by the presence of leg tremor was significantly earlier in G93A-hSOD1 tg mice with CCI (**Figure 9B**). G93A-hSOD1 tg mice with neonatal CCI also had a significantly abbreviated lifespan compared to age-matched non-injured sham G93A-hSOD1 tg mice (**Figures 9C,D**). G93A-hSOD1 tg mice with neonatal CCI died about 15 days earlier than their tg sham controls (**Figure 9D**).

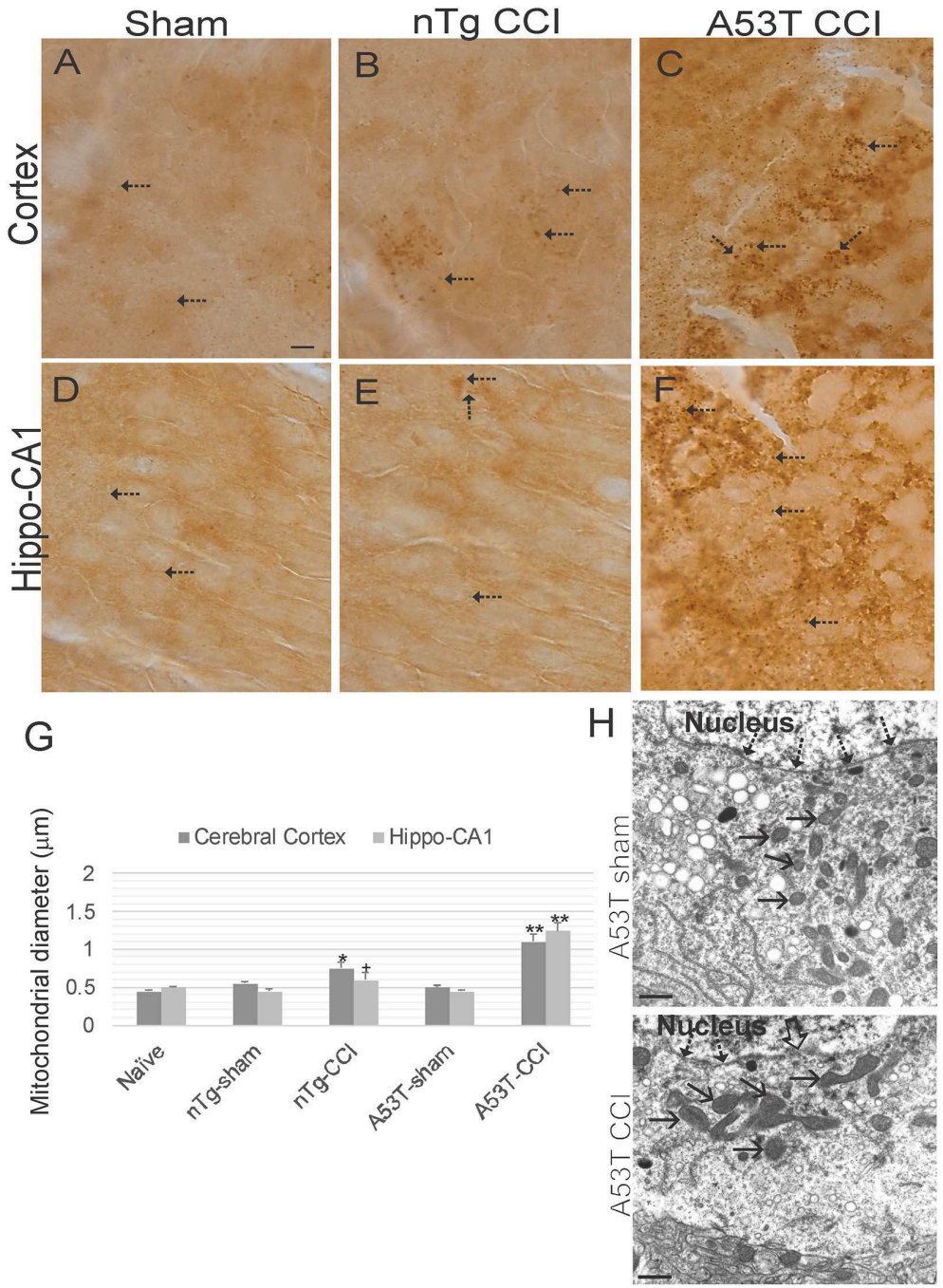

FIGURE 7 | Mitochondrial morphology abnormalities in forebrain are exacerbated in mutant A53T-αSyn after neonatal cortical contusion injury (CCI). SOD2 immunostaining showing mitochondria in neonatal mouse cerebral cortex **(A–C)** and hippocampus **(D–F)** at 24 h after injury at postnatal day 7. **(A–C)** In cerebral cortex mitochondria in shams were fine and barely visible (by light microscopy) speck-like particles dispersed throughout the neuropil (**A**, arrows). In non-Tg mice after CCI clusters of larger swollen mitochondria were observed, (**B**, arrows), and in mutant A53T-hαSyn mice with CCI large swollen mitochondria were found commonly throughout the cortical neuropil (**C**, arrows). **(D–F)** In hippocampus swollen mitochondrial were most conspicuous in mutant A53T-αSyn mice with CCI (**F**, arrows) though some isolated cells appeared with clusters of swollen mitochondria in non-Tg mice with CCI. Scale bar A (same for **B–F**) = 10 μm. **(G)** Mitochondrial diameter measured (1,000x) in cross-sectional profiles in hippocampus and cerebral cortex at 24 h after injury at postnatal day 7. Values are mean ± SD (n = 10 mice/group). $+p < 0.05$, $*p < 0.01$, or $**p < 0.005$ compared to sham. **(H)** EM of ipsilateral cortical neurons at 24 h after sham or CCI procedure on mutant A53T-hαSyn mice. Hatched arrows identify the nuclear membrane. Open arrow (lower panel) identifies breach in the nuclear membrane of CCI mouse cortical neuron. Solid arrows identify cross-sectional profiles of mitochondria in the perikaryon. Mitochondria are swollen in the neuron of CCI mice. Scale bars = 1 μm.

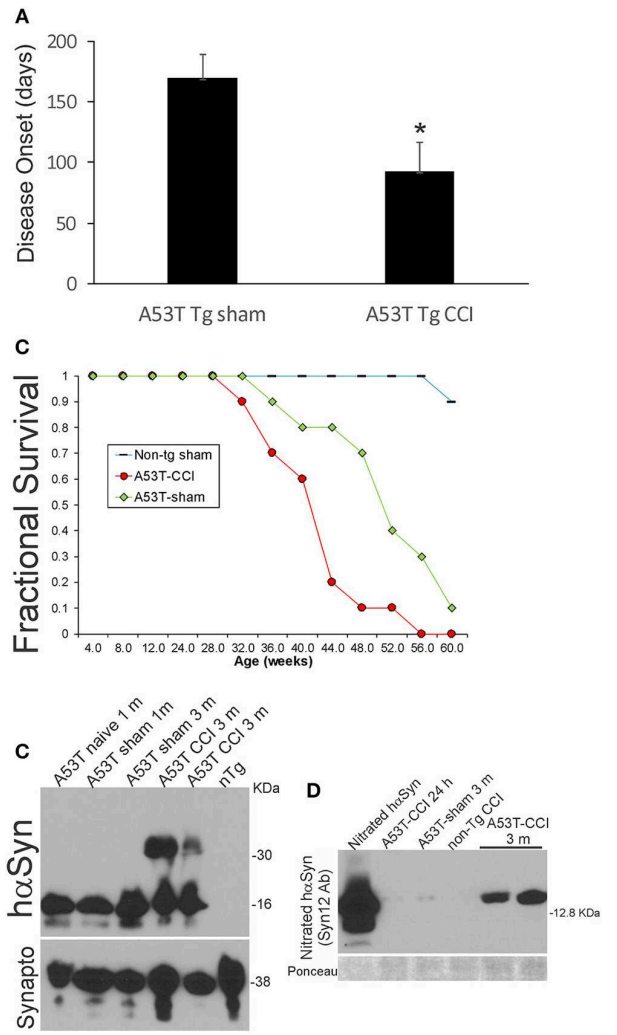

FIGURE 8 | Early-life brain trauma accelerates the development of later-life PD and proteinopathy in mutant A53T-αSyn Tg mice. **(A)** PD-like disease onset occurs significantly (*$p < 0.01$) earlier in mutant A53T-αSyn Tg mice with postnatal day 7 CCI compared to sham-procedure mutant A53T-αSyn Tg mice. Values are mean ± SD ($n = 10$ mice/group). **(B)** Kaplan-Meier plot showing that PD-like disease onset, neurological decline, and death occur earlier in mutant A53T-αSyn Tg mice with postnatal day 7 CCI compared to sham-procedure mutant A53T-αSyn Tg mice. **(C)** Western blotting shows advanced hαSyn oligomerization in forebrain at 3 months of age in mutant A53T-αSyn Tg mice with postnatal day 7 CCI compared to naïve and sham-procedure mutant A53T-αSyn Tg mice. Synaptophysin (Synapto) immunoblot shows protein loading. **(D)** Western blotting shows advanced hαSyn nitration in forebrain at 3 months of age in mutant A53T-αSyn Tg mice with postnatal day 7 CCI compared to age-matched sham-procedure mutant A53T-αSyn Tg mice and mutant A53T-αSyn Tg mice with CCI at 24 h. Ponceau S-stained membrane shows protein loading.

Acute Brain Injury in Early Life Did Not Affect the Deposition of Amyloid in APP-PS1 tg Mice

Although early life brain injury did not after acute mortality (**Figure 1B**) or apparent morbidity in APP-PS1 mice, we assayed for later-life brain pathology by counting the number of neocortical Aβ deposits at 6 months of age. Neonatal APP-PS1 tg mice with p7 CCI did not accumulate more Aβ deposits compared to age-matched non-injured sham APP-PS1 mice (**Figure 10**).

DISCUSSION

This study shows that acute outcome after acquired brain injury in newborns is influenced significantly by mutant genes that cause adult-onset neurodegenerative disease and that the development of later-life age-related neurodegenerative disease is influenced significantly by early-life brain injury. Specifically, genes causing PD and ALS worsen mortality and morbidity in mice with neonatal CCI. Reciprocally, mice genetically predisposed to develop PD or ALS later in life have accelerated disease when they have early-life TBI. Worse acute outcome in PD- and ALS–destined mice with neonatal TBI is associated with exacerbated oxidative damage. More severe mitochondriopathy is also seen in PD mice with neonatal TBI. Accelerated later-life disease is associated with exacerbated PD-related proteinopathy. Thus, in experimental settings, mutant genes that manifest their clinical phenotype in adulthood can have major impact on acquired CNS injury in infancy and, perhaps, childhood. From this study, it seems evident that neonatal brain injury and adult-onset neurodegeneration are more interrelated and intersecting than realized previously.

Precedent exists for genetic factors influencing acute and long-term neurologic outcome after acquired brain injury in human adults, children, and newborns. For example in adults, *neuroglobin* gene haplotype has a strong influence on outcome after TBI (49), *bcl-2* gene single nucleotide polymorphisms also influence outcome after TBI (50), and a*poE* genotype predicts outcome following subarachnoid hemorrhage (51). In children, single nucleotide polymorphisms in genes related to dopamine neurotransmission (D2 dopamine receptor, dopamine transporter, catechol-o-methytransferase, and ankyrin repeat and kinase domain containing (1) have roles in short- and long-term neurobehavioral recovery after TBI (20). In term newborns, *catalase* gene (21) and *interleukin-6* gene (22–24) polymorphisms are associated with higher susceptibility to cerebral palsy after hypoxia-ischemia. In preterm infants, glial glutamate transporter gene *EAAT2* polymorphisms associate with greater risk of cerebral palsy (25). The novel information revealed in our study is the demonstration that pathogenic genes causing adult-onset neurodegenerative can have dramatic acute and long-term impacts on neonatal mice with acquired brain injury.

Pathogenic mechanisms of mutant genes that cause neurodegeneration in adults thus appear to influence brain responses to acute injury long before the spontaneous development of age-related neurodegenerative disease. In hαSyn-A53T tg mice with neonatal CCI, we found exacerbated protein oxidation and mitochondrial damage compared to non-tg neonatal CCI mice at 1-day of recovery. Moreover, hαSyn oligomerization and nitration were accelerated after early-life brain injury. In previous studies of a mouse model of ALS, acute peripheral nerve avulsion induces rapid spinal

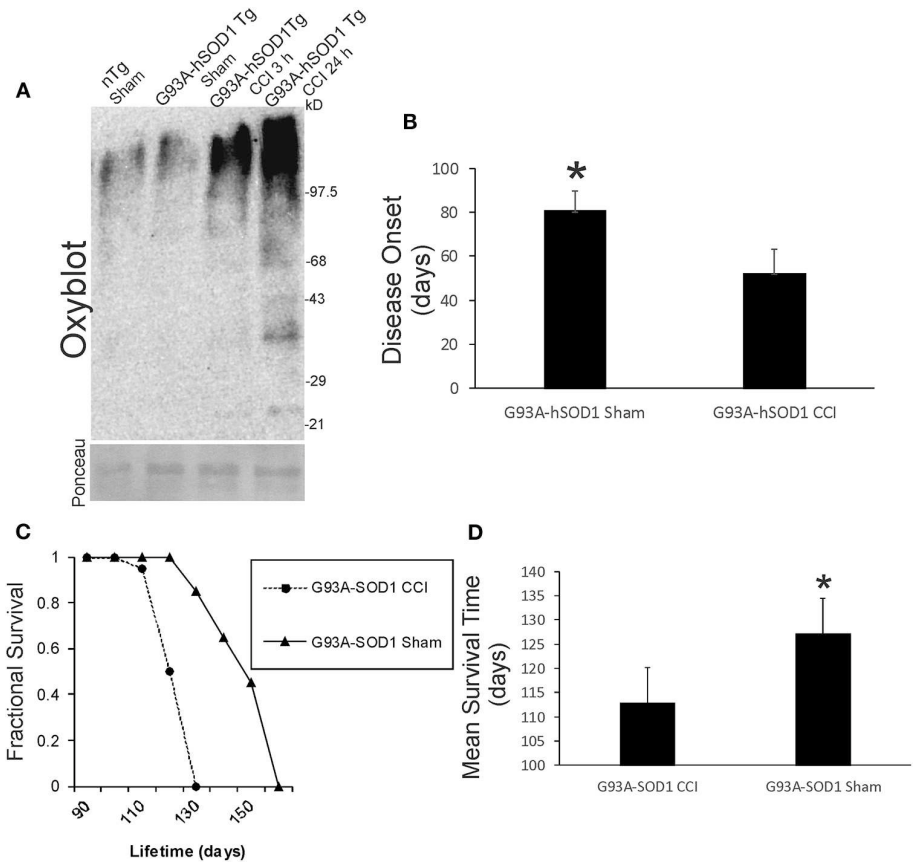

FIGURE 9 | Early-life brain trauma in ALS mice causes severe oxidative damage and accelerates the development of later-life ALS in G93A-hSOD1 Tg mice. **(A)** Oxyblot showing protein carbonyls in forebrain of sham and cortical contusion injury (CCI) mice 3 and 24 h after injury at postnatal day 7. Molecular weight standards (in kD) shown at right. Ponceau S-stained membrane shows protein loading for each lane. **(B)** Neonatal CCI at p7 in G93A-hSOD1 Tg mice causes an earlier disease onset compared to tg mice without CCI. Values are mean ± SD ($n = 10$ mice/group). Asterisk significantly ($p < 0.05$) later compared to CCI. **(C)** Kaplan-Meier plot showing that ALS-like disease onset, neurological decline, and death occur earlier in G93A-hSOD1 Tg mice with postnatal day 7 CCI compared to sham-procedure G93A-hSOD1 Tg mice. (**D)** Graph showing the mean survial of G93A-hSOD1 Tg mice with and without CCI. Values are mean ± SD ($n = 10$ mice/group). Asterisk significantly ($p < 0.05$) later compared to CCI.

motor neuron necrosis rather than the usual apoptosis of motor neurons seen in non-tg mice (52), and, in this study, we found severe protein oxidative damage in neonatal ALS mice with brain injury. Electrophysiological and ion channel activities of cultured embryonic motor neurons (53, 54) and early postnatal motor neurons in acute spinal cord slices (55) from a mutant hSOD1 mouse model of ALS are abnormal long before these mice show a clinical phenotype or overt neuronal cell death. Similarly, mitochondriopathy exists before clinical features and neurodegeneration emerge in these mice (31, 54, 56). Thus, individuals with "adult-onset" neurodegenerative disease may be primed or predisposed to have worse clinical and pathological outcomes after early-life CNS injury. It would be interesting to know if infants and children that have unexplained poor outcomes in intensive care units have genetic risk factors such a mutant genes that would eventually cause PD and ALS.

The influences of the human mutant genes on outcome after neonatal brain injury in mice were manifested acutely and over long-term. Mice harboring hαSyn-A53T and hSOD1-G93A mutations had significantly worse 48-h survival after CCI. The hαSyn-A53T transgene is driven by a Thy-1 neuron-specific promoter (27) and the hSOD1-G93A transgene is driven by the endogenous hSOD1 promoter (28), but, while the hαSyn has a much more restricted tissue expression of the mutant protein compared to the hSOD1 mice, there could be critical autonomic and peripheral responses after the insult unaccounted for in both mouse lines. The mice were not be instrumented and monitored for clinically relevant physiology, as in neonatal large animal models (57). In this regard, we do not know the physiological basis of why hαSyn-A53T and hSOD1-G93A mice had greater risk of death after acute brain injury, but it appears unrelated to their essential Tg nature because mice harboring human APP and PS1 mutant genes had survival rates similar to non-Tg mice. In the injured 24 h-surviving hαSyn-A53T mice, we observed exacerbated protein oxidation and mitochondrial injury. In G93A-hSOD1 mice with neonatal TBI severe protein oxidation was observed at 3 and 24 h after the insult. It is possible that this pathology contributed to their early deterioration and could

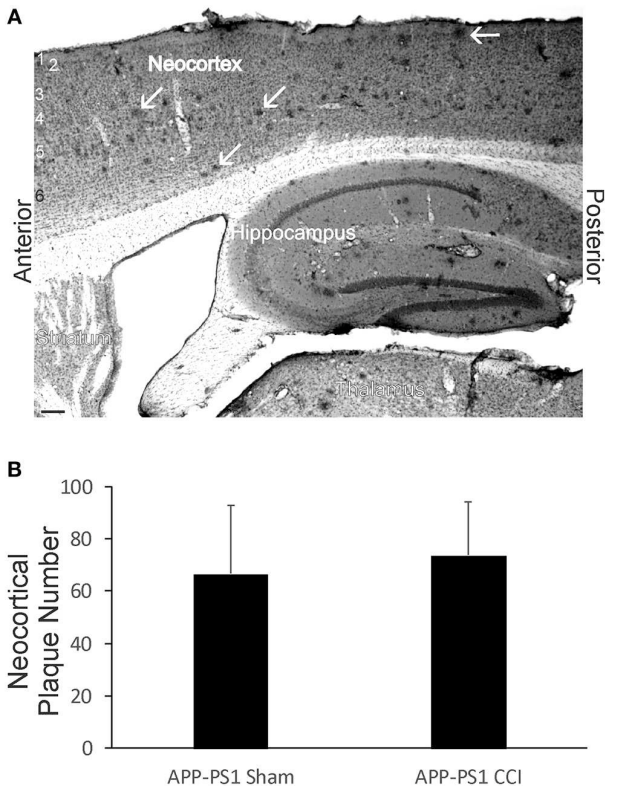

FIGURE 10 | Early-life brain trauma in APP-PS1 mice does not alter the cortical accumulation of Aβ. **(A)** Sagittal section stained immunohistochemically for Aβ. Cortical layers identified by numbers (left). White arrows identify parenchymal deposits of Aβ. Bar = 103 μm. **(B)** Graph showing the mean number of Aβ deposits in frontal-patietal-occipital cortex in APP-PS1 Tg mice with and without CCI. Values are mean ± SD ($n = 6$ mice/group).

be mechanisms related to the "priming" predisposition of age-related disease in these mice. At 1-month of age, clinical motor deficits and neuropathology in cerebral cortex, white matter, midbrain, and brainstem of hαSyn-A53T mice with neonatal TBI were significantly more severe than in non-Tg mice with CCI and sham hαSyn-A53T. Later in life hαSyn-A53T mice with neonatal TBI manifested much earlier onset of PD-like symptoms and eventiually developed fatal disease much earlier than sham hαSyn-A53T mice. The accelerated disease onset occurred in the presence of greater hαSyn proteinopathy. A similar acceleration of disease onset and death was seen in ALS mice with neonatal brain injury. Perhaps early-life brain injury, starting with the initial p7 mild traumatic damage to cerebral cortex, triggers seeding effects on synucleinopathy or hSOD1 misfolding that spreads in a connectivity-related prion-like mechanism that damages vulnerable regions and nuclei throughout the neuraxis. New hypotheses for PD and ALS pathogenesis describe prion-like (prionoid) spreading of abnormal proteins (38), thus accounting for the progression and staging of neuropathology throughout the nervous system in preclinical individuals through advanced disease (58).

Mutations in αSyn cause some forms of familial PD (5, 6). Aggregated and nitrated hαSyn forms are toxic entities in familial and sporadic forms of PD. αSyn is an abundant soluble monomeric protein that can associate with mitochondrial membranes (37, 59–61), and the pathogenesis of hαSyn-linked PD in mice involves the association hαSyn with mitochondria and activation of the mitochondrial permeability transition pore (27, 37). We found exacerbated mitochondrial damage in neonatal hαSyn-A53T mice with TBI compared to neonatal sham hαSyn-A53T mice. αSyn can polymerize into insoluble fibrils due to a conformational change from an α-helical coil to a β-pleated sheet (62). We found exacerbated aggregation of mutant hαSyn in neonatal hαSyn-A53T mice with TBI compared to neonatal sham hαSyn-A53T mice. hαSyn mutations cause increased levels of protofibrils, possibly being the more toxic form of the protein (63). hαSyn protofibrils might also be toxic by making membranes of cells more porous (64). Of particular relevance to our experimental model is that hαSyn fibrils are transported in neurons anterogradely and retrogradely, and they appear to propagate after transport and undergo neuron-to-neuron transmission independently of synapses and cell-to-cell-contacts (18). We found remote degeneration in the SNc and PPN in young hαSyn-A53T mice after CCI. Nitration of hαSyn, footprinting the presence of potent reactive nitrogen species like peroxynitrite, is a major signature of human PD and other proteinopathies and might be critical to the aggregation, toxicity, and spreading processes (46, 65). We found elevated hαSyn nitration in neonatal hαSyn-A53T mice with TBI compared to neonatal sham hαSyn-A53T mice. Aggregation and nitration of wildtype and mutated hαSyn is associated with enhanced cell death in cultured cells (46). We found exacerbated neuropathology in mutant hαSyn in neonatal hαSyn-A53T mice with TBI compared to neonatal non-Tg mice with TBI and sham hαSyn-A53T mice. Over-expression of wildtype or mutant hαSyn in cultured cells elevates the generation of intracellular reactive oxygen species and causes mitochondrial deficits (66, 67); moreover, expression of mutant hαSyn increases cytotoxicity to dopamine oxidation products (68). We found elevated protein oxidation in neonatal hαSyn-A53T mice with TBI compared to neonatal sham hαSyn-A53T mice. This precedent on hαSyn molecular pathology and our new findings suggest that acquired brain injury in early life can engage rapidly the mechanisms of age-related pathogenesis in neurodegenerative disease for acute responses, even in the immature brain, and then sustain or perpetuate these mechanisms to influence later-life disease outcomes.

In our study, we did not find an effect of human mutant APP and PS1 on acute outcome in injured neonatal mice. This is not surprising considering the limited age-related clinical phenotypes and neuropathology in this mouse model (4, 30). While these mice accumulate with aging large quantities of Aβ protein in brain, they do not develop fatal neurological disease or any major neurodegeneration, as defined by neuronal cell and synaptic loss, neurofibrillary tangle, and tauopathy (30, 69–71); thus, modeling ineffectively that seen in human AD (72–75). In this study, we did not find an effect of neonatal CCI on later-life Aβ deposition in neocortex. Despite the Aβ proteinopathy, overt mitochondrial pathology and protein oxidative damage are minimal in APP/PS1 Tg mice (30, 76) in comparision to that seen in hαSyn-A53T and G93A-hSOD1 mice (27, 32).

Thus, it could be the robust bioenergetic and oxidative stress pathology in the hαSyn-A53T and G93A-hSOD1 mice that is recruited acutely and driving the deleterious responses of the immature brain to acquired injury. Neonatal brain injury in human tau Tg mice might yield more provocative acute and long-term results.

This study has limitations. We did not have available hαSyn-wildtype and hSOD1-wildtype mouse pups subjected to CCI for a comparison with the hαSyn-A53T and hSOD1-G93A mice with CCI. This comparison would have been useful to see if the hαSyn and hSOD1 overexpression *per se* was harmful or whether the detelerious effects were related to potential toxic gains in protein function due to the mutations. However, in an adult mouse model of cortical injury-induced target deprivation, wildtype hSOD1 overexpression afforded significant protection against retrograde neuronal apoptosis (45). We also did not compare male to female mouse responses. We have observed sex differences in neonatal mice after cerebral hypoxia-ischemia subacutely and over long-term (77) and in adult G93A-hSOD1 mice (32). We are also uncertain whether the apparent neuronal degeneration and loss in this mouse model mirrors that seen in human neurons (78).

ETHICS STATEMENT

All animal studies were performed in accordance with institutional guidelines and laws of the United States of America. No research in this study involved human participants.

AUTHOR CONTRIBUTIONS

LM conceived and designed experiments, performed experiments, analyzed data, wrote paper. MW performed experiments and analyzed data. AH performed experiments and worked on paper.

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REFERENCES

1. Kumar S, Yadav N, Pandey S, Thelma BK. Advances in the discovery of genetic risk factors for complex forms of neurodegenerative disorders: contemporary approaches, success, challenges, and prospects. *J Genet*. (2018) 97:625–48. doi: 10.1007/s12041-018-0953-5
2. van Den Eden SK, Tanner CM, Bernstein AL, Fross RD, Leimpeter A, Bloch DA, et al. Incidence of Parkinson's disease: variations by age, gender and race ethnicity. *Am J Epidemol*. (2003) 157:1015–22. doi: 10.1093/aje/kwg068
3. Wang M-D, Little J, Gomes J, Cashman NR, Krewski D. Identification of risk factors associated with onset and progression of amyotrophic lateral sclerosis using systematic review and meta-analysis. *NeuroToxicol*. (2017) 61:101–30. doi: 10.1016/j.neuro.2016.06.015
4. Martin LJ. Mitochondrial and cell death mechanisms in neurodegenerative disease. *Pharmaceuticals. (*2010) 3:839–915. doi: 10.3390/ph3040839
5. Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, et al. Mutation in the α-synuclein gene identified in families with Parkinson's disease. *Science*. (1997) 276:2045–7. doi: 10.1126/science.276.5321.2045
6. Singleton, AB, Farrer M, Johnson J, Singleton A, Hague S, Kachergus J, et al. Alpha-synuclein locus triplication causes Parkinson's disease. *Science*. (2003) 302:841. doi: 10.1126/science.1090278
7. Roozenbeek B, Maas Al, Menon DK. Changing patterns in the epidemiology of traumatic brain injury. *Nat Rev Neurol*. (2013) 9:231–6. doi: 10.1038/nrneurol.2013.22
8. Mendez MF, Paholpak P, Lin A, Zhang JY, Teng E. Prevalence of traumatic brain injury in early versus late-onset Alzheimer's disease. *J Alzheimers Dis*. (2015) 47:985–93. doi: 10.3233/JAD-143207
9. Crane PK, Gibbons LE, Dams-O'Connor K, Trittschuh E, Leverenz JB, Keene CD, et al. Association of traumatic brain injury with late-life neurodegenerative conditions and neuropathological findings. *JAMA Neurol*. (2016) 73:1062–9. doi: 10.1001/jamaneurol.2016.1948
10. Cruz-Haces M, Tang J, Acosta G, Fernandez J, Shi R. Pathological correlations between traumatic brain injury and chronic neurodegenerative diseases. *Transl Neurodegener*. (2017) 6:20. doi: 10.1186/s40035-017-0088-2
11. Hubble JP, Cao T, Hassanein RE, Neuberger JS, Koller WC. Risk factors for Parkinson's disease. *Neurology*. (1993) 43:1693–97. doi: 10.1212/WNL.43.9.1693
12. McKee AC, Gavett BE, Stern RA, Nowinski CJ, Cantu RC, Kowall NW, et al. TDP-43 proteinopathy and motor neuron disease in chronic traumatic encephalopathy. *J Neuropath Exp Neurol*. (2010) 69:918–29. doi: 10.1097/NEN.0b013e3181ee7d85
13. Beretta S, Carri MT, Beghi E, Chio A, Ferrarese C. The sinister side of Italian soccer. *Lancet Neurol*. (2003) 2:656–7. doi: 10.1016/S1474-4422(03)00579-9
14. Chio A, Benzi G, Dossena M, Mutani R, Mora G. Severely increased risk of amyotrophic lateral sclerosis among Italian professional football players. *Brain*. (2005) 128:472–6. doi: 10.1093/brain/awh373
15. Scarmeas N, Shih T, Stern Y, Ottman R, Rowland LP. Premorbid weight, body mass, and varsity athletics in ALS. *Neurology*. (2002) 59:773–5. doi: 10.1212/WNL.59.5.773
16. Beghi E, Logroscino G, Chio A, Hardiman O, Millul A, Mitchell D, et al. Amyotrophic lateral sclerosis, physical exercise, trauma and sports: result of a population-based pilot case-control study. *Amyotroph Lateral Scler*. (2010) 11:289–92. doi: 10.3109/17482960903384283
17. Chen H, Richard M, Sandler DP, Umbach DM, Kamel F. Head injury and amyotrophic lateral sclerosis. *Am J Epidemiol*. (2007) 166:810–6. doi: 10.1093/aje/kwm153
18. Brettschneider J, Del Tredici K, Lee VM, Trojanowski JQ. Spreading of pathology in neurodegenerative diseases: a focus on human studies. *Nat Rev Neurosci*. (2015) 16:109–20. doi: 10.1038/nrn3887
19. Brambrink AM, Ichord RN, Martin LJ, Koehler RC, Traystman RJ. Poor outcome after hypoxia-ischemia in newborns is associated with physiological abnormalities during early recovery. *Exp Toxic Pathol*. (1999) 51:151–62. doi: 10.1016/S0940-2993(99)80089-X
20. Treble-Barna A, Wade Sl, Martin LJ, Pilipenko V, Yeates KO, Taylor HG, et al. Influence of dopamine-related genes on neurobehavioral recovery after traumatic brain injury during early childhood. *J Neurotrauma*. (2017) 34:1919–31. doi: 10.1089/neu.2016.4840
21. Esih K, Goricar K, Dolzan V, Rener-Primec Z. The association between antioxidant enzyme polymorphisms and cerebral palsy after perinatal hypoxic-ischaemic encephalopathy. *Eur J Paed Neurol. (*2016) 20:704–8. doi: 10.1016/j.ejpn.2016.05.018
22. Bi D, Chen M, Zhang X, Wang H, Xia L, Shang Q, et al. The association between sex-related interleukin-6 gene polymorphisms and the risk for cerebral palsy. *J Neuroflamm*. (2014) 11:100. doi: 10.1186/1742-2094-11-100

23. Calkavur S, Akisu M, Olukman O, Balim Z, Berdeli A, Cakmak B, et al. Genetic factors that influence short-term neurodevelopmental outcome in term hypoxic-ischaemic encephalopathic neonates. *J Intl Med Res*. (2011) 39:1744–56. doi: 10.1177/147323001103900517
24. Wu YW, Croen LA, Torres AR, De Water JV, Grether JK, Hsu NN. Interleukin-6 genotype and risk for cerebral palsy in term and near-term infants. *Ann Neurol*. (2009) 66:663–70. doi: 10.1002/ana.21766
25. Rajatileka S, Odd D, Robinson MT, Spittle AC, Dwomoh L, Williams M, et al. Variants of the EAAT2 glutamate transporter gene promoter are associated with cerebral palsy in preterm infants. *Mol Neurobiol*. (2018) 55:2013–24. doi: 10.1007/s12035-017-0462-1
26. Ferriero DM. Neonatal brain injury. *New Engl J Med*. (2004) 351:1985–95. doi: 10.1056/NEJMra041996
27. Martin LJ, Semenkow S, Hanaford A, Wong M. The mitochondrial permeability transition pore regulates Parkinson's disease development in mutant α-synuclein transgenic mice. *Neurobiol Aging*. (2014) 35:1132–52. doi: 10.1016/j.neurobiolaging.2013.11.008
28. Gurney ME, Pu H, Chiu AY, Dal Canto MC, Polchow CY, Alexander DD, et al. Motor neuron degeneration in mice that express a human Cu, Zn superoxide dismutase mutation. *Science*. (1994) 264:1772–5. doi: 10.1126/science.8209258
29. Jankowsky JL, Slunt HH, Ratovitski T, Jenkins NA, Copeland NG, Borchelt DR. Co-expression of multiple transgenes in mouse CNS: a comparison of strategies. *Biomolec Eng*. (2001) 17:157–65. doi: 10.1016/S1389-0344(01)00067-3
30. LaClair KD, Donde A, Ling JP, Jeong YH, Chhabra R, Martin LJ, et al. Depletion of TDP-43 decreases fibril and plaque β-amyloid and exacerbates neurodegeneration in an Alzheimer's mouse model. *Acta Neuropathol*. (2016) 132:859–73. doi: 10.1007/s00401-016-1637-y
31. Martin LJ, Liu Z, Chen K, Price AC, Pan Y, Swaby JA, et al. Motor neuron degeneration in amyotrophic lateral sclerosis mutant superoxide dismutase-1 transgenic mice: mechanisms of mitochondriopathy and cell death. *J Comp Neurol*. (2007) 500:20–46. doi: 10.1002/cne.21160
32. Martin LJ, Gertz B, Pan Y, Price AC, Molkentin JD, Chang Q. The mitochondrial permeability transition pore in motor neurons: involvement in the pathobiology of ALS mice. *Exp Neurol*. (2009) 218:333–46. doi: 10.1016/j.expneurol.2009.02.015
33. Natale JE, Cheng Y, Martin LJ. Thalamic neuron apoptosis emerges rapidly after cortical damage in immature mice. *Neuroscience*. (2002) 112:665–76. doi: 10.1016/S0306-4522(02)00098-2
34. Mueller D, Shamblott MJ, Fox HE, Gearhart JD, Martin LJ. Transplanted human embryonic germ cell-derived neural stem cells replace neurons and oligodendrocytes in the forebrain of neonatal mice with excitotoxic brain damage. *J Neurosci Res*. (2005) 82:592–608. doi: 10.1002/jnr.20673
35. Martin LJ, Liu Z. Adult olfactory bulb neural precursor cell grafts provide temporary protection from motor neuron degeneration, improve motor function, and extend survival in amyotrophic lateral sclerosis mice. *J Neuropathol Exp Neurol*. (2007) 66:1002–18. doi: 10.1097/nen.0b013e318158822b
36. Wong M, Martin LJ. Skeletal muscle-restricted expression of human SOD1 causes motor neuron degeneration in transgenic mice. *Hum Mol Genet*. (2010) 19:2284–302. doi: 10.1093/hmg/ddq106
37. Martin LJ, Pan Y, Price AC, Sterling W, Copeland NG, Jenkins NA, et al. Parkinson's disease α-synuclein transgenic mice develop neuronal mitochondrial degeneration and cell death. *J Neurosci*. (2006) 26:41–50. doi: 10.1523/JNEUROSCI.4308-05.2006
38. Martin LJ, Brambrink AM, Price AC, Kaiser A, Agnew DM, Ichord RN, et al. Neuronal death in newborn striatum after hypoxia-ischemia is necrosis and evolves with oxidative stress. *Neurobiol Dis*. (2000) 7:169–91. doi: 10.1006/nbdi.2000.0282
39. Wu D, Martin LJ, Northington FJ, Zhang J. Oscillating-gradient diffusion magnetic resonance imaging detects acute subcellular changes in the mouse forebrain after neonatal hypoxia-ischemia. *J Cereb Blood Flow Metabol*. (2018). doi: 10.1177/0271678X18759859. [Epub ahead of print].
40. Wong-Riley M. Changes in the visual system of monocularly sutured or enucleated cats demonstrable with cytochrome oxidase histochemistry. *Brain Res*. (1979)171:11–28. doi: 10.1016/0006-8993(79)90728-5
41. Al-Abdulla NA, Martin LJ. Apoptosis of retrogradely degenerating neurons occurs in association with the accumulation of perikaryal mitochondria and oxidative damage to the nucleus. *Am J Pathol*. (1998) 153:447–56. doi: 10.1016/S0002-9440(10)65588-5
42. Martin LJ, Brambrink A, Koehler RC, Traystman RJ. Primary sensory and forebrain motor systems in the newborn brain are preferentially damaged by hypoxia-ischemia. *J Comp Neurol*. (1997) 377:262–85. doi: 10.1002/(SICI)1096-9861(19970113)377:2<262::AID-CNE8>3.0.CO;2-1
43. Northington FJ, Ferriero DM, Graham EM, Traystman RJ, Martin LJ. Early neurodegeneration after hypoxia-ischemia in neonatal rat is necrosis while delayed neuronal death is apoptosis. *Neurobiol Dis*. (2001) 8:207–19. doi: 10.1006/nbdi.2000.0371
44. Mueller-Burke D, Koehler RC, Martin LJ. Rapid NMDA receptor phosphorylation and oxidative stress precede striatal neurodegeneration after hypoxic ischemia in newborn piglets and are attenuated with hypothermia. *Int J Devl Neurosci*. (2008) 26:67–76. doi: 10.1016/j.ijdevneu.2007.08.015
45. Martin LJ, Price AC, McClendon KB, Al-Abdulla NA, Subramaniam JR, Wong PC, et al. Early events of target deprivation/axotomy-induced neuronal apoptosis *in vivo*: oxidative stress, DNA damage, p53 phosphorylation and subcellular redistribution of death proteins. *J Neurochem*. (2003) 85:234–47. doi: 10.1046/j.1471-4159.2003.01659.x
46. Giasson BI, Duda JE, Murray IVJ, Chen Q, Souza JM, Hurtig HI, et al. Oxidative damage linked to neurodegeneration by selective alpha-synuclein nitration in synucleinopathy lesions. *Science*. (2000) 290:985–9. doi: 10.1126/science.290.5493.985
47. Kopp VJ, Jobson M. Does isoflurane or isoflurane plus hyperoxia induce apoptotic cell death? *Anesth Analg*. (2013) 117:1023. doi: 10.1213/ANE.0b013e3182a231b5
48. Martin LJ, Kaiser A, Price AC. Motor neuron degeneration after sciatic nerve avulsion in adult rat evolves with oxidative stress and is apoptosis. *J Neurobiol*. (1999) 40:185–201. doi: 10.1002/(SICI)1097-4695(199908)40:2<185::AID-NEU5>3.0.CO;2-%23
49. Chuang PY, Conley P, Poloyac SM, Okonkwo DO, Ren D, Sherwood PR, et al. Neuroglobin genetic polymorphisms and their relationship to functional outcomes after traumatic brain injury. *J Neurotrauma*. (2010) 27:999–1006. doi: 10.1089/neu.2009.1129
50. Hoh NZ, Wagner AK, Alexander SA, Clark RB, Beers SR, Okonkwo DO, et al. Bcl2 genotypes: functional and neurobehavioral outcomes after severe traumatic brain injury. *J Neurotrauma*. (2010) 27:1413–27. doi: 10.1089/neu.2009.1256
51. Gallek MJ, Conley YP, Sherwood PR, Horowitz MB, Kassam A, Alexander SA. APOE genotype and functional outcome following aneurismal subarachnoid hemorrhage. *Biol Res Nurs*. (2009) 10:2050212. doi: 10.1177/1099800408323221
52. Martin LJ, Chen K, Liu Z. Adult motor neuron apoptosis is mediated by nitric oxide and Fas death receptor linked by DNA damage and p53 activation. *J Neurosci*. (2005) 25:6449–59. doi: 10.1523/JNEUROSCI.0911-05.2005
53. Chang Q, Martin LJ. Glycine receptor channels in spinal motoneurons are abnormal in a transgenic mouse model of amyotrophic lateral sclerosis. *J Neurosci*. (2011) 31:2815–27. doi: 10.1523/JNEUROSCI.2475-10.2011
54. Chang Q, Martin LJ. Voltage-gated calcium channels are abnormal in cultured spinal motoneurons in the G93A-SOD1 transgenic mouse model of ALS. *Neurobiol Dis*. (2016) 93:78–95. doi: 10.1016/j.nbd.2016.04.009
55. Van Zundert B, Izaurieta P, Fritz E, Alvarez FJ. Early pathogenesis in the adult-onset neurodegenerative disease amyotrophic lateral sclerosis. *J Cell Biochem*. (2012) 113:3301–12. doi: 10.1002/jcb.24234
56. Bendotti C, Calvaresi N, Chiveri L, Prelle A, Moggio M, Braga M, et al. Early vacuolization and mitochondrial damage in motor neurons of FALS mice are not associated with apoptosis or with changes in cytochrome oxidase histochemical reactivity. *J Neurol Sci*. (2001) 191:25–33. doi: 10.1016/S0022-510X(01)00627-X
57. Koehler RC, Yang Z-J, Lee JK, Martin LJ. Perinatal hypoxic-ischemic brain injury in large animal models: relevance to human neonatal encephalopathy. *J Cereb Blood Flow Metabol*. (2018) 38:2092–11. doi: 10.1177/0271678X18797328

58. Braak H, de Vos RAI, Bohl J, Tredici KD. Gastric α-synuclein immunoreactive inclusions in Meissner's and Auerbach's plexuses in cases staged for Parkinson's disease-related brain pathology. *Neurosci Lett*. (2006) 396:67–72. doi: 10.1016/j.neulet.2005.11.012
59. Lesuisse C, Martin LJ. Long-term culture of mouse cortical neurons as a model for neuronal development, aging, and death. *J Neurobiol*. (2002) 51:9–23. doi: 10.1002/neu.10037
60. Maroteaux L, Campanelli JT, Scheller RH. Synuclein: a neuron-specific protein localized to the nucleus and presynaptic nerve terminals. *J Neurosci*. (1998) 8:2804–15. doi: 10.1523/JNEUROSCI.08-08-02804.1988
61. Nakamura K, Nemani VM, Wallender EK, Kaehlcke K, Ott M, Edwards RH. Optical reporters for the conformation of α-synuclein reveal a specific interaction with mitochondria. *J Neurosci*. (2008) 28:12305–17. doi: 10.1523/JNEUROSCI.3088-08.2008
62. Serpell LC, Berriman J, Jakes M, Goedert M, Crowther RA. Fiber diffraction of synthetic alpha synuclein filaments shows amyloid-like cross-beta conformation. *Proc Natl Acad Sci USA*. (2000) 97:4897–902. doi: 10.1073/pnas.97.9.4897
63. Conway KA, Lee SJ, Rochet JC, Ding TT, Williamson RE, Lansbury PT Jr. Acceleration of oligomerization, not fibrilization, is a shared property of both alpha-synuclein mutations linked to early-onset Parkinson's disease: implications for pathogenesis and therapy. *Proc Natl Acad Sci USA*. (2000) 97:571–6. doi: 10.1073/pnas.97.2.571
64. Caughey B, Lansbury PT. Protofibrils, pores, fibril, and neurodegeneration: separating the responsible protein aggregates from the innocent bystanders. *Annu Rev Neurosci*. (2003) 26:267–98. doi: 10.1146/annurev.neuro.26.010302.081142
65. Ischiropoulos H. Oxidative modification of alpha-synuclein. *Ann NY Acad Sci*. (2003) 991:93–100. doi: 10.1111/j.1749-6632.2003.tb07466.x
66. Hsu LJ, Sagara Y, Arroyo A, Rockenstein E, Sisk A, Mallory M, et al. Alpha-synuclein promotes mitochondrial deficit and oxidative stress. *Am J Pathol*. (2000) 157:401–10. doi: 10.1016/S0002-9440(10)64553-1
67. Junn E, Mouradian MM. Human alpha-synuclein over-expression increases intracellular reactive oxygen species levels and susceptibility to dopamine. *Neurosci Lett*. (2002) 320:146–50. doi: 10.1016/S0304-3940(02)00016-2
68. Tabrizi SJ, Orth M, Wilkinson JM, Taanman JW, Warner TT, Cooper JM, et al. Expression of mutant alpha-synuclein causes increased susceptibility to dopamine toxicity. *Hum Mol Genet*. (2000) 9:2683–9. doi: 10.1093/hmg/9.18.2683
69. Dickson DW. Building a more perfect beast: APP transgenic mice with neuronal loss. *Am J Pathol*. (2004) 164:1143–6. doi: 10.1016/S0002-9440(10)63202-6
70. Perez SE, Dar S, Ikonomovic MD, DeKosky ST, Mufson EJ. Cholinergic forebrain degeneration in the APPswe/PS1ΔE9 transgenic mouse. *Neurobiol Dis*. (2007) 28:3–15. doi: 10.1016/j.nbd.2007.06.015
71. Xu G, Gonzales V, Borchelt DR. Aβ deposition does not cause the aggregation of endogenous tau in transgenic mice. *Alzh Dis Assoc Dis*. (2002) 3:196–201 doi: 10.1097/00002093-200207000-00011
72. Braak H, Alafuzoff I, Arzberger T, Kretzschmar, Del Tredici K. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta Neuropathol*. (2006) 112:389–404. doi: 10.1007/s00401-006-0127-z
73. Braak H, Thal DR, Ghebremedhin E, Del Tredici K. Stages of the pathologic process in Alzheimer's disease: age categories from 1 to 100 years. *J Neuropath Exp Neurol*. (2011) 70:960–9. doi: 10.1097/NEN.0b013e318232a379
74. Sze C-I, Troncoso JC, Kawas C, Mouton P, Price DL, Martin LJ. Loss of the presynaptic vesicle protein synaptophysin in hippocampus correlates with cognitive decline in Alzheimer's disease. *J Neuropathol Exp Neurol*. (1997) 56:933–94. doi: 10.1097/00005072-199708000-00011
75. Terry RD, Masliah E, Salmon DP, Butters N, Deteresa R, Hill R, et al. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. *Ann Neurol*. (1991) 30:572–80. doi: 10.1002/ana.410300410
76. Choudhry F, Howlett DR, Richardson JC, Francis PT, Williams RJ. Pro-oxidant diet enhances β/γ secretase-mediated APP processing in APP.PS1 transgenic mice *Neurobiol Aging*. (2012) 33:960–8. doi: 10.1016/j.neurobiolaging.2010.07.008
77. Burnsed JC, Chavez-Valdez R, Shanaz-Hossain M, Kesevan K, Martin LJ, Zhang J, et al. Hypoxia-ischemia and therapeutic hypothermia in the neonatal mouse brain- a longitudinal study. *PLoS One*. (2015) 10:e0118889. doi: 10.1371/journal.pone.0118889
78. Martin LJ, Chang Q. DNA damage response and repair, DNA methylation, and cell death in human neurons and experimental animal neurons are different. *J Neuropath Exp Neurol*. (2018) 77:636–55. doi: 10.1093/jnen/nly040

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MINI REVIEW
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Approaches to Multimodality Monitoring in Pediatric Traumatic Brain Injury

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Traumatic brain injury (TBI) is a leading cause of morbidity and mortality in children. Improved methods of monitoring real-time cerebral physiology are needed to better understand when secondary brain injury develops and what treatment strategies may alleviate or prevent such injury. In this review, we discuss emerging technologies that exist to better understand intracranial pressure (ICP), cerebral blood flow, metabolism, oxygenation and electrical activity. We also discuss approaches to integrating these data as part of a multimodality monitoring strategy to improve patient care.

Keywords: multimodality monitoring, autoregulation, traumatic brain injury, pediatrics, neurocritical care

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INTRODUCTION

Traumatic brain injury (TBI) represents an alteration of brain function or other evidence of brain pathology that is caused by an external force (1). In children, TBI is a leading cause of morbidity and mortality in the United States and poses significant financial burden to the United States healthcare system (2). While treatment against primary TBI insult is prevention, subsequent insults may occur over ensuing days leading to secondary brain injury. Fundamentally, neurocritical care is aimed at rapidly detecting such insults and treating against them.

Much of secondary brain injury develops when mismatch exists between cerebral metabolic demand and energy substrate delivery as well as other pathophysiologic cascades of mechanisms leading to cell damage and death. Emerging technologies have developed to better monitor cerebral physiology in real-time. These technologies capture continuous recordings of intracranial pressure (ICP), cerebral oxygenation, cerebral blood flow, cerebral metabolism, and electrical activity. Each of these modalities alone can provide insight into potentially pathological physiology, but when interrelationships between these modalities are observed, they can offer greater insights into cerebral physiologic dynamics.

Monitoring CBF and metabolism in neurocritical care requires combining techniques that provide enough spatial and temporal resolution data. When a patient presents with TBI, the initial assessment requires high spatial resolution imaging to understand affected neuroanatomy. Anatomical imaging should continue to be employed judiciously to avoid secondary insults (3). Once obtained and initial interventions are performed, techniques with high temporal resolution can be employed for long-term continuous monitoring to understand ensuing physiology.

In this review, we describe existing neuromonitoring modalities that characterize the physiologic profile of TBI (**Table 1**). While neuroimaging is important for neurocritical care management, it is beyond the scope of this review. We describe approaches that may be taken to use neuromonitoring modalities to create an environment of recovery and amelioration against secondary injury. We also describe challenges that exist when addressing these strategies in the pediatric population.

TABLE 1 | Frequent multimodal monitoring techniques.

Technique	Physiology	Units	Resolution	Advantages	Disadvantages	Pediatric considerations
External ventricular catheter (EVD)	Intracranial pressure (ICP)	Mm Hg	Low-moderate spatial, high temporal	Allows global measurements of ICP, allows therapeutic/diagnostic drainage.	Increased infection risk, difficult placement in effaced ventricles. Cannot measure ICP unless clamped.	ICP thresholds may vary with age.
Intraparenchymal ICP Monitor	Intracranial Pressure	Mm Hg	Low spatial, high temporal	Continuous measurements. Easy placement. Lower infection risk.	Units may drift over time. No direct therapeutic benefit.	ICP thresholds may vary with age.
Near Infrared Spectroscopy (NIRS)	Oxygen saturation	%	Low spatial, high temporal	Allows non-invasive measurements of brain parenchymal oxygenation.	Difficult to interpret in setting of hematoma/ edema.	Thresholds for normative values are not well established
Brain tissue Oxygention ($PbtO_2$)	Oxygen tension	Torr	Low spatial, high temporal	Direct measurements of brain oxygen content	Invasive, may reflect regional changes rather than global.	Needs to be placed using bolt, which may not be feasible with thin skull.
Transcranial Doppler Ultrasound (TCD)	Mean flow velocities (MVF)	Cm/sec	Low-moderate spatial, moderate-high temporal	Non-invasive, can provide bedside assessments of vasospasms, hyperemia, autoregulation, or arterial occlusions	Limited diagnostic specificity in absence of anatomical imaging	Mean flow velocities change with age
Laser Doppler flowmetry (LD)	Mean flow velocities (MFV)	Cm/sec	Low spatial, high temporal	Can assess microcirculatory blood flow changes	Invasive, prone to probe migration	Not well-described in children
Thermal diffusion flowmetry (TD)	Cerebral blood flow	mL / 100 g / min	Low spatial, high temporal	Provides continuous, direct measurements of parenchymal perfusion	Invasive, recording suspends with increased pulsatility or temperature	Not well-described in children
Cerebral microdialysis (CMD)	Concentrations of cerebral metabolites	Mmol/L	Low spatial, moderate temporal	Provides direct biomarkers of metabolic crisis	Invasive, requires hourly vial retrieval for analysis	Normative values not well-established
Continuous Electroencephalography (cEEG)	Discrete and continuous variables (e.g., seizures, alpha power/variability, etc.)	N/A	Low-moderate spatial, high temporal	Diagnostic for seizures. Sensitive for encephalopathy, ischemia, and sedation monitoring.	Lacks neuroanatomical visualization. Requires expert proficiency for interpretation	Background activity changes with age
Pupillometry	Pupil size, pupil reactivity	Mm, neurological pupil index (NPI)	Low spatial, moderate temporal	Objective measurements of pupil size. Can relate to injury burden in setting of ICP crisis	Lacks diagnostic specificity of ABI in absence of other neuromonitoring modalities	Normative values are still limited

NEUROMONITORING TECHNIQUES

Intracranial Pressure

Intracranial pressure (ICP) represents the pressure within the intracranial vault. Pathological increases in ICP can have profound consequences, including insufficient cerebral perfusion pressures (CPP) leading to ischemia and herniation. Maintaining appropriate ICP and CPP parameters is a critical therapeutic strategy for secondary injury prevention. The external ventricular drain (EVD) represents the gold standard technique for ICP monitoring. The advantage of the EVD is that it allows global ICP measurements while allowing for therapeutic drainage of cerebral spinal fluid (CSF). Disadvantages include its invasive nature, challenge of implementation when ventricular effacement exists, and inability to produce continuous ICP measurements without synchronized drainage. Intraparenchymal ICP monitoring consists of a thin cable with an electronic or fiberoptic transducer inserted directly into brain parenchyma. This technique can provide continuous measurements and can be implemented using a multi-lumen bolt to correlate with changes in other monitors, but is unable to drain CSF and has potential to lose accuracy (i.e., drift) over several days. The EVD and intraparenchymal ICP probe can be used in conjunction to achieve effective diagnostic and treatment utility.

Due to changing physiologic values and different pressure-volume relationships as children age, criteria for intracranial hypertension (ICH) are nebulous (4). Fifteen studies involving 857 pediatric patients have demonstrated association between ICH and poor outcome (4–19). One retrospective study found that use of ICP monitoring vs. no ICP monitoring was associated with reduced mortality in severely head injured patients (20). Another study utilized retrospective analysis to investigate 36 institutions using the Pediatric Health Information System database and found that hospitals with higher standardized ICP monitoring rates had better patient outcomes with lower rates of mortality or severe disability (21). A subsequent study by the same investigators used propensity-weighted effective analysis linking two national databases and reported no significant difference in functional survival between patients who underwent ICP monitoring and those who did not undergo ICP monitoring, but rather an association with monitoring and higher mortality, discharge to hospice, or either tracheostomy or gastrostomy tube placement (22). The authors cautioned that findings could be due to unmeasured differences between the groups. Current guidelines in pediatric TBI support a treatment threshold of 20 mm Hg (19), although there is uncertainty about how similar the autoregulatory curve changes with age (23).

Brain Tissue Oxygenation

The brain has a high metabolic demand and contains limited stores of high-energy substrates. Continuous oxygen inflow is thus necessary to meet such demand. In TBI, fluctuations in oxygen delivery can emerge due to various processes and interventions. Techniques exist to provide continuous measurements of cerebral oxygenation.

Near-infrared spectroscopy (NIRS) provides non-invasive monitoring of cellular tissue oxygenation. Infrared light is emitted by diodes and detected by silicon phosphodiode optodes placed over the scalp of the frontal lobes. It is absorbed at wavelengths with the presence of oxygenated and deoxygenated hemoglobin whose concentration indexes cerebral oxygenation. The non-invasive nature of NIRS is advantageous, though it can be difficult to interpret in the setting of a scalp hematoma, intracranial hemorrhage, cerebral edema, and fluctuations in intracranial blood volumes (24, 25). In pediatric TBI, changes in NIRS values are associated with changes in ICP, mean arterial pressure and carbon dioxide content (26).

Continuous monitoring of cerebral oxygen partial pressure and temperature in brain tissue ($P_{bt}O_2$) can be measured using a micro-Clark electrode (27). This technique uses a closed electrochemical polarographic micro-cell for oxygen measurements and a thermocouple (type K) for temperature measurements. Four studies investigated the association of $P_{bt}O_2$ with clinical outcomes after pediatric TBI. One study analyzed over 8,000 h of monitoring from 46 children with severe TBI and observed that $P_{bt}O_2$ levels of 30 mmHg represented the highest combined sensitivity and specificity for favorable outcomes (28). The sensitivity was low (20%) and observations of elevated $P_{bt}O_2$ values in some patients with ICH and compromised CPP suggested the need to better understand the relationship of $P_{bt}O_2$ with outcomes. A prospective observational study of 52 children with severe TBI investigating the association of $P_{bt}O_2$ values and outcomes and found that worsened outcomes were associated with $P_{bt}O_2$ values <10 mmHg such associations were stronger with $P_{bt}O_2$ levels <5 mmHg persisting >1 h (29). A sub analysis of 28 children in this group revealed that in patients whose $P_{bt}O_2$ changed more in response to changes in PaO2 had worse outcomes (30). Current TBI guidelines recommend maintaining $P_{bt}O_2$ values >15 mm Hg in adults (31) and 10 mmHg in children (19). The recent BOOST-II trial was a randomized multicenter prospective clinical trial of 119 adult patients with severe TBI who were randomized to treatment protocols based on either ICP plus $P_{bt}O_2$ monitoring vs. ICP monitoring alone (32).The study revealed that a management protocol based on $P_{bt}O_2$ plus ICP monitoring reduced the proportion of time with brain tissue hypoxia. Results also showed that treatment informed on $P_{bt}O_2$ plus ICP monitoring was consistent with reduced monitoring and increased proportions of patients with good recovery as compared to ICP monitoring alone, although the study was not powered for clinical efficacy. The upcoming trial, BOOST-III will test the primary hypothesis that such dual monitoring therapy is associated with functional outcome after adult TBI. The Approaches and Decisions in Acute Pediatric TBI trial (ADAPT) has recently completed enrollment and will implement a comparative effectiveness strategy on multicenter data to investigate the association of $P_{bt}O_2$ monitoring with outcomes after pediatric TBI (33).

Cerebral Blood Flow

Adequate $P_{bt}O_2$ and substrate delivery ultimately depends upon CBF. Several neurocritical care interventions are aimed at optimizing CPP, thus CBF monitoring techniques can help in guiding therapy. In children, CBF values increase from their lowest values at birth to peak at ages 3–5 years, then decrease toward adult levels (34, 35). It therefore remains critical for age-specific ranges to be considered and CBF values to be interpreted in context of metabolic demand.

Transcranial Doppler (TCD) ultrasonography is a non-invasive technique which provides continuous or intermittent bedside assessments of CBF. The technique utilizes the Doppler shift principle to derive red blood cell mean flow velocities (MFV) from pulsed ultrasound waves directed toward basal cerebral arteries, from which CBF can be inferred. TCD has traditionally been utilized for the assessment of cerebrovascular vasospasm (CVS) and arterial occlusions but has also shown utility in the assessment of several other physiologic processes including hyperemia, autoregulation, and critical closing pressure. In critically ill children, MFV are known to change with age (36). One study prospectively investigated 69 children with severe TBI who underwent TCD testing and observed that children with good outcomes were more likely to have normal than abnormal flow velocities, and no patient with a single low flow velocity measurement had good neurologic outcome (37). TCD was also used by the same investigators in a prospective observational study to observe the incidence of cerebral vasospasms after pediatric TBI, and they found that middle cerebral artery vasospasms occurred in 8.5% of children with moderate TBI and 33.5% of children with severe TBI. Basilar artery vasospasms

occurred in 3% of children with moderate TBI and 21% of children with severe TBI (38). A recent survey of practices in pediatric neurocritical care centers showed that 74% of centers used TCD for clinical care, often for determining timing of neuroimaging, manipulating CPP, and deciding whether to perform surgical interventions (39).

Laser Doppler (LD) flowmetry functions similarly to TCD, particularly in assessing microcirculatory changes. A fiberoptic laser probe is placed onto brain parenchyma and detects light reflected by red blood cells to derive MFV. Changes in LD flowmetry are associated with impaired autoregulation (40), though the technique is prone to artifact produced by probe migration (41). Thermal diffusion (TD) flowmetry is an invasive technique that provides continuous quantitative brain perfusion measurements. This technique uses two thermistors within the probe, a proximal source set at the temperature of surrounding tissue and a distal censor heated 2 degrees Celsius higher. TD flowmetry takes advantage of the capacity of blood to dissipate heat to quantify CBF in units of mL/100 g/min (42). Current literature also indicates that TD values below 15 mL/100 g/min are associated with CVS in adult patients after aneurysmal subarachnoid hemorrhage (43). While these techniques are utilized in children with TBI in select centers (44), there is a lack of literature describing their findings.

Cerebral Metabolism

Cerebral metabolism monitoring allows clinicians to better understand the effect of physiologic processes on the critically ill brain. Cerebral microdialysis (CMD) allows for direct measurement of cerebral metabolites including lactate, pyruvate, glycerol, glutamate, or glucose. The technique utilizes a catheter with a semipermeable dialysis membrane at its tip placed into brain parenchyma. Perfusate, an osmolar solution with electrolytic properties like CSF, passes along the membrane before exiting through outlet tubing. Microvials are then removed and placed in a bedside analyzer. In adult TBI, anaerobic metabolite patterns manifesting with elevated lactate or lactate-pyruvate ratios are associated with poor outcome (45–48).

A series investigating nine children with severe TBI found that a low glutamine/glutamate ratio was associated with increased morbidity, while a high ratio was associated with clinical improvement (49). Brain metabolism changes with increasing age, as myelination and synapse growth increase CBF during the first decade of life (50, 51). These phenomena likely play a role in what CMD parameters may be critical within the pediatric population, requiring future work to establish its effective use.

Electroencephalography

Electroencephalography (EEG) is a technique that assesses cerebral cortical function through brain wave recordings. Historically, use of continuous EEG (cEEG) has been most fruitful in pediatric neurocritical care for detection of seizures (52). Retrospective work on critically ill children who underwent cEEG monitoring has shown that seizures independently contribute toward short-term outcomes (53). cEEG also has utility in monitoring depth of sedation, degree of encephalopathy (54), and trending cerebral ischemia (55). Intracortical EEG (iEEG) has been increasingly utilized in adult neurocritical care (56) and is associated with improved signal-noise ratio, detection of seizures not captured on cEEG, clarification of equivalent cEEG patterns and detection of cortical spreading depolarizations (57). One pediatric TBI study utilized iEEG showing that 3/11 patients had epileptiform abnormalities not captured on scalp EEG (58). Quantitative EEG (qEEG) utilizes mathematical algorithms to compress raw cEEG into graphical data. This can manifest as a color dense spectral array (CDSA) or rhythmic spectrogram, making detection of pathologic patterns such as seizures and ischemia easier to recognize for bedside clinicians. In the previously described study of pediatric TBI patients undergoing iEEG, both surface and intracortical alpha-delta ratios, a qEEG measure, were associated with CPP (58).

Pupillometry

The pupilometer is a non-invasive handheld device that provides objective measures of pupil reactivity before and after a light stimulus. In management of ICP, abnormalities of pupil reactivity are often associated with neurological deterioration and poor outcome (59). Abnormal pupillary reactivity correlates with cerebral herniation, third nerve compression and brainstem perfusion (60). Traditional clinical methods of monitoring pupillary size and reactivity through observation with light are highly subjective (61), leading to the need for more sensitive and objective methods of detecting changes. In addition to providing objective measurements of pupil size, other variables including pupil reactivity (NPi), latency time and constriction and latency velocities can be assessed with pupillometry (62). Characterization of changes within these variables may help distinguish pathologic ICP increases in selected patients. A prospective study of 90 children without intracranial or ophthalmologic pathology was performed capturing pupillometry data, providing initial pediatric normative values (61).

APPROACHES TO MULTIMODAL MONITORING IN PEDIATRIC NEUROCRITICAL CARE

Multimodal monitoring (MMM) has allowed for a wealth of physiological data to be acquired in critically ill patients, but the interpretation of such complex, high-resolution data remains challenging. Integrated MMM platforms exist that output these data in time-synchronized formats to allow clinicians to explore real-time physiologic-interrelationships. One can explore trends in continuous quantitative values for physiologic variables such as ICP or $P_{bt}O_2$, as well as analysis of time-synchronized waveforms in ICP, TCD ultrasound MFV or EEG.

Various approaches can guide clinical management based on MMM data. Traditional methods prior to the advent of MMM focus on threshold-based algorithms. Under this approach, specific normative values are set for each physiologic variable explored and algorithms are designed to manage against specific perturbations. This methodology largely lacks exploration of the etiology of such perturbations and thus is limited in providing

physiology-directed care. For instance, one may be able to treat against an ICP >20 mmHg under such an algorithm but may not consider whether such ICP elevation is related to hyperemia, a plateau wave, cerebral edema, or seizures.

Decision-making algorithms can be used to explore MMM data. Perturbations in specific physiologic variables can be initially identified, and trends in other variables may be used to better understand perturbations to direct care. For instance, if an ICP elevation is associated with an increase in $P_{bt}O_2$ and MFV, then this might suggest hyperemia and one may consider hyperventilation to reduce ICP by decreasing intracranial arterial blood volume. In contrast, if an ICP elevation is associated with a decrease in $P_{bt}O_2$ and MFV, this may suggest evolving cerebral edema and hypertonic saline could be considered.

Machine learning represents a powerful set of techniques in which multivariate data can be analyzed to discern inherent patterns. Cluster analysis has had wide use in genomics as a method to link individuals with shared characteristics to hypothesized groups. Using this technique to assess CMD in TBI patients, perturbed local chemistry was found to correlate with changes in CPP and ICP (63). Hierarchical cluster analysis has been utilized in TBI patients to distinguish specific physiologic states that were enriched for those who died, contracted an infection, and suffered multiple organ failure (64). A challenge to developing effective machine learning tools is the limited amount of clean data available and lack of annotation possible in a critical care environment.

An essential element to interpreting neurophysiologic data is determining whether one physiologic process mediates changes observed in other processes. Causal mediation analysis tests for such by linking treatment, outcome, and mediator variables. In a prospective studying observing the association of non-convulsive seizures with outcome in subarachnoid hemorrhage patients, mediated analysis linked clinical symptoms and serum biomarkers of inflammation as causal factors toward patient outcome (65).

Model-based derivatives have emerged that combine physiologic variables into mathematical models to predict physiologic states. The pressure-reactivity index (PRx) (66), mean velocity index (Mx) (67), oxygen reactivity index (ORx) (68), and cerebral oxygenation index (COx) (69) are among several indices that explore changes in ICP, MFV, arterial blood pressure (ABP), $P_{bt}O_2$, and NIRS oxygen saturation to assess cerebral autoregulation. These indices utilize linear and multivariate regression analyses to formulate correlation coefficients within a moving window. When such derivations are explored over a range of vital signs, optimal conditions may be discernible (**Figure 1**). For instance, when PRx is observed over a range of CPP, an optimal CPP can be formulated, representing the lower threshold at which CPP may be maintained for an optimal autoregulatory state (70).

CHALLENGES AND FUTURE DIRECTIONS

Adoption of emerging MMM techniques has led to an explosion of physiologic data. Like all data however, these can be subject to artifact, technical error, and misinterpretation. Challenges exist in effectively diagnosing physiologic states based on MMM and guiding care. Normative values must be recognized for all physiologic variables across ages and demographics. Artifact must be recognized and excluded. Invasive monitoring techniques increase the risk of infection and bleeding and these must be weighed in the decision of device placement. A study investigating the implementation of intracranial MMM in adult neurocritical care found that in 61

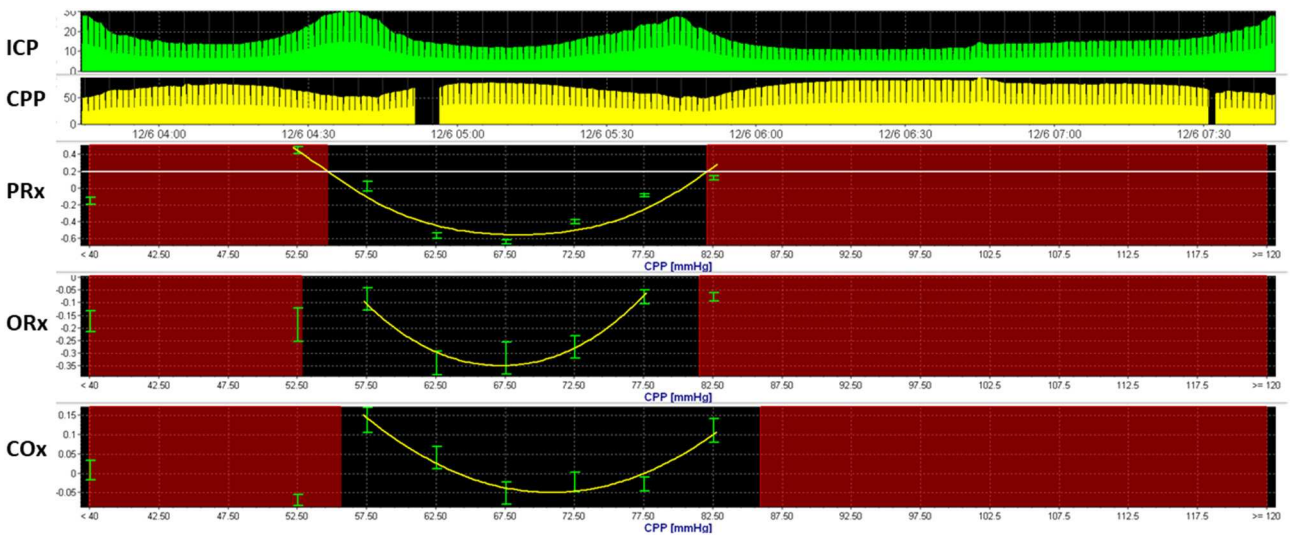

FIGURE 1 | Optimal cerebral perfusion pressure based upon model-based indices of cerebral autoregulation. Multimodal monitoring data is recorded from a 3-year-old boy with severe TBI. Here, an optimal cerebral perfusion pressure (CPPopt) is estimated using three model-based indices of cerebral autoregulation, including the pressure reactivity index (PRx), oxygen-reactivity index (ORx), and cerebral oximetry index. U-shaped curves can be observed using all three indices, with CPPOpt ranging from 66 to 71 mmHg.

patients, 5% of patients experienced intracranial hematoma and 3% experienced a CNS infection (71). There are no studies that have investigated the association of MMM on outcomes or adverse events in pediatric TBI, and such work that includes age stratification is needed either through controlled-observational trials or comparative effectiveness studies. Ultimately, safe and effective methods of understanding brain physiology in real time and in a multimodal approach has the potential to prevent secondary brain injury in children with TBI and improve outcomes.

AUTHOR CONTRIBUTIONS

BA, BB, SF, and PA contributed toward the preparation, development, and critical review of this manuscript.

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REFERENCES

1. Menon DK, Shwab K, Wright DW, Maas AIR. Position statement: definition of traumatic brain injury. *Arch Phys Med Rehabil.* (2010) 91:1637–40. doi: 10.1016/j.apmr.2010.05.017
2. Graves JM, Rivara FP, Vavilala MS. Health care costs 1 year after pediatric traumatic brain injury. *Am J Public Health.* (2015) 105:e35–41. doi: 10.2105/AJPH.2015.302744
3. Martin M, Cook F, Lobo D, Vermersch C, Attias A, Ait-Mamar B, et al. Secondary insults and adverse events during intrahospital transport of severe traumatic brain injured patients. *Neurocritical Care.* (2017) 26:87–95. doi: 10.1007/s12028-016-0291-5
4. Shapiron K, Marmarou A. Clinical applications of the pressure-volume index in treatment of pediatric head injuries. *J Neurosurg.* (1982) 56:819–25. doi: 10.3171/jns.1982.56.6.0819
5. Chambers IR, Treadwell L, Mendelow AD. Determination of threshold levels of cerebral perfusion pressure and intracranial pressure in severe head injury by using receiver-operating characteristic curves: an observational study in 291 patients. *J Neurosurg.* (2001) 94:412–6. doi: 10.3171/jns.2001.94.3.0412
6. Adelson PD, Ragheb J, Kanev P, Brockmeyer D, Beers SR, Brown SD, et al. Phase II clinical trial of moderate hypothermia after severe traumatic brain injury in children. *Neurosurgery.* (2005) 56:740–54. doi: 10.1227/01.NEU.0000156471.50726.26
7. Alberico AM, Ward JD, Choi SC, Marmarou A, Young HF. Outcome after severe head injury. Relationship to mass lesions, diffuse injury, and ICP course in pediatric and adult patients. *J Neurosurg.* (1987) 67:648–56. doi: 10.3171/jns.1987.67.5.0648
8. Bruce DA, Raphaely RC, Goldberg AL, Zimmerman RA, Bilaniuk LT, Schut L, et al. Pathophysiology, treatment and outcome following severe head injury in children. *Childs Brain.* (1979) 5:174–91. doi: 10.1159/000119817
9. Cruz J, Nakyama P, Imamura JH, Rosenfeld KG, de Souza HS, Giorgetti, et al. Cerebral extraction of oxygen and intracranial in severe, acute, pediatric brain trauma: preliminary novel management strategies. *Neurosurgery.* (2002) 50:774–9. doi: 10.1097/00006123-200204000-00017
10. Downward C, Hulka F, Mullins RJ, Piatt J, Chestnut R, Quint P, et al. Relationship of cerebral perfusion pressure and survival in pediatric brain-injured patients. *J Trauma.* (2000) 49:654–8. doi: 10.1097/00005373-200010000-00012
11. Jagannathan J, Okonkwo DO, Yeoh HK, Dumont AS, Saulie D, Haizlip J, et al. Long-term outcomes and prognostic factors in pediatric patients with severe traumatic brain injury and elevated intracranial pressure. *J Neurosurg Pediatr.* (2008) 2:240–9. doi: 10.3171/PED.2008.2.10.240
12. Kasoff SS, Lansen TA, Holder D, Filippo JS. Aggressive physiologic monitoring of pediatric head trauma patients with elevated intracranial pressure. *Pediatr Neurosci.* (1988) 14:241–9. doi: 10.1159/000120397
13. Michaud LJ, Rivara FP, Grady MS, Reay DT. Predictors of survival and severity of disability after severe brain injury in children. *Neurosurgery.* (1992) 31:254–64. doi: 10.1097/00006123-199208000-00010
14. Pfenninger J, Santi A. Severe traumatic brain injury in children - are the results improving? *Swiss Med Wkly.* (2002) 132:116–20.
15. Wahlstrom MR, Olivecrona M, Koskinen LO, Rydenhag B, Naredi B. Severe traumatic brain injury in pediatric patients: treatment and outcome using intracranial pressure targeting therapy - the Lund concept. *Intensive Care Med.* (2005) 31:832–9. doi: 10.1007/s00134-005-2632-2
16. White JR, Farukhi Z, Bull C, Christensen J, Gordon T, Paidas C, et al. Predictors of outcome in severely head-injured children. *Crit Care Med.* (2001) 29:534–40. doi: 10.1097/00003246-200103000-00011
17. Barzilay Z, Augarten A, Sagy M, Shahar E, Yahav Y, Boichis H. Variables affecting outcome from severe brain injury in children. *Intensive Care Med.* (1998) 14:417–21. doi: 10.1007/BF00262899
18. Esparza J, M-Portillo J, Sarabia M, Yuste JA, Roger R, Lamas E. Outcome in children with severe head injuries. *Childs Nerv Syst.* (1985) 1:109–14. doi: 10.1007/BF00706691
19. Kochanek PM, Tasker RC, Bell MJ, Adelson PD, Carney N, Vavilala MS, et al. Management of pediatric severe traumatic brain injury: 2019 consensus and guidelines-based algorithm for first and second tier therapies. *Pediatr Crit Care Med.* (2019) 20:269–79. doi: 10.1097/PCC.0000000000001737
20. Akhoury F, Kryriakides TC. Intracranial pressure monitoring in children with severe traumatic brain injury: National Trauma Data Bank-based review of outcomes. *JAMA Surg.* (2014) 149:544–8. doi: 10.1001/jamasurg.2013.4329
21. Bennett TD, Riva-Cambrin J, Keenan HT, Korgenski EK, Bratton SL. Variation in intracranial pressure monitoring and outcomes in pediatric traumatic brain injury. *Arch Pediatr Adolesc Med.* (2012) 166:641–7. doi: 10.1001/archpediatrics.2012.322
22. Bennett TD, DeWitt PE, Greene TH, Srivastava R, Riva-Cambrin J, Nance ML, et al. (2017). Functional outcome after intracranial pressure monitoring for severe children with severe traumatic brain injury. *JAMA Pediatr.* 171:965–71. doi: 10.1001/jamapediatrics.2017.2127
23. Udomphorn Y, Armsted WM, Vavilala MS. Cerebral blood flow and autoregulation after pediatric traumatic brain injury. *Pediatric Neurol.* (2008) 38:225–34. doi: 10.1016/j.pediatrneurol.2007.09.012
24. Robertson CS, Gopinath SP, Chance B. A new application for near infra-red spectroscopy: detection of delayed intracranial hematomas after head injury. *J Neurotrauma.* (1995) 12:591–600. doi: 10.1089/neu.1995.12.591
25. Gill S, Rajneesh KF, Owen CM, Yeh J, Hsu M, Binder DK. Early optical detection of cerebral edema *in vivo*. *J Neurosurg.* (2011) 114:470–7. doi: 10.3171/2010.2.JNS091017
26. Adelson PD, Nemoto E, Colak A, Painter M. The use of Near Infrared Spectroscopy (NIRS) in children after traumatic brain injury. a preliminary report. *Acta Neurochir Suppl.* (1998) 71:250–4. doi: 10.1007/978-3-7091-6475-4_72
27. Dings J, Miexensberger J, Jager A, Roosen K. Clinical experience with 118 brain tissue oxygen partial pressure catheter probes. *Neurosurgery.* (1998) 43:1082–94. doi: 10.1097/00006123-199811000-00045
28. Stippler M, Ortiz V, Adelson PD, Chang YF, Tyler-Kabara EC, Wisniewski SR, et al. Brain tissue oxygenation monitoring after severe traumatic brain injury in children: relationship to outcome and association with other clinical parameters. *J Neurosurg Pediatr.* (2012) 10:383–91. doi: 10.3171/2012.8.PEDS12165
29. Figaji AA, Zwane E, Thompson C, Fieggen AG, Argent AC, Le Roux PD, et al. (2009). Brain tissue oxygen tension monitoring in pediatric severe traumatic brain injury. Part 1: relationship with outcome. *Childs Nerv Syst.* (2012) 25:1325–33. doi: 10.1007/s00381-009-0822-x

30. Figaji AA, Zwane E, Graham FA, Argent AC, Le Roux PD, Peter JC. The effect of increased inspired fraction of oxygen on brain tissue oxygen tension in children with severe traumatic brain injury. *Neurocrit Care.* (2010) 12:430–7. doi: 10.1007/s12028-010-9344-3
31. Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons. Guide for the management of severe traumatic brain injury. *J Neurotrauma*. (2007) 24(suppl 1):S1–106. doi: 10.1089/neu.2007.9999
32. Okonkwo DO, Shutter LA, Moore C, Temkin NR, Puccio AM, Madden CJ, et al. Brain oxygen optimization in severe traumatic brain injury phase-II: a phase II randomized trial. *Crit Care Med.* (2017) 45:1907–14. doi: 10.1097/CCM.0000000000002619
33. Bell MJ, Adelson PD, Wisniewski SR, Investigators of the ADAPT study. Challenges and opportunities for pediatric severe TBI - review of the evidence and exploring a way forward. *Childs Nerv Syst.* (2017) 33:1663–7. doi: 10.1007/s00381-017-3530-y
34. Zwienenberg M, Muizelaar P. Severe pediatric head injury: the role of hyperemia revisited. *J Neurotrauma.* (1999) 16:937–43. doi: 10.1089/neu.1999.16.937
35. Chiron C, Raynaud C, Maziere B, Zilbovicius M, Laflamme L, Masure MC et al. Changes in regional cerebral blood flow during brain maturation in children and adolescents. *J Nucl Med.* (1992) 33:696–703.
36. Mandera M, Larysz D, Wojtacha M. Changes in cerebral hemodynamics assessed by transcranial Doppler ultrasonography in children after head injury. *Childs Nerve Syst.* (2002) 18:124–8. doi: 10.1007/s00381-002-0572-5
37. O'Brien NF, Maa T, Moore-Clingenpeel M, Rosenberg N, Yeates KO, et al. Relationship between cerebral blood flow velocities and neurodevelopmental outcomes in children with moderate to severe traumatic brain injury. *Childs Nerv Syst.* (2018) 34:663–72. doi: 10.1007/s00381-017-3693-6
38. O'Brien N, Maa T, Yeates KO. The epidemiology of vasospasm in children with moderate-to-severe traumatic brain injury. *Crit Care Med.* (2015) 43:674–85. doi: 10.1097/CCM.0000000000000745
39. LaRovere KL, Tasker RC, Wainwright M, Reuter-Rice K, Appavu B, Miles D, et al. (2019). Transcranial doppler ultrasound during critical illness in children: survey of practices in pediatric neurocritical care centers. *Pediatr Crit Care Med*. doi: 10.1097/PCC.0000000000002118. [Epub ahead of print].
40. Arbit E, DiResta GR. Application of laser Doppler flowmetry in neurosurgery. *Neurosurg Clin N Am.* (1996) 7:741–8. doi: 10.1016/S1042-3680(18)30359-0
41. Obeid AN, Barnett NJ, Dougherty G, Ward G. A critical review of laser Doppler flowmetry. *J Med Eng Technol.* (1990) 14:178–81. doi: 10.3109/03091909009009955
42. Vajkoczy P, Roth H, Horn P, Lucke T, Thome C, Hubner U, et al. Continuous monitoring of regional cerebral blood flow: experimental and clinical validation of a novel thermal diffusion microprobe. *J Neurosurg.* (2000) 93:265–74. doi: 10.3171/jns.2000.93.2.0265
43. Vajkoczy P, Horn P, Thome C, Munch E, Schmiedek P. Regional cerebral blood flow monitoring in the diagnosis of delayed ischemia following aneurysmal subarachnoid hemorrhage. *J Neurosurg.* (2003) 98:1227–34. doi: 10.3171/jns.2003.98.6.1227
44. Figaji AA, Fleggen AG, Mankahla N, Enslin N, Rohlwink UK. Targeted treatment in severe traumatic brain injury in the age of precision medicine. *Childs Nerv Syst.* (2017) 33:1651–61. doi: 10.1007/s00381-017-3562-3
45. Oddo M, Levine JM, Frangos S, Maloney-Wilensky E, Carrera E, Daniel RT, et al. Brain lactate metabolism in humans with subarachnoid hemorrhage. *Stroke*. (2012) 43:1418–21. doi: 10.1161/STROKEAHA.111.648568
46. Cesarini KG, Enblad P, Ronne-Engstrom E, Marklund N, Salci K, Nilsson P, et al. Early cerebral hyperglycolysis after subarachnoid haemorrhage correlates with favourable outcome. *Acta Neurochir*. (2002) 144:1121–31. doi: 10.1007/s00701-002-1011-9
47. Timofeev I, Czosnyka M, Carpenter KL, Nortie J, Kirkpatrick PJ, Al-Rawi PG, et al. Interaction between brain chemistry and physiology after traumatic brain injury: impact of autoregulation and microdialysis catheter location. *J Neurotrauma.* (2011) 28:849–60. doi: 10.1089/neu.2010.1656
48. Timofeev I, Carpenter KL, Nortje J, Al-Rawi PG, O'Connell MT, Czosnyka M, et al. Cerebral extracellular chemistry and outcome following traumatic brain injury: a microdialysis study of 223 patients. *Brain.* (2011) 134:484–94. doi: 10.1093/brain/awq353
49. Tolias CM, Richards D, Bowery N, Sgouros S. Extracellular glutamate in the brains of children with severe head injuries: a pilot microdialysis study. *Childs Nerv Syst.* (2002) 18:368–374. doi: 10.1007/s00381-002-0623-y
50. Takahashi T, Shirane R, Sato S, Yoshimotor T. Developmental changes of cerebral blood flow and oxygen metabolism in children. *AJNR Am J Neuroradiol.* (1999) 20:917–22.
51. Kehrer M, Schoning M. A longitudinal study of cerebral blood flow over the first 30 months. *Pediatr Res.* (2009) 66:560–4. doi: 10.1203/PDR.0b013e3181ba1a29
52. Appavu B, Riviello JJ. Electroencephalographic patterns in neurocritical care: pathologic contributors or epiphenomena? *Neurocritic Care*. (2018) 29:9–19. doi: 10.1007/s12028-017-0424-5
53. Payne ET, Zhao X, Frndova H, McBrain K, Sharma R, Hutchinson JS, et al. Seizure burden is independently associated with short term outcome in critically ill children. *Brain.* (2014) 137:1429–38. doi: 10.1093/brain/awu042
54. Friedman D. Encephalopathy and coma. In: LaRoche SM, editor. *Handbook of ICU EEG Monitoring*. New York, NY: Demos Medical Publishing (2013). p. 131–8.
55. Foreman B, Claassen J. Quantitative EEG for the detection of brain ischemia. *Crit Care.* (2012) 16:216. doi: 10.1186/cc11230
56. Waziri A, Claassen J, Stuart RM, Arif H, Schmidt JM, Mayer SA, et al. Intracortical electroencephalography in acute brain injury. *Ann Neurol.* (2009) 66:366–77. doi: 10.1002/ana.21721
57. Hartings JA, Wilson JA, Hinzman JM, Pollandt S, Dreier JP, DiNapoli V, et al. Spreading depression in continuous electroencephalography of brain trauma. *Ann Neurol.* (2014) 76:681–94. doi: 10.1002/ana.24256
58. Appavu B, Foldes S, Temkit M, Jacobson A, Burrows BT, Brown D, et al. Intracranial electroencephalography in pediatric severe traumatic brain injury. *Pediatric Crit Care Med.* (2019). doi: 10.1097/PCC.0000000000002136. [Epub ahead of print].
59. Litvan I, Saposnik G, Maurino J, Gonzalez L, Saizar R, Sica RE, et al. Pupillary diameter assessment: need for a graded scale. *Neurology*. (2000) 54:530–1. doi: 10.1212/WNL.54.2.530
60. Ritter AM, Muizelaar JP, Barnes T, Choi S, Fatouros P, Ward J, et al. Brain stem blood flow, pupillary response, and outcome in patients with severe head injury. *Neurosurgery*. (1999) 44:941–8. doi: 10.1097/00006123-199905000-00005
61. Boev AN, Fountas KN, Karampelas I, Boev C, Machinis TG, Feltes C, et al. Quantitative pupillometry: normative data in healthy pediatric volunteers. *J Neurosurg.* (2005) 103(6 Suppl):496–500. doi: 10.3171/ped.2005.103.6.0496
62. Martinez-Ricarte F, Castro A, Poca MA, Sahuquillo J, Exposito L, Arribas M, et al. Infrared pupillometry. Basic principles and their application in the non-invasive monitoring of neurocritical care patients. *Neurologia.* (2013) 28:41–51. doi: 10.1016/j.nrleng.2010.07.001
63. Nelson DW, Bellander BM, Maccallum RM, Axelsson J, Alm M, Wallin M, et al. Cerebral microdialysis of patients with severe traumatic brain injury exhibits highly individualistic patterns as visualized by cluster analysis with self-organizing maps. *Critic Care Med.* (2004) 32:2428–36. doi: 10.1097/01.CCM.0000147688.08813.9C
64. Cohen MJ, Grossman AD, Morabito D, Knudson MM, Butte AJ, Manley GT. Identification of complex metabolic states in critically injured patients using bioinformatics cluster analysis. *Critic Care Med.* (2010) 14:R10. doi: 10.1186/cc8864
65. Claassen J, Albers D, Schmidt JM, De Marchis GM, Pugin D, Falo CM, et al. Nonconvulsive seizures in subarachnoid hemorrhage link inflammation and outcome. *Ann Neurol.* (2014) 75:771–81. doi: 10.1002/ana.24166
66. Zweifel C, Lavinio A, Steiner LA, Radolovich D, Smielewski P, Timofeev I, et al. Continuous monitoring of cerebrovascular pressure reactivity in patients with head injury. *Neurosurg Focus.* (2008) 25:E2. doi: 10.3171/FOC.2008.25.10.E2
67. Budohoski KP, Reinhard M, Aries MJ, Czosnyka Z, Smielewski P, Pickard JD. Monitoring cerebral autoregulation after head injury. Which component of transcranial Doppler velocity is optimal? *Neurocritic Care*. (2012) 17:211–8. doi: 10.1007/s12028-011-9572-1

68. Jaeger M, Schuhmann MU, Soehle M, Meixensberger J. Continuous assessment of cerebrovascular autoregulation after traumatic brain injury using brain tissue oxygen pressure reactivity. *Critic Care Med.* (2006) 34:1783–8. doi: 10.1097/01.CCM.0000218413.51546.9E
69. Healy RJ, Vorrilla-Vaca A, Ziai W, Mirski MA, Hogue CW, Geocadin R, et al. Glasgow coma scale score fluctuations are associated with a NIRS-based index of cerebral autoregulation in acutely comatose patients. *J Neurosurg Anesthesiol.* (2019) 31:306–10. doi: 10.1097/ANA.0000000000000513
70. Aries MJ, Czosnyka M, Budohoski KP, Steiner LA, Lavinio A, Kolias G, et al. Continuous determination of optimal cerebral perfusion pressure in traumatic brain injury. *Critic Care Med.* (2012) 40:2456–63. doi: 10.1097/CCM.0b013e3182514eb6
71. Stuart RM, Scmidt M, Kurtz P, Waziri A, Helbok R, Mayer SA, et al. Intracranial multimodal monitoring for acute brain injury: a single institution review of current practices. *Neurocrit Care.* (2010) 12:188–98. doi: 10.1007/s12028-010-9330-9

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REVIEW
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Longitudinal Neuroimaging in Pediatric Traumatic Brain Injury: Current State and Consideration of Factors That Influence Recovery

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Traumatic brain injury (TBI) is a leading cause of death and disability for children and adolescents in the U.S. and other developed and developing countries. Injury to the immature brain varies greatly from that of the mature, adult brain due to numerous developmental, pre-injury, and injury-related factors that work together to influence the trajectory of recovery during the course of typical brain development. Substantial damage to brain structure often underlies subsequent functional limitations that persist for years following pediatric TBI. Advances in neuroimaging have established an important role in the acute management of pediatric TBI, and magnetic resonance imaging (MRI) techniques have a particular relevance for the sequential assessment of long-term consequences from injuries sustained to the developing brain. The present paper will discuss the various factors that influence recovery and review the findings from the present neuroimaging literature to assess altered development and long-term outcome following pediatric TBI. Four MR-based neuroimaging modalities have been used to examine recovery from pediatric TBI longitudinally: (1) T_1-weighted structural MRI is sensitive to morphological changes in gray matter volume and cortical thickness, (2) diffusion-weighted MRI is sensitive to changes in the microstructural integrity of white matter, (3) MR spectroscopy provides a sensitive assessment of metabolic and neurochemical alterations in the brain, and (4) functional MRI provides insight into the functional changes that occur as a result of structural damage and typical developmental processes. As reviewed in this paper, 13 cohorts have contributed to only 20 studies published to date using neuroimaging to examine longitudinal changes after TBI in pediatric patients. The results of these studies demonstrate considerable heterogeneity in post-injury outcome; however, the existing literature consistently shows that alterations in brain structure, function, and metabolism can persist for an extended period of time post-injury. With larger sample sizes and multi-site cooperation, future studies will be able to further examine potential moderators of outcome, such as the developmental, pre-injury, and injury-related factors discussed in the present review.

Keywords: traumatic brain injury, pediatric, neuroimaging, longitudinal, brain development, neuroplasticity

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INTRODUCTION

Recent estimates suggest that a child under the age of 14 sustains a traumatic brain injury (TBI) every 60 s in the United States (1). While TBI-related deaths in children have substantially decreased over the past decade, TBI remains the leading cause of death among children and adolescents (2). Of the survivors, ∼62% of children who sustained moderate-to-severe injuries, and 14% of those with milder injuries suffer from long-term disability (3). The trajectory of recovery from an injury sustained to the developing brain differs greatly from that of the mature, adult brain (4, 5). Thus, an understanding of the long-term effects of early brain injury on subsequent neurodevelopment is vital for the accurate understanding and prediction of a child's outcome and recovery.

Currently, falls, sports- and recreation-related blunt force trauma, and motor vehicle accidents are the leading causes of pediatric TBI (1, 3). These mechanisms commonly give rise to acceleration-deceleration injuries that result in diffuse axonal injury (DAI), which refers to the extensive structural damage that occurs to otherwise highly organized neural tissue due to the abrupt stretching, twisting, and shearing of axons in the event of a mechanical blow. DAI is critically related to functional outcomes following early brain injury, as it leads to reductions in white matter integrity, disrupting the connectivity of the neural networks that give rise to behavioral and cognitive function (6). Plasticity moves anteriorly during typical neural development, where the frontal and temporal regions of the brain are among the last to develop (7, 8). Due to the close proximity of these brain regions to the bony structure of the anterior and middle fossa of the skull (9), they are the most vulnerable in acceleration-deceleration injuries. For this reason, early brain insult likely affects the maturation of the frontal and temporal cortices, as well as the white matter pathways connecting them to other areas of the brain. Such disruption is known to have detrimental and long-term consequences on the development of critical neurobehavioral functions localized within these regions, such as executive function (10, 11), learning and memory (12), emotional control (13), behavioral self-regulation (14), and social adaptive behavior (15).

Despite the fact that injury to the developing brain has potentially more devastating long-term consequences than injury to the adult brain (16), there is substantially less literature on the long-term consequences of pediatric TBI compared to adults with TBI. In particular, relatively few studies have utilized these MRI methods for the longitudinal assessment of recovery from early brain injury. In addition to the great number of developmental, pre-injury, and injury-related factors that influence outcome after pediatric TBI (17), a major reason for the lack of longitudinal research lies in the substantial cost associated with clinical imaging. Additionally, sensitive measurement tools that are suitable for the prediction of outcome in a pediatric population have only recently become available. The literature on early brain development has increased 10-fold over the last 25 years as technological advances have been made in neuroimaging techniques, specifically those involving the use of magnetic resonance imaging (MRI; see **Figure 1**). Likewise, advances in the field of neuroimaging have established an important role in identifying the sequelae and determining the acute management of pediatric TBI over the last two decades (18).

Although computed tomography (CT) is necessary for the rapid evaluation of primary head trauma complications that require immediate intervention (e.g., extra-axial hemorrhage, skull fracture, etc.), its clinical utility beyond this is generally somewhat limited, as the extent of axonal damage due to DAI is commonly underestimated with CT. Structural MRI is not only more sensitive to identifying DAI than CT, but it also has a particular relevance for the sequential assessment of the longitudinal consequences of brain injury (19). While structural MRI (sMRI) has greater prognostic utility in TBI than CT, it is unable to fully account for the complexity of pediatric TBI neuropathology when only used in the first weeks following the injury (20). Serial volumetric analysis, however, can provide insight into long-term neurodegeneration that occurs as a result of ongoing secondary injury pathology. More advanced techniques, such as diffusion-weighted MRI (dMRI), magnetic resonance spectroscopy (MRS), and functional MRI (fMRI) have greater sensitivity to the primary and secondary injuries after TBI, therefore establishing increased value for predicting long-term outcome after injuries are sustained to the developing brain (21, 22). Diffusion tensor imaging (DTI) is a dMRI technique that is sensitive to the long-term pathological effects of DAI on the microstructural integrity of white matter (23, 24); however, DTI is unable to reveal the underlying processes for such effects. MRS allows for the non-invasive measurement of metabolites in the brain, which vary by anatomic region and change rapidly as the brain develops through the adolescent years. Through the examination of intracellular metabolic status, MRS is able to detect several metabolites that are sensitive to the pathology associated with secondary brain injury cascades and is therefore capable of providing direct evidence of microscopic neuronal injury. Substantial damage to brain structure can occur in pediatric TBI, and such damage often underlies subsequent functional limitations in physical, emotional, cognitive, behavioral, adaptive, and academic abilities that persist for years following the injury (25). Adults who suffered from childhood TBI 15-years prior report significantly poorer perceptions of their health-related quality of life due to ongoing functional limitations, regardless of injury severity (26). There is an intimate relationship between brain structure and function, and this complimentary relationship extends toward the use of functional and structural neuroimaging modalities in the evaluation of long-term outcome following brain injury.

Abbreviations: AD, axial diffusivity; ADC, apparent diffusion coefficient; Cho, choline; Cr, creatine; CVR, cerebrovascular responsiveness; DAI, diffuse axonal injury; dMRI, diffusion-weighted magnetic resonance imaging; DTI, diffusion tensor imaging; FA, fractional anisotropy; fMRI, functional magnetic resonance imaging; IHTT, inter-hemispheric transfer time; MD, mean diffusivity; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; msTBI, moderate-to-severe traumatic brain injury; mTBI, mild traumatic brain injury; NAA, N-acetyl aspartate; RD, radial diffusivity; ROI, region-of-interest; SES, socioeconomic status; sMRI, structural magnetic resonance imaging; SRC, sport-related concussion; TBI, traumatic brain injury; TBSS, tract-based spatial statistics.

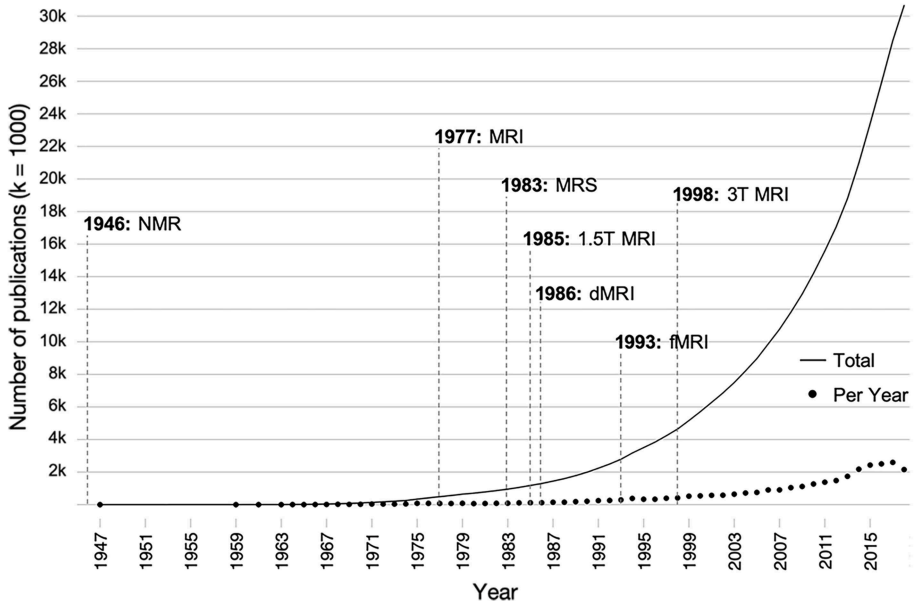

FIGURE 1 | Influence of the development of various magnetic resonance-based imaging modalities on the number of publications on brain development over time. Individual points indicate the number of papers published per a given year, and the solid line indicates the total number of publications over all time. Publications were found using the search terms (brain AND development OR neurodevelopment) AND (childhood OR adolescent OR pediatric) AND (structure OR function) in PubMed. dMRI, diffusion magnetic resonance imaging; fMRI, functional magnetic resonance imaging; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NMR, nuclear magnetic resonance; T, tesla.

Prior to our review of the present longitudinal neuroimaging literature, we will discuss several developmental, injury-related, and pre-injury factors that are known to influence development and recovery from damage to an immature brain. We believe that such a discussion is vital, as the field currently lacks a complete understanding of the way in which these factors interact with each other to further complicate the trajectory of recovery in the presence of injury-induced alterations to brain development. The complex interaction that occurs among such influences may have unpredictable negative consequences for otherwise adaptive structural and functional neuroplasticity that occurs in response to tissue damage (5). While there is an appreciation in the field for the importance of considering such factors in relation to planning rehabilitation and estimating the overall recovery period these factors are less often included in neuroimaging analyses. There is considerable heterogeneity post-injury, which can lead to inconsistent results in the neuroimaging literature. Understanding the ways in which developmental, injury-related, and pre-injury factors may impact neuroplasticity in the developing brain may be key to explaining more of this variance.

Following this discussion, we will briefly review the findings from longitudinal studies employing MR-based neuroimaging modalities to increase our current understanding of altered development and long-term outcome following pediatric TBI. Recent reviews of studies utilizing various neuroimaging modalities in children with moderate-to-severe TBI [msTBI; (27)] and of studies utilizing sMRI (28) or dMRI (29) to evaluate outcome from mild-to-severe pediatric TBI have been published. However, no reviews of the current literature, have focused solely on longitudinal neuroimaging studies (i.e., imaging at least two points in time) using various MR-based modalities to characterize outcome following mild-to-severe pediatric TBI; henceforth, such studies will be the focus of the present review. Furthermore, we will discuss whether the developmental, injury-related, and pre-injury factors known to influence plasticity and recovery from early TBI are considered in analyses conducted by the longitudinal studies reviewed here. Finally, we will conclude with a discussion of the current gaps in the literature and provide suggestions for future directions that should be taken in the field.

FACTORS THAT INFLUENCE PLASTICITY AND RECOVERY

An important distinction between pediatric and adult TBI is that the primary cause of pediatric injuries vary significantly by age group and can present in various ways (1, 30, 31). Various types of head injuries (e.g., blunt, penetrating, acceleration/deceleration) are closely related to the circumstantial mechanisms that caused them (32), yet great heterogeneity exists in the clinical presentation manifested by TBI, suggesting that similar heterogeneity exists in the underlying pathological features of the damaged brain. No two brain injuries are equal due to the complex interaction of inter-individual differences in the timing and circumstances in which the injury occurred, the severity, biomechanics, and nature of the injury itself, and intra-individual factors such as age, sex, and quality of the pre-injury environment

(33–36). For this reason, it is essential that such factors are considered in the assessment of outcome and prediction of recovery following pediatric brain injury.

Developmental Factors

The central nervous system is inherently plastic in its capacity to respond to the environment and experience in a dynamic manner through modification of its neural circuitry (37). The phenomenological nature of neuroplasticity is linked to the development of the brain and function across the lifespan, and it is a beneficial property in the context of healthy development (17, 38). In the context of early brain injury, however, the influence of plasticity on brain development may be detrimental, as the interrupted developmental processes can be altered permanently or cease entirely (39, 40).

Age at Injury

A major difference between a mature and a developing brain is the presumed capacity for heightened plasticity in the latter (40, 41). Historically, research of the effects that age at the time of injury has on outcome suggests that worse cognitive outcomes are associated with a younger age when injury occurred, and injuries sustained before age eight were believed to have the worst prognosis (33, 42, 43). More recently, a complex, non-linear relationship between age at injury and cognitive outcome has been demonstrated in the literature (17, 44, 45). Developmental research suggests that there are critical periods for the acquisition of specific skill sets (46). A critical period in development designates a maximally-sensitive, developmental phase of enhanced experience-expectant plasticity when the brain is heavily influenced by environmental demands (37). During critical periods, the brain undergoes significant structural and functional growth as it learns, adapts, and makes connections with other parts of the brain. This heightened sensitivity, however, simultaneously increases the brain's vulnerability to disruption in the environment, therefore heightening its susceptibility to insult. Brain damage that occurs during a critical period can have a more profound effect on skill acquisition relative to the effects of injuries that occur during non-critical periods (42, 47), as predetermined developmental processes are derailed, natural resources are depleted, and the typical developmental course that guides recovery is no longer available (48, 49). The timing of a brain injury is therefore important to consider, because injuries that occur during critical brain development periods tend to result in more extensive damage to whatever region is currently undergoing accelerated maturation, and subsequently, greater deficits can occur in whatever functions are to be localized in that region (50). An in-depth examination of the impact of age-at-injury on brain maturation is needed, however, as "critical periods" for injury likely depend on the outcome measure used (e.g., language function vs. executive functions). Longitudinal studies suggest that the cognitive skills of children with early brain insults (before age 10) tend to develop slower than that of non-brain injured children (17, 50), due to a heightened vulnerability in skill acquisition during critical periods (51, 52).

Time Since Injury

Time since injury is also an important factor to consider, as atypical timing of neural development may result in progressive functional deterioration that occurs due to a child's inability to effectively interact with the environment (42). Alternatively, the child may grow into the deficit in later years, where certain functional deficits do not emerge until the child reaches the appropriate stage of development for some skill to develop (17, 53–55). For example, higher-order executive functions develop later in adolescence and deficits may not be evident until the child reaches the appropriate age at which those functions typically emerge. Over time, dysfunction can become more apparent as the child grows into the deficit and fails to acquire the same skills his or her peers are developing. The result is arrested functional maturation over time, in which deficits become more apparent as the child ages (17, 53, 56).

Injury-Related Factors

Severity of the Injury

More severe injuries are associated with worse physical and cognitive performance in the subacute ($\leq$7 days post-injury), acute ($\leq$90 days post-injury), and chronic (>90 days post-injury) periods of recovery from pediatric TBI (57). TBI severity is typically categorized as mild, moderate, or severe based on the patient's initial clinical presentation, and the primary measures used to classify injury severity in children include the Glasgow Coma Scale [GCS; (58)] and the Pediatric Coma Scale (59), where scores between 13–15, 9–12, and 3–8 indicate mild, moderate, and severe injuries, respectively. Complicated mild TBI is sometimes used to designate the severity of an injury when GCS is between 13 and 15 but abnormal day-of-injury imaging results are present [e.g., skull fracture, intracranial lesion; (60, 61)]. Other common severity indices include the duration of posttraumatic amnesia, the duration of loss of consciousness or coma, and the length of hospital stay. In a large study of 2,940 children who sought medical treatment for TBI, 84.5% suffered from mild injuries, 13.2% suffered from moderate injuries, and 2.3% suffered from severe injuries (62). The results of a meta-analysis (63) demonstrated no statistically significant effects on overall neurocognitive outcome after mild TBI (mTBI), whereas children with complicated mTBI and msTBI have been shown to recover at slower rates and have poor cognitive outcomes up to several years post-injury (44, 60, 64).

Lesion Characteristics

The heterogeneity of various biomechanical, pathological, and physiological mechanisms of primary and secondary injuries are reflected by structural imaging abnormalities observed in chronic TBI [for a review, see (19, 65)]. Size, laterality, location, and extent of the lesion can all impact post-injury outcome. Poorer outcomes after pediatric TBI have consistently been seen in patients with larger, more diffuse, and bilateral injuries (66). Smaller, unilateral lesions tend to demonstrate the greatest plasticity, resulting in relatively good recovery (67, 68), and it is suggested that such focal damage forces the interhemispheric transfer of function, resulting in minimal impact on functional abilities (69). Other studies investigating laterality have reported

that right vs. left hemisphere lesions to the frontal lobe lead to somewhat different impairment profiles across cognitive domains (53, 56, 70, 71). In contrast to that of adult TBI, the relationship between lesion location and outcome following pediatric TBI is not consistently documented (72). Intact (i.e., undamaged) frontal and parietal cortices are important for functional reorganization or the recruitment of additional cerebral regions to compensate for the functions localized in the damaged region (73); however functional outcome has not been linked to functional reorganization, *per se* (19, 74, 75). It is possible that incomplete functional localization of the immature brain during early childhood leads to a less severe impact of lesion location or laterality on recovery. Rather, the extent of damaged tissue is the strongest predictor of outcome, suggesting that the integrity of the whole brain network may be necessary for efficient functioning in children (17).

Mechanism of Injury

Unintentional blunt force trauma to the head involves contact forces that produce focal lacerations, fractures, and contusions to the brain, scalp, and skull, and often results in epidural hemorrhages. Acceleration-deceleration injuries involve inertial forces, which cause excessive movement of the brain, yielding more diffuse injuries such as concussion, subdural hematoma, and diffuse vascular damage (76, 77). Anthropometric development and age-specific biomechanical properties of a growing child's skull, face, brain, and neck muscles make children more or less susceptible to specific injuries that are less often or not seen in adults [see **Figure 2**; (78)]. Children have a greater head-to-body ratio, which increases the probability that damage will occur to the head in the event of trauma. Furthermore, a greater head-to-body ratio contributes to the relative weight of the head compared to the rest of the body, which results in different dynamics of head acceleration between children and adults. Relative to adults, children also have a greater relative proportion of cerebral blood volume and water content due to the degree of myelination that has occurred, making the brain softer and more susceptible to acceleration-deceleration injury. Because a child's brain tissue, skull, and neck musculature is not fully developed, they are more susceptible to posttraumatic edema, ischemic insult, and DAI when exposed to the inertial forces and direct blows associated with falls, sports-related injuries, and motor vehicle accidents, which are the most common mechanisms of injury in children (22, 35).

Pre-injury Factors

Sex

Biological sex is likely to affect neurodevelopment after early brain injury, and MRI research in typical human development demonstrated differential rates of cortical development in males and females, where gray matter density peaks around age 10 in females but not until age 12 in males (7, 79, 80). There is also evidence for greater dendritic volume in the left hemisphere (81) and increased bilateral cortical activation (82) in the young female brain. The animal literature suggests that sex-related differences in the development of gray and white matter is influenced by endogenous hormones, specifically the increased progesterone levels in females. Research using rodent TBI-models report that females recover better than males [for a review, see (83)], and many studies have provided evidence for the neuroprotective effects of progesterone against secondary mechanisms of brain injury, although results have been somewhat conflicting. Increased levels of progesterone have been shown to reduce brain edema, increase neuronal survival, and impact the expression of genes involved in the regulation of inflammatory responses and apoptosis in brain injured rats (83, 84). Progesterone has also been implicated as a promotor of axon regeneration and remyelination (85, 86), and this is supported by research demonstrating sex differences in neuroplasticity following early brain injury to rats (87).

In human research, biological sex plays an important role in psychosocial development, where females have an increased risk for developing emotional and psychiatric disorders, and males have an increased risk for social and behavioral problems within the first 6–12 months following childhood TBI (88–90). In a longitudinal study of quality of life following mild-to-severe TBI sustained during childhood (91), female sex significantly predicted poorer outcomes across the majority of health-related quality of life measures as well as overall satisfaction with perceived quality of life. This conflicts with the findings above regarding hormones, suggesting that this issue may require a more nuanced approach. In particular, the impact of puberty on outcome is relatively understudied even though it plays a major role in brain development. These findings underscore the importance of considering demographic characteristics, including intersections between these variables, when assessing outcome and predicting recovery from early brain injury.

Socioeconomic Status

There is substantial evidence supporting the beneficial effects of an enriched environment on brain development (92–95), and more recent research has further demonstrated the effect on outcome following childhood brain injury. In a longitudinal study of functional outcome for children with TBI vs. orthopedic injury, home environment was found to moderate the effects of TBI on 7-year outcome (96). In particular, the results of this study demonstrated significantly poorer outcomes in those with TBI vs. orthopedic injury when the home environment had low enrichment (e.g., less access to educational resources and familial support), whereas both patient groups from more facilitative and enriching home environments recovered similarly well. Similar findings have been shown in other longitudinal studies, where children from higher functioning families with greater resources and more enriching home environments have better psychosocial, behavioral, and overall functional outcomes years after suffering from early brain injury (88, 97, 98). Socioeconomic status (SES) is a major determinant of how enriching one's environment is, and recent research provides evidence for the direct impact of SES on typical brain development (99, 100). Significant associations between low SES and long-term psychosocial and behavioral outcomes after pediatric TBI have also been demonstrated in the literature (101, 102).

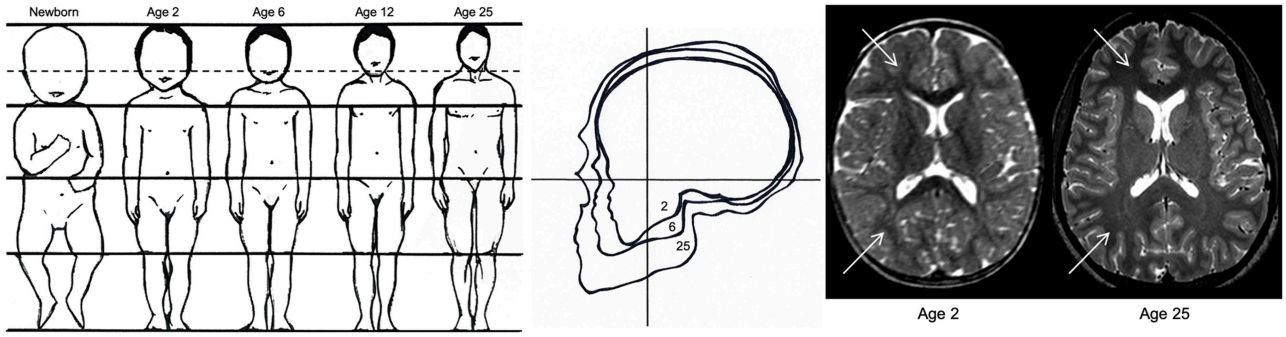

FIGURE 2 | Anthropometric differences between children and adults. The image on the left demonstrates the decreasing ratio of head-to-body size from birth to adulthood, which increases the likelihood of traumatic brain injury in children relative to adults. The image in the middle reflects the increasing ratio between facial and cranial size between ages 2, 6, and 25, demonstrating the greater risk for skull trauma in children relative to adults. The image on the right reflects the difference in T_2-weighted contrast hyperintensity (indicated by white arrows) due to less myelination and a greater concentration of water in a 2-year-old brain relative to a fully developed 25-year-old brain. The immaturity of the white matter in the newborn makes the brain "softer" and more prone to acceleration-deceleration injury. Adapted from Pinto et al. (78).

LONGITUDINAL NEUROIMAGING OF PEDIATRIC TRAUMATIC BRAIN INJURY

The PubMed database was searched for English-language articles focusing on longitudinal MRI studies in young patients with a history of TBI using the following search criteria: [In Title: (pediatric OR adolescent OR child OR children OR youth)] AND [In Title: (traumatic brain injury OR brain injury OR TBI OR concussion)] AND [All Fields: (longitudinal OR chronic OR long-term OR outcome)] AND [All Fields: (MRI OR neuroimaging OR imaging)]. No time period restrictions were applied, and the latest search was undertaken on July 21, 2019. Additional searches in the references of previously published studies were conducted in an attempt to identify further articles. We excluded published study protocols, conference abstracts, articles not available in English, and experiments involving non-human subjects. The title and abstract of the retrieved articles were examined against all inclusion criteria, and the full text article was retrieved if all criteria were met. The assessment of eligibility was performed by two investigators (HML and EAW) independently with the requirement of consensus. In case of disagreement, a third expert was consulted (ELD or KC). Four longitudinal studies of sport-related concussion (SRC) in children or adolescents were excluded due to the failure to provide details or adequate definitions of concussion. In total, we identified 19 research articles that met the following four inclusion criteria: (a) the studies involved children or adolescents who sustained a TBI prior to the age of 19; (b) MRI-based methods were employed to measure brain structure and/or function; (c) changes in brain structure and/or function were assessed over at least two separate points in time (i.e., longitudinal studies). One additional study (103) was published after the initial search date and was considered for inclusion at that time, bringing the total included studies in this review to 20. Of these studies, 6 collected sMRI, 12 collected dMRI, 4 collected MRS, and 2 collected fMRI data for their longitudinal analyses.

In the following sections, we briefly describe the longitudinal studies from the current literature that evaluate change in brain structure and/or function over time using sMRI, dMRI, MRS, and/or fMRI. We will begin with a summary of the characteristics of the included studies and provide a basic description of the methods used for analysis and the outcome measures of interest. We will then summarize the overall findings of the studies for each respective imaging modality. A summary of the imaging modalities, their clinical utility in TBI populations, common outcome measures used, and the included studies that utilized them can be found in **Table 1**. The following data was extracted from each article, and details are summarized in **Tables 2–5**: patient and control group demographic characteristics (age and sex distribution), age and developmental stage at injury, post-injury time interval, injury severity, MR-based outcome measure(s) assessed, and analysis method(s) used. We extracted additional information regarding the racial/ethnic distribution and SES of patient and control groups, mechanism of injury, primary injuries (determined by day-of-injury CT scan), MR image acquisition details (including field strength, scanner model), and functional/behavioral domains assessed, and these details are summarized in **Supplementary Tables S1–S4**.

Structural Magnetic Resonance Imaging

There is a relatively liThere is a relatively limited number of longitudinal studies using structural, T_1-weighted MRI to evaluate outcome following pediatric TBI. Six published studies were found (see **Table 2**), and these studies evaluated samples who were injured between early childhood and adolescence (ages 5–18). All samples were first evaluated within the subacute or acute post-injury periods, and follow-up time points occurred between 4- and 36-months post-injury. Three analysis methods were used across the six studies: four studies utilized semi- or fully automatic ROI region-of-interest (ROI) approaches to measure longitudinal changes in gray matter density (105–108), one study measured volumetric change longitudinally

TABLE 1 | Overview of the utility of magnetic resonance-based imaging modalities used in the reviewed longitudinal investigations of pediatric traumatic brain injury.

Modality	Method	Underlying neural processes	Pathological sensitivity	Interpretation of parameters	Included studies
Structural	Morphometry	Relaxation times of tissues	Regional volume	Gray matter density Jacobian determinant	(104–108)
			Cortical thickness	Thickness of cortical gray matter	(109)
	Diffusion	Brownian motion of water molecules	White matter integrity Diffuse axonal injury Demyelination Wallerian degeneration Cytotoxic edema Hemorrhage Axonal damage	**FA:** anisotropic movement of water molecules along fiber bundles; reflects white matter organization **ADC/MD:** average diffusivity; reflects the degree of overall diffusion magnitude **AD:** diffusivity along the primary axis; reflects the direction of diffusion magnitude **RD:** diffusion perpendicular to the main diffusion direction; reflects the direction of diffusion magnitude	(103, 106–108, 110–116)
			Structural connectivity	**Degree:** the number of connections between modules **MOD:** modules of connected regions that work together to support a given function **E_{glob}:** how efficiently information is transferred globally throughout a network **E_{loc}:** how efficiently information is transferred locally throughout a network **Betweenness centrality:** a reflection of the importance of some region for the transfer of information between other regions **Small-worldness**: a ratio reflecting the balance between network segregation and integration **Normalized clustering coefficient:** a measure of the level of segregation of the entire system	(117)
Metabolic	Spectroscopy	Intracellular metabolic status	Neuronal death Axonal damage Inflammation Demyelination Astrocytosis	**NAA:** marker of neuronal metabolism and integrity **Cho:** marker of cellular membrane turnover **Cr and Lac:** markers of energy metabolism	(110, 118–120)
Functional	Task-based	Blood oxygen level dependent (BOLD)	Functional activation	**Regional activity:** level of activity in different areas of the brain determined by BOLD signal	(121)
			Blood flow	**CVR:** change in cerebral blood flow in response to a vasodilatory stimulus	(122)

AD, axial diffusivity; ADC, apparent diffusion coefficient; Cho, choline; Cr, creatine; CVR, cerebrovascular responsiveness; E_{glob}, global efficiency; E_{loc}, local efficiency; FA, fractional anisotropy; Lac, lactate; MD, mean diffusivity; MOD, modularity; NAA, N-acetyl aspartate; RD, radial diffusivity.

using tensor-based morphometry [TBM; (104)], and one study used surface-based morphometry (SBM) to measure changes in cortical thickness (109).

Methodology and Outcome Measurement

ROI approaches are typically used to address a specific anatomical hypothesis and involve manual or automatic segmentation of the specific region(s) to be compared between subjects. TBM (123) is an advanced whole-brain approach that involves the non-linear registration of individual subject data to a template brain space using deformation tensor fields, in which differences in the anatomical structure of each individual brain is preserved and quantified from the properties of the deformation fields via Jacobian determinants. Concerns associated with multiple comparisons exist for both whole-brain and ROI approaches (when more than one ROI is analyzed), and it is necessary to correct for this by including the appropriate statistical correction procedures. SBM is used for cortical thickness analyses and involves the initial non-linear alignment of cortical curvature across subjects and the spatial normalization data from each subject is registered to template space. Cortical thickness comparisons can then be made between subjects at homologous locations along the cortex.

TABLE 2 | Summary of structural magnetic resonance imaging studies.

Study	Sample characteristics	Age at injury	Time since injury	Severity	Analysis method	Dataset
Dennis et al. (104)	Post-acute (T1) **TBI-Slow:** *N* = 11 (8M, 3F) Age = 14.1 ± 1.9 **TBI-Normal:** *N* = 10 (8M, 2F) Age = 16.0 ± 2.6 **HC:** *N* = 26 (15M, 11F) Age = 14.5 ± 3.0 Chronic (T2) **TBI-Slow:** *N* = 11 (8M, 3F) Age = 15.0 ± 2.0 **TBI-Normal:** *N* = 10 (8M, 2F) Age = 17.0 ± 2.8 **HC:** *N* = 26 (15M, 11F) Age = 15.6 ± 3.0	**Late Childhood—Adolescence** (ages 8–18)	T1: ∼2–5 mo T2: ∼14–17 mo	Moderate-Severe **TBI-Slow:** GCS = 8.8 ± 3.6 **TBI-Normal:** GCS = 9.4 ± 4.0	TBM (ANTs) **Measure:** Volume **Covariates:** age, sex, scanner, scan interval, ICV	a
Levin et al. (105)	Post-acute (T1) **mmTBI:** *N* = 28 (20M, 8F) Age = 9.7 ± 2.7 **sTBI:** *N* = 25 (15M, 10F) Age = 10.3 ± 3.1	**Early Childhood—Adolescence** (ages 5–15)	T1: ∼3 mo T2: ∼36 mo	Mild-Severe **mmTBI:** GCS = 13.5 ± 1.7 **sTBI:** GCS = 5.7 ± 2.0	ROI analysis (in-house software) **ROIs:** rCC, gCC, anterior bCC, middle bCC, posterior bCC, iCC, sCC **Covariates:** CC area/total brain area ratio	Ind
Mayer et al. (106)	Post-acute (T1) **TBI:** *N* = 15 (13M, 2F) Age = 13.47 ± 2.20 **HC:** *N* = 15 (12M, 3F) Age = 13.40 ± 1.84 Chronic (T2) **TBI:** *N* = 10 **HC:** *N* = 10	**Late Childhood—Adolescence** (ages 10–17)	T1: ∼3 wk 15.87 ± 4.93 da T2: ∼4 mo 127.82 ± 14.60 da	Mild GCS = 13–15 LOC < 30 min PTA < 24 h	ROI analysis (Freesurfer) **Measures:** Volume, Cortical Thickness **ROIs:** Thal, HiC **Covariates:** ICV	b
Wilde et al. (109)	Post-acute (T1) **TBI:** *N* = 20 (11M, 9F) Age = 13.6 ± 2.9 **OI:** *N* = 21 (15M, 6F) Age = 12.1 ± 2.5 Chronic (T2) **TBI:** *N* = 20 (11M, 9F) Age = 14.8 ± 2.9 **OI:** *N* = 21 (15M, 6F) Age = 13.2 ± 2.6	**Late Childhood—Adolescence** (ages 7–17)	T1: ∼3 mo **TBI:** 4.0 ± 1.0 **OI:** 4.7 ± 2.6 T2: ∼18 mo **TBI:** 18.5 ± 3.6 **OI:** 18.4 ± 4.2	Complicated Mild—Severe GCS = 7.9 ± 4.0 ISS = 22.6 ± 11.6	SBM (FreeSurfer) **Measure:** Cortical Thickness	c
Wu et al. (107)	Acute (T1) **SRC:** *N* = 10 (6M, 4F) Age = 14.58 ± 1.60 **OI:** *N* = 12 (9M, 3F) Age = 14.06 ± 1.70 **TDC:** *N* = 8	**Pre-adolescence—Adolescence** (ages 12–17)	T1: ∼96 h 21–116 h T2: ∼3 mo 84–143 da	Mild GCS = 14–15 LOC = 0–5 min PTA = 0–180 min	ROI analysis (FreeSurfer) **Measure:** Volume **ROIs:** rostral anterior CG, caudal anterior CG, posterior CG, isthmus CG, total CC **Covariates:** ICV	d
Wu et al. (108)	Post-acute (T1) **TBI:** *N* = 23 (15M, 8F) Age = 12.9 ± 3.2 **OI:** *N* = 25 (18M, 7F) Age = 11.8 ± 2.7	**Late Childhood—Adolescence** (ages 7–17)	T1: ∼3 mo **TBI:** 4.0 ± 0.9 **OI:** 4.2 ± 1.0 T2: ∼18 mo **TBI:** 18.9 ± 1.5 **OI:** 18.8 ± 1.3	Complicated Mild—Severe GCS = 7.5 ± 4.1	ROI analysis (Freesurfer) **Measure:** Volume **ROIs:** gCC, bCC, sCC, total CC **Covariates:** ICV	c

Datasets that overlapped with others reviewed in this article are specified in the last column (Ind = individual study). ANTs, advanced normalization tools; bCC, body of the corpus callosum; CC, corpus callosum; F, female; CG, cingulum; gCC, genu of the corpus callosum; GCS, Glasgow Coma Scale; HC, healthy control; HiC, hippocampus; iCC, isthmus of the corpus callosum; ICV, intracranial volume; ISS, injury severity scale; LOC, loss of consciousness; M, male; mmTBI, mild/moderate traumatic brain injury; OI, orthopedic injury; PTA, posttraumatic amnesia; rCC, rostrum of the corpus callosum; ROI, region of interest; SBM, surface-based morphometry; sCC, splenium of the corpus callosum; SRC, sports-related concussion; sTBI, severe traumatic brain injury; T1, time 1; T2, time 2; TBI, traumatic brain injury; TBI-Normal, traumatic brain injury with normal inter-hemispheric transfer time; TBI-Slow, traumatic brain injury with slow inter-hemispheric transfer time; TBM, tensor-based morphometry; TDC, typically developing children; Thal, thalamus.

TABLE 3 | Summary of diffusion-weighted imaging studies.

Study	Sample Characteristics	Age at Injury	Time since Injury	Severity	Analysis Method	Dataset
Dennis et al. (110)	Post-acute (T1) **TBI-Slow:** *N* = 15 (10M, 5F) Age = 13.9 ± 2.3 **TBI-Normal:** *N* = 14 (11M, 3F) Age = 13.9 ± 3.2 **HC:** N = 23 (11M, 12F) Age = 15.3 ± 2.8 Chronic (T2) **TBI-Slow:** *N* = 9 (7M, 2F) Age = 14.9 ± 2.0 **TBI-Normal:** *N* = 9 (7M, 2F) Age = 16.7 ± 2.8 **HC:** *N* = 21 (14M, 7F) Age = 15.3 ± 3.2	**Late Childhood—Adolescence** (ages 8-18)	T1: ∼2-5 mo **TBI-Slow:** 12.0 ± 4.7 wk **TBI-Normal:** 12.5 ± 5.1 wk T2: ∼13-19 mo **TBI-Slow:** 61.2 ± 4.8 wk **TBI-Normal:** 67.2 ± 6.1 wk	Moderate-Severe *Post-acute* **TBI-Slow:** GCS = 9.6 ± 3.9 **TBI-Normal:** GCS = 8.3 ± 4.0 *Chronic* **TBI-Slow:** GCS = 7.7 ± 2.9 **TBI-Normal:** GCS = 9.4 ± 4.2	Tractography (autoMATE, Camino) **Measures:** FA, MD, AD, RD **ROIs:** CST, CGC, CGH, IFO, ILF, UF, ARC, gCC, anterior bCC, posterior bCC, iCC, sCC **Covariates:** age, sex, scanner	a
Dennis et al. (111)	Post-acute (T1) **TBI-Slow:** *N* = 11 (8M, 3F) Age = 14.1 ± 1.9 **TBI-Normal:** *N* = 10 (8M, 2F) Age = 16.0 ± 2.6 **HC:** *N* = 20 (12M, 8F) Age = 14.5 ± 3.0 Chronic (T2) **TBI-Slow:** *N* = 11 (8M, 3F) Age = 15.0 ± 2.0 **TBI-Normal:** *N* = 10 (8M, 2F) Age = 17.0 ± 2.8 **HC:** *N* = 20 (12M, 8F) Age = 15.6 ± 3.1	**Late Childhood—Adolescence** (ages 8-18)	T1: ∼2-5 mo T2: ∼14-17 mo	Moderate-Severe **TBI-Slow:** GCS = 8.8 ± 3.6 **TBI-Normal:** GCS = 9.4 ± 4.0	Tractography (autoMATE) **Measures:** FA, MD, AD, RD **ROIs:** ATR, CST, IFO, ILF, ARC, FX, CGC, rCC gCC, anterior bCC, posterior bCC, iCC, sCC **Covariates:** age, sex, scanner, scan interval	a
Ewing-Cobbs et al. (112)	Post-acute (T1) **TBI:** *N* = 16 (12M, 4F) **OI:** *N* = 18 (10M, 8F) Chronic (T2) **TBI:** *N* = 16 (12M, 4F) **OI:** *N* = 18 (10M, 8F)	**Late Childhood—Adolescence** (ages 6-15)	T1: ∼3 mo 3.88 ± 1.63 T2: ∼24 mo 24.75 ± 7.74	Mild-Severe 19% GCS = 13-15 44% GCS = 9-12 69% GCS = 3-8 ISS = 21.56 ± 10.93	TBSS (FSL) **Measures:** FA, AD, RD **ROIs:** ILF, SLF, IFO, UF, CGC, CGH, CST **Covariate:** age at injury	Ind
Genc et al. (113)	Post-acute (T1) **TBI:** *N* = 78 (50M, 28F) Age = 10.44 ± 2.21 **HC:** *N* = 30 (20M, 10F) Age = 10.60 ± 2.88 Chronic (T2) **TBI:** *N* = 15	**Early Childhood—Pre-adolescence** (ages 5-14)	T1: ∼1-2 mo 5.55 ± 3.05 wk T2: ∼24 mo 22.3 ± 2.3 mo	Mild-Severe GCS = 13.08 ± 2.71 LOC = 3.31 ± 3.07 hr LHS = 2.76 ± 5.33 da	TBSS (FSL) **Measures:** FA, MD, AD, RD **Covariates:** age, sex	Ind
Mayer et al. (106)	Post-acute (T1) **TBI:** *N* = 15 (13M, 2F) Age = 13.47 ± 2.20 **HC:** *N* = 15 (12M, 3F) Age = 13.40 ± 1.84 Chronic (T2) **TBI:** *N* = 10 **HC:** *N* = 10	**Late Childhood—Adolescence** (ages 10-17)	T1: ∼3 wk 15.87 ± 4.93 da T2: ∼4 mo 127.82 ± 14.60 da	Mild GCS = 13-15 LOC < 30 min PTA < 24 hr	ROI analysis (AFNI, FSL, Freesurfer) **Measures:** FA, AD, RD **ROIs:** Thal, HiC **Covariates:** ICV	b
Mayer et al. (114)	Post-acute (T1) **TBI:** *N* = 15 (13M, 2F) Age = 13.47 ± 2.20 **HC:** *N* = 15 (12M, 3F) Age = 13.40 ± 1.84 Chronic (T2) **TBI:** *N* = 11 (10M, 1F) Age = 13.82 ± 2.27 **HC:** *N* = 12 (9M, 3F) Age = 13.58 ± 1.93	**Late Childhood—Adolescence** (ages 10-17)	T1: ∼ 3 wk 15.87 ± 4.93 da T2: ∼4 mo 127.82 ± 14.60 da	Mild GCS = 13-15 LOC < 30 min PTA < 24 hr	ROI analysis (AFNI, FSL) **Measures:** FA **ROIs:** gCC, bCC, sCC, ACR, SCR, CG, IC, CP	b

(Continued)

TABLE 3 | Continued

Study	Sample Characteristics	Age at Injury	Time since Injury	Severity	Analysis Method	Dataset
Van Beek et al. (115)	Post-acute (T1) **TBI:** *N* = 20 (13M, 7F) Age = 10.8 ± 1.6 **HC:** *N* = 20 (13M, 7F) Age = 10.9 ± 1.5 Chronic (T2) **TBI:** *N* = 18 (12M, 6F) Age = 11.2 ± 1.6 **HC:** *N* = 18 (13M, 5F) Age = 11.4 ± 1.5	**Late Childhood—Pre-adolescence** (ages 7-13)	T1: ∼1 mo 20 ± 7 da T2: ∼6-8 mo 201 ± 22 da	Mild GCS = 13-15 LOC < 30 min PTA < 24 hr	Tractography (ExploreDTI, TrackVis) **Measures:** FA, MD, AD, RD **ROIs:** gCC, sCC, SLF, ILF	Ind
Verhelst et al. (103)	Pre-intervention (T1) **TBI:** *N* = 16 (9M, 7F) Age = 15.6 ± 1.8 **HC:** *N* = 16 (9M, 7F) Age = 15.6 ± 1.8 Post-intervention (T2) **TBI:** *N* = 16 (9M, 7F) **HC:** *N* = 16 (9M, 7F)	**Late Childhood—Adolescence** (ages 9-15)	T1: ≥ 12 mo 2.25 ± 1.02 T2: ∼8 wk post-T1	Moderate-Severe 38% LOC ≥ 30 50% GCS < 13 100% Positive CT	Tractography (MRtrix3); Whole-brain FBA (CSD); ROI analysis (TDI) **Measures:** FA, MD, FC **ROIs:** gCC, CGC, CGH, SLF-I, SLF-II, SLF-III **Covariates:** age, ICV	Ind
Wilde et al. (116)	Post-acute (T1) **TBI:** *N* = 20 (11M, 9F) Age = 13.6 ± 2.9 **OI:** *N* = 21 (15M, 6F) Age = 12.1 ± 2.5 Chronic (T2) **TBI:** *N* = 20 (11M, 9F) Age = 14.8 ± 2.9 **OI:** *N* = 21 (15M, 6F) Age = 13.2 ± 2.6	**Late Childhood—Adolescence** (ages 7-17)	T1: ∼3 mo **TBI:** 4.0 ± 1.0 **OI:** 4.7 ± 2.6 T2: ∼18 mo **TBI:** 18.5 ± 3.6 **OI:** 18.4 ± 4.2	Complicated Mild-Severe GCS = 7.9 ± 4.0 ISS = 22.6 ± 11.6	TBSS (FSL) **Measures:** FA, ADC	c
Wu et al. (107)	Acute (T1) **SRC:** *N* = 10 (6M, 4F) Age = 14.58 ± 1.60 **OI:** *N* = 12 (9M, 3F) Age = 14.06 ± 1.70 **HC:** *N* = 8	**Pre-adolescence—Adolescence** (ages 12-17)	T1: ∼96 hr 21-116 hr T2: ∼3 mo 84-143 da	Mild GCS = 14-15 LOC = 0-5 min PTA = 0-180 min	Tractography (Phillips 3D Fiber Tracking software) **Measure:** FA, ADC **ROIs:** gCC, bCC, sCC, total CC, UF, CG	d
Wu et al. (108)	Post-acute (T1) **TBI:** *N* = 23 (15M, 8F) Age = 12.9 ± 3.2 **OI:** *N* = 25 (18M, 7F) Age = 11.8 ± 2.7	**Late Childhood—Adolescence** (ages 7-17)	T1: ∼3 mo **TBI:** 4.0 ± 0.9 **OI:** 4.2 ± 1.0 T2: ∼18 mo **TBI:** 18.9 ± 1.5 **OI:** 18.8 ± 1.3	Complicated Mild-Severe GCS = 7.5 ± 4.1	Tractography (Philips 3D Fiber Tracking software) **Measures:** FA, ADC **ROIs:** gCC, bCC, sCC, total CC	c
Yuan et al. (117)	Pre-intervention (T1) **TBI:** *N* = 17 (10M, 7F) Age = 13.72 ± 2.77 **HC:** *N* = 11 (3M, 8F) Age = 13.37 ± 2.08 Post-intervention (T2) **TBI:** *N* = 10 **HC:** *N* = 11 (3M, 8F)	**Late Childhood—Adolescence** (ages 9-18)	T1: > 1 yr 5.91 ± 3.10 T2: ∼3 mo post-T1	Complicated Mild-Severe GCS = 10.53 ± 4.8	Tractography (Diffusion Toolkit/TrackVis) + Graph Theoretical Analysis (Brain Connectivity Toolbox) **Measures:** E_{glob}, E_{loc}, MOD, γ, λ, σ, nodal degree, nodal clustering coefficient, nodal local efficiency, nodal betweenness centrality	Ind

Datasets that overlapped with others reviewed in this article are specified in the last column (Ind, individual study). ACR, anterior corona radiata; AD, axial diffusivity; ADC, apparent diffusion coefficient; AFNI, Analysis of Functional Neuroimages; ARC, arcuate fasciculus; ATR, anterior thalamic radiation; bCC, body of the corpus callosum; CC, corpus callosum; CG, cingulum; CGC, cingulum cingulate; CGH, cingulum hippocampus; CP, cerebellar peduncle; CSD, constrained spherical deconvolution; CST, corticospinal tract; CT, computed tomography; E_{glob}, global efficiency; E_{loc}, local efficiency; F, female; FA, fractional anisotropy; FBA, fixel-based analysis; FC, fiber cross-section; FSL, FMRIB Software Library; FX, fornix; gCC, genu of the corpus callosum; GCS, Glasgow Coma Scale; HC, healthy control; HiC, hippocampus; IC, internal capsule; iCC, isthmus of the corpus callosum; ICV, intracranial volume; IFO, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; ISS, injury severity scale; LHS, length of hospital stay; LOC, loss of consciousness; M, male; MD, mean diffusivity; MOD, modularity; OI, orthopedic injury; PTA, posttraumatic amnesia; rCC, rostrum of the corpus callosum; RD, radial diffusivity; ROI, region of interest; sCC, splenium of the corpus callosum; SCR, superior corona radiata; SLF, superior longitudinal fasciculus; SRC, sports-related concussion; T1, time 1; T2, time 2; TBI, traumatic brain injury; TBI-Normal, traumatic brain injury with normal inter-hemispheric transfer time; TBI-Slow, traumatic brain injury with slow inter-hemispheric transfer time; TBSS, tract-based spatial statistics; TDC, typically developing children; TDI, track-density imaging; Thal, thalamus; UF, uncinate fasciculus; γ, normalized clustering coefficient; λ, normalized characteristic path length; σ, small-worldness.

TABLE 4 | Summary of magnetic resonance spectroscopy studies.

Study	Sample characteristics	Age at injury	Time since injury	Severity	Analysis method	Dataset
Babikian et al. (118)	Post-acute (T1) **TBI-Slow:** *N* = 14 (9M, 5F) Age = 14.0 ± 2.5 **TBI-Normal:** *N* = 17 (13M, 4F) Age = 14.3 ± 3.3 **HC:** *N* = 48 (23M, 25F) Age = 15.6 ± 2.7 Chronic (T2) **TBI-Slow:** *N* = 12 **TBI-Normal:** *N* = 12 **HC:** *N* = 35	**Late Childhood—Adolescence** (ages 8–18)	T1: ∼3 mo **TBI-Slow:** 11.6 ± 4.2 wk **TBI-Normal:** 12.6 ± 5.5 wk T2: ∼16 mo **TBI-Slow:** 63.7 ± 7.8 wk **TBI-Normal:** 69.5 ± 8.0 wk	Moderate-Severe **TBI-Slow:** Initial GCS = 8.9 ± 3.6 Low GCS = 7.0 ± 3.6 **TBI-Normal:** Initial GCS = 8.2 ± 3.9 Low GCS = 8.3 ± 4.0	Whole-brain (MIDAS) **Measures:** NAA, Cho, Cr **ROIs:** Frontal, Temporal, Parietal, and Occipital GM, gCC, bCC, sCC, HiC, CB	a
Dennis et al. (110)	Post-acute (T1) **TBI-Slow:** *N* = 15 (10M, 5F) Age = 13.9 ± 2.3 **TBI-Normal:** *N* = 14 (11M, 3F) Age = 13.9 ± 3.2 **HC:** *N* = 23 (11M, 12F) Age = 15.3 ± 2.8 Chronic (T2) **TBI-Slow:** *N* = 9 (7M, 2F) Age = 14.9 ± 2.0 **TBI-Normal:** *N* = 9 (7M, 2F) Age = 16.7 ± 2.8 **HC:** *N* = 21 (14M, 7F) Age = 15.3 ± 3.2	**Late Childhood—Adolescence** (ages 8–18)	T1: ∼2–5 mo **TBI-Slow:** 12.0 ± 4.7 wk **TBI-Normal:** 12.5 ± 5.1 wk T2: ∼13–19 mo **TBI-Slow:** 61.2 ± 4.8 wk **TBI-Normal:** 67.2 ± 6.1 wk	Moderate-Severe *Post-acute* **TBI-Slow:** GCS = 9.6 ± 3.9 **TBI-Normal:** GCS = 8.3 ± 4.0 *Chronic* **TBI-Slow:** GCS = 7.7 ± 2.9 **TBI-Normal:** GCS = 9.4 ± 4.2	Whole-brain (MIDAS, autoMATE) **Measures:** NAA, Cho **ROIs:** CST, CGC, IFO, ILF, UF, CGH, ARC, gCC, anterior bCC, posterior bCC, iCC, sCC **Covariates:** age, sex, scanner	a
Holshouser et al. (119)	Post-acute (T1) **mmTBI:** *N* = 32 (26M, 6F) Age = 12.2 ± 3.3 **sTBI:** *N* = 32 (21M, 11F) Age = 12.0 ± 3.8 **HC:** *N* = 63 (33M, 30F) Age = 12.6 ± 3.3	**Early Childhood—Adolescence** (ages 4–18)	T1: ∼2 wk **mmTBI:** 11.7 ± 3.2 da **sTBI:** 11.5 ± 3.7 da T2: ∼12 mo **mmTBI:** 12.2 ± 0.96 mo **sTBI:** 12.1 ± 0.63	Complicated Mild—Severe **mmTBI:** GCS = 13.6 ± 2.0 LOC = 0.63 ± 0.55 da LHS = 5.88 ± 3.01 da **sTBI:** GCS = 4.4 ± 1.8 LOC = 5.53 ± 5.81 da LHS = 17.4 ± 10.1 da	MV single slice (LCModel) **Measures:** NAA, Cho, Cr, Lac **ROIs:** Frontal, temporal, parietal, and occipital GM and WM, BG, BS, CC, Thal, CB **Covariate:** age	Ind
Yeo et al. (120)	Initial (T1) **TBI:** *N* = 36 (30M, 6F) Age = 13.62 ± 3.59 **HC:** *N* = 14 (4M, 10F) Age = 15.29 ± 1.60 Follow-up (T2) **Short TI:** *N* = 13 **Medium TI:** *N* = 14 **Long TI**: *N* = 9	**Late Childhood—Adolescence** (ages 6–18)	T1: ∼3.5 wk 35.46 ± 33.95 da T2: ∼5, 13, or 24 wk **Short TI:** 1.50 ± 2.46 wk **Medium TI:** 9.29 ± 2.73 wk **Long TI:** 21.22 ± 6.22 wk	Complicated Mild-Severe GCS = 8.11 ± 4.60	MV single slice (LCModel) **Measures:** NAA, Cho, Cr **ROIs:** Anterior and posterior compartments of supraventricular slab	Ind

Datasets that overlapped with others reviewed in this article are specified in the last column (Ind, individual study). ARC = arcuate fasciculus; bCC, body of the corpus callosum; BG, basal ganglia, BS, brainstem; BS, brainstem; CB, cerebellum; CC, corpus callosum; CGC, cingulum bundle cingulate; CGH, cingulum bundle hippocampal; Cho, choline; Cr, creatine; CST, corticospinal tract; F, female; gCC, genu of the corpus callosum; GCS, Glasgow Coma Scale; GM, gray matter; HC, healthy control; HiC, hippocampus; iCC, isthmus of the corpus callosum; IFO, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; Lac, lactate; LHS, length of hospital stay; LOC, loss of consciousness; M, male; MIDAS, Metabolite Imaging and Data Analysis System; mmTBI, mild/moderate traumatic brain injury; MV, multi-voxel; NAA, N-acetyl aspartate; sCC, splenium of the corpus callosum; sTBI, severe traumatic brain injury; T1, time 1; T2, time 2; TBI, traumatic brain injury; TBI-Normal, traumatic brain injury with normal inter-hemispheric transfer time; TBI-Slow, traumatic brain injury with slow inter-hemispheric transfer time; Thal, thalamus; TI, time interval; UF, uncinate fasciculus; WM, white matter.

Summary of Longitudinal Findings

Overall, the results of morphometric studies evaluating longitudinal change after pediatric TBI demonstrated widespread volumetric differences and cortical thinning over time, when compared to the rates of change in typically developing or orthopedically injured children of the same age. Volumetric differences, indicative of greater atrophy or cortical thinning between acute and chronic periods after pediatric TBI were consistently shown in the corpus callosum (104, 105, 108), superior and middle frontal gyri, middle temporal gyri,

TABLE 5 | Summary of functional magnetic resonance imaging studies.

Study	Sample Characteristics	Age at Injury	Time since Injury	Severity	Analysis Method	Dataset
Cazalis et al. (121)	Post-acute (T1) **TBI:** *N* = 6 (5M, 1F) Age = 16.7 ± 0.7 Chronic (T2) **TBI:** *N* = 6 (5M, 1F) Age = 17.7 ± 0.8	**Adolescence** (ages 15-17)	T1: 3–6 mo 4.5 ± 1.0 mo T2: ∼15–18 mo 16.5 ± 3.1 mo	Complicated Mild-Severe GCS = 9.4 ± 5.1	Task-based ROI analysis (FSL) **Measure:** Working Memory Load (response accuracy + reaction time across four conditions) **ROIs:** Left SMC (MNI *xyz* = −40, −32, 56; 20 mm radius), ACC (MNI *xyz* = 0, 34, 28; 14 mm radius)	a
Mutch et al. (122)	Initial (T1) **SRC:** *N* = 6 (3M, 3F) Age = 15.67 ± 0.82 **HC:** *N* = 24 (15M, 9 F) Mean age = 18.5	**Adolescence** (ages 15-17)	T1: 115.7 ± 113.6 da T2: 218.8 ± 150.3 da	Mild ICCS guidelines	Whole-brain CVR mapping (SPM) **Measures:** CVR	Ind

Datasets that overlapped with others reviewed in this article are specified in the last column (Ind, individual study). ACC, anterior cingulate cortex; CVR, cerebrovascular responsiveness; F, female; FSL, FMRIB Software Library; GCS, Glasgow Coma Scale; HC, healthy control; ICCS, International Consensus on Concussion in Sports; M, male; MNI, Montreal Neurological Institute; ROI, region-of-interest; SMC, sensorimotor cortex; SPM, Statistical Parametric Mapping; SRC, sports-related concussion; T1, time 1; T2, time 2; TBI, traumatic brain injury.

postcentral gyri, and lateral or middle occipital gyri (104, 106). One study, however, found no differences in morphometry between TBI and controls groups across time (107). In a supplementary analysis, in which SES was included as a covariate, Dennis et al. (104) additionally found volumetric decreases in the amygdala and middle cerebellar peduncles as well as increased volume in the superior frontal gyrus in those with TBI. In support of the findings of volumetric change over time, Wilde et al. (109) demonstrated cortical thinning in the superior parietal and right paracentral regions and cortical thickening in lateral and medial orbitofrontal regions and in the cingulate of those with TBI (see **Figure 3**).

In a subgroup analysis, Dennis et al. (104) divided patients into TBI-Slow and TBI-Normal groups according to previously determined differences in inter-hemispheric transfer time [IHTT; see (124, 125)]. Over the first year post-injury, relative volume increases were seen in several gray matter regions in the TBI-Slow group, including the superior frontal gyrus, cingulate cortex, superior parietal lobe, parietal operculum, precuneus, cuneus, and inferior occipital gyrus. Decreased volume in several white matter regions was also seen in the TBI-Slow group, including the internal capsule (extending into the right thalamic region) and superior corona radiata. Volumetric changes in the TBI-Normal group, however, were similar to those seen in the healthy control group over the same period of time (see **Figure 4**). After controlling for SES, supplementary subgroup analyses revealed further volumetric decreases in the anterior corona radiata, posterior thalamic radiation, superior temporal gyrus, and precentral gyrus, and further volumetric increases in the inferior frontal and supramarginal gyri of the TBI-Slow group, relative to the healthy controls. In light of these findings, the authors suggest that trajectories of outcome might be divergent, where a subset of patients experienced relatively good recovery, characterized by developmentally-expected decreases in gray matter volume and IHTT rates that are comparable to typically developing children of the same age, whereas the other subset of patients experienced relatively poor recovery, marked by decreased white matter volume, which is reflected in slow IHTT. Although no evidence was found in support of a specific moderator for good or poor recovery trajectories, these findings clearly support a relationship between structural change and functional outcome following pediatric TBI.

Diffusion-Weighted Magnetic Resonance Imaging

Twelve studies assessing longitudinal changes in white matter after pediatric TBI were found (see **Table 3**), and all of them utilized diffusion tensor imaging (DTI) to do so. All studies evaluated children who were injured between the ages of 5–18; two of these studies focused on injuries that occurred during early childhood through pre-adolescence (112, 113), while the remainder focused on children who were injured later. Apart from two studies, where children were evaluated before and after the implementation of an intervention one or more years post-injury (103, 117), all studies enrolled children during the acute or subacute phase of injury and evaluated them again between 3- and 24-months post-injury. Several analytical approaches were used to assess longitudinal change in white matter integrity across these studies: two studies used ROI analysis (106, 114), whole-brain approaches were used by four studies, including tract-based spatial statistics [TBSS; (112, 113, 116)] or fixel-based analysis [FBA; (103)], which was supplemented by ROI analysis and probabilistic tractography. The remaining seven studies used deterministic tractography (107, 108, 110, 111, 115, 117), and one of these studies (117) also implemented graph theoretical analysis to investigate longitudinal differences in structural connectivity between children with TBI and healthy controls following 10-weeks of cognitive training.

Methodology and Outcome Measurement

The most basic of the approaches used is ROI analysis, which involves the quantification of diffusion metrics within a specific

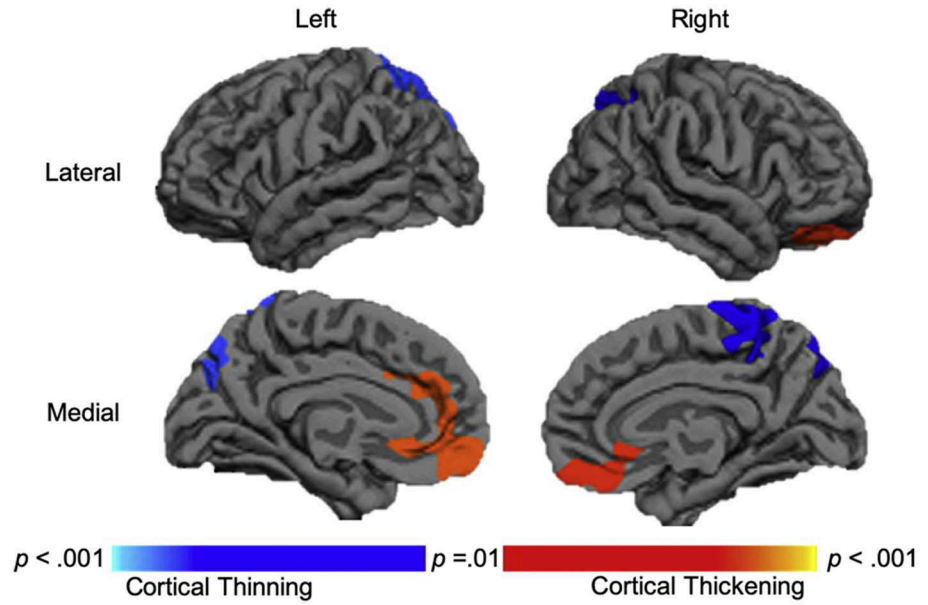

FIGURE 3 | Longitudinal changes in cortical thickness in the traumatic brain injury group relative to the orthopedic injury group. Regions with relative cortical thinning are reflected by blue shading, and regions with relative cortical thickening are reflected by red-orange shading in those with traumatic brain injury over the 3-month to 18-month post-injury interval. Adapted from Wilde et al. (109).

area by extracting the mean parameter of interest from the voxels that fall within that region. As in volumetric analyses, ROI analyses of diffusion data are often used to address an *a priori* hypothesis but can also be used in a whole-brain approach. ROI analysis can be used to measure diffusion properties of both gray and white matter, and it can be sensitive to small changes, particularly if analyses are focused on a specific region that is prone to pathology. TBSS (126) is a whole-brain approach that involves the initial registration of subject data to template space, but this is followed by an additional step where averaged FA values from the major white matter tracts of all subjects are projected onto an alignment-invariant tract representation, called the FA skeleton. FBA is a whole-brain approach used to evaluate the organization of multiple fiber populations, or *fixels* within a single voxel (127). Fixel-based measures, such as fiber cross-section (FC), a measurement of fixel diameter, can identify tracts that are affected by regions with crossing fibers, overcoming this inherent limitation of the diffusion tensor model (128). A more recent approach toward analyzing white matter microstructure is tractography, which is used to reconstruct individual white matter pathways from tensor field data embedded within the underlying voxels. Measures of anisotropy and diffusivity are be sampled from various regions or across the entire reconstructed tract. Tractography has advantages over the other approaches described, majorly due to the fact that it does not necessarily rely on the registration of subject data to template space. Rather, subject data can be analyzed individually, and this allows for the assessment of interindividual differences in white matter pathology that cannot be obtained through whole-brain, voxel-wise approaches toward diffusion data analysis. Finally, tractography can also be used in combination with cortical parcellation maps obtained through morphometric analyses to create structural connectivity maps using graph theory (129). Whole brain structural connectivity can be modeled as a complex structural network and depicted as graphs composed of nodes and edges, where the nodes represent anatomical regions or voxels, and the edges are reflected in white matter fiber bundles representing the structural connectivity between nodes. Graph theory allows for the analysis of complex networks in which multimodal neuroimaging can be used to characterize the topological properties of brain connectivity through commonly used measures of local and global network connectivity, which are described in **Table 1** [for a review, see (130)].

Common diffusion metrics used in tensor-based approaches (i.e., ROI analysis, TBSS, tractography) include fractional anisotropy (FA), apparent diffusion coefficient (ADC, also called mean diffusivity–MD), and axial and radial diffusivity (AD and RD, respectively). FA is highly sensitive to the presence of disorganized white matter; however, it cannot identify specific changes in shape or distribution of the diffusion tensor ellipsoid and should therefore not be considered a biomarker of white matter integrity when interpreted alone (131). ADC/MD reflect the degree of overall diffusion magnitude, and changes in ADC/MD reflect variations in the ratio of intra- to extracellular water concentrations, whereas AD and RD more precisely describe the directional magnitude of diffusion. Variations in ADC/MD in white matter are suggestive of changes in fiber density, axonal diameter, myelination, and neuronal or glial loss, whereas decreased ADC/MD in the gray matter has been

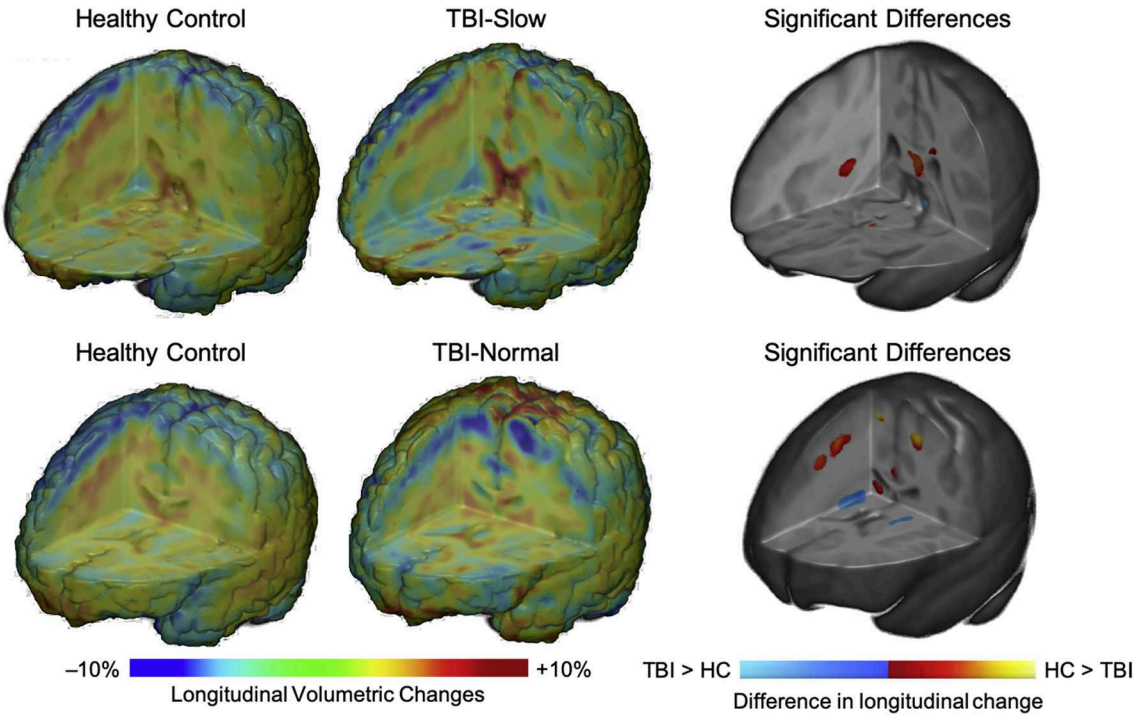

FIGURE 4 | Regional volumetric changes in healthy controls vs. patients with slow interhemispheric transfer time (TBI-Slow) and healthy controls vs. patients with normal interhemispheric transfer time (TBI-Normal) groups. Longitudinal changes in regional volume are shown for healthy controls vs. TBI-Slow (top panel), and healthy controls vs. TBI-Normal (bottom panel). Colors in the group-averaged Jacobian determinants (left and center images) represent the percent of longitudinal volumetric change over a 12-month interval, according to the bottom left color bar. Beta values are overlaid on a minimal deformation template from the healthy controls, demonstrating the difference in longitudinal change, with beta values colored according to the bottom right color bar. Blue areas are those with greater increases in the TBI-Slow or TBI-Normal groups, relative to healthy controls, red-yellow areas are those with greater increases in the healthy controls, relative to the TBI groups. Images are shown in radiologic view (right = left). Adapted from Dennis et al. (104).

attributed to cytotoxic edema. Increases in FA that result from decreases in both AD and RD are suggestive of axonal degeneration (132, 133), whereas decreases in FA resulting from increased RD without change in AD suggests demyelination or Wallerian degeneration (134, 135). When considering brain maturation or recovery, increases in AD accompanied by decreases in RD are suggestive of axonal restoration that is preceded by remyelination, and such processes are often shown to occur with a gradual increase in FA (136, 137), though the specificity of these metrics, and their relation to specific forms of pathology requires additional investigation.

Summary of Longitudinal Findings

Overall, mixed results were seen in terms of longitudinal changes in white matter integrity following pediatric TBI. Mayer et al. (106) conducted a vertex-wise ROI analysis to investigate microstructural changes in gray matter regions. Despite long-term changes in gray matter density (see the summary of sMRI findings), no changes in FA from 3-weeks to 4-months post-injury were seen in the thalamus or hippocampi of the mTBI group, relative to the healthy controls. The authors suggest that these results, albeit inconclusive, might indicate differential time-courses of recovery for FA and gray matter density following pediatric mTBI. In an earlier study conducted on the same sample, Mayer et al. (114) used ROI analysis to investigate diffusion abnormalities in white matter following pediatric mTBI and found significant FA increases between 3-weeks to 4-months post-injury for the mTBI patients, relative to healthy controls, in the genu, body, and splenium of the corpus callosum, the right anterior thalamic radiation, and bilaterally in the superior corona radiata, internal capsules, cingulum bundles, and cerebral peduncles.

Ewing-Cobbs et al. (112) used TBSS to evaluate change in FA, AD, and RD between 3- and 24-months post-injury in younger (∼8 years), middle (∼10 years), or older (∼13.5 years) children at the time of injury. In the sample of children who completed the scans at both time points, a significant increase in FA was seen over time in the left corticospinal tract, where FA was consistently lower in children who sustained a TBI at a younger age, but FA increased at a lesser rate over time in the children who sustained a TBI at an older age. These results suggest that children who are injured at an earlier age recover more quickly than those injured at later ages. Genc et al. (113) used TBSS to address the impact of injury severity on changes in FA and diffusivity over the first 2 years post-injury. Their results demonstrate that injury severity predicts increases in MD of the genu of the corpus callosum, right superior longitudinal fasciculus, retrolenticular internal capsule, and anterior and posterior corona radiata over

time. Injury severity also predicted increased AD in the genu of the corpus callosum and left anterior corona radiata, as well as increased RD in the right posterior corona radiata, although no associated were seen between injury severity and changes in FA of any pathway. In contrast to the results of Ewing-Cobbs et al. (112), longitudinal changes in diffusivity were not moderated by age at injury; however, a positive relationship between age at evaluation and rate of increase in MD, AD, and RD over time was seen. Wilde et al. (116) used TBSS to evaluate changes in FA and ADC of white matter and subcortical structures in pediatric msTBI vs. patients with orthopedic injury over a period of 3- to 18-months post-injury, and their results suggest different rates of change over time across several structures. In the msTBI group, decreased FA occurred along with increased ADC in the anterior temporal white matter, genu of the corpus callosum, and parietal white matter, which suggests continued degeneration in these regions. Decreases in both FA and ADC were seen over time in the frontal and parietal white matter, splenium of the corpus callosum, brainstem, and cerebellum of those with msTBI, which may be attributed to ongoing changes that result from secondary brain injury mechanisms. These findings are compared to those seen in the orthopedic injury group over the same period of time, where general increases in FA and decreases in ADC were seen across the majority of regions, presumably reflecting developmental myelination, which is typical of healthy individuals within this age group.

Using tractography, Van Beek et al. (115) found decreased FA and increased RD in the genu and splenium of the corpus callosum of children with mTBI, relative to controls, over the first 8 months post-injury. These changes occurred along with relatively poorer verbal working memory abilities in the mTBI group, which suggests a deficit in the development of these skills over time, possibly due to the slow maturation of commissural white matter fibers relative to healthy children of the same age. Similar results were seen in a study by Wu et al. (107), where decreases in FA and increases in ADC were seen over the first 3-months post-injury in the splenium and total corpus callosum of adolescents with sports-related concussion compared to those with orthopedic injury and healthy adolescents. A similar examination in a group of children or adolescents with complicated mild-to-severe TBI by Wu et al. (108) revealed increases in ADC of the splenium of the corpus callosum in those with TBI over a period between 3- and 18-months post-injury; however, FA increased at a similar rate across both TBI and orthopedic injury groups during this same period. These findings suggest that while similar rates of maturation occurred over time in the corpus callosum for all participants, some level of atrophy also occurred in this region for those with pediatric TBI relative to controls (see **Figure 5**). Although no significant differences were observed in processing speed abilities of these two groups, a negative relationship between increased ADC in the splenium and decreased processing speed abilities was evident in the TBI group.

The relationship between white matter integrity and processing speed over time is supported by the results of sub-group analyses based on IHTT differences in adolescents with TBI [see (124, 125)]. For example, Dennis et al. (111) found a decline in white matter integrity, marked by increased MD, RD, and AD, in the anterior midbody, posterior midbody, isthmus, and splenium of the corpus callosum, fornix, left cingulum, left arcuate, and bilateral anterior thalamic radiations, inferior fronto-occipital fasciculi, and inferior longitudinal fasciculi in the TBI-Slow group over the first year post-injury; these changes were not seen in the TBI-Normal or healthy control groups (see **Figure 6**). In a different experiment using a subset of the same sample, Dennis et al. (110) used DTI tractography along with MRS to demonstrate that decreases in FA, due to increases in MD and RD, were only present in tracts of the TBI-Slow group. The TBI-Slow group also showed longitudinal abnormalities in metabolic levels of *N*-acetyl aspartate, which is indicative of poorer neuronal health (as discussed in the next section).

Two studies used dMRI to evaluate changes in microstructural integrity in pediatric TBI that occur following a cognitive intervention. Verhelst et al. (103) used a whole-brain FBA approach to assess the effects of restorative cognitive training on white matter integrity in children and adolescents who sustained a TBI at least 12 months prior. Their results indicated no significant differences in FA, MD, or FC in any white matter tracts of interest in the patient group following 8-weeks of participation in an intervention designed to improve attention, working memory, and executive function. In terms of the relationship between structural and functional change following training, however, improvement on a task of verbal working memory was significantly associated with reduced MD in the left superior longitudinal fasciculus, and improvement on a task of visual processing speed was significantly associated with increased FA in a cluster of fixels in the right precentral gyrus. Based on their overall findings, the authors suggest that functional recovery may precede structural recovery, and longer periods of cognitive training may be necessary for underlying structural changes to occur. The results of a similar investigation of network changes in structural connectivity following 10-weeks of attention and executive function training do not fully support this idea, however. Using graph theoretical analysis, Yuan et al. (117) found that initially elevated small-worldness and normalized clustering coefficient were significantly reduced following training in children with TBI, such that small-worldness more closely approximated that of the healthy controls, and these structural changes occurred along with improved performance on measures of attention and executive function. Considering the training-induced reductions in normalized clustering coefficient that were also seen in the TBI group, the authors argue that the network response to the intervention was likely driven by small, local (rather than long-distance) changes in structural connectivity that occurred throughout the network. The resulting reduction in small-worldness suggests that a partial normalization of the balance between segregation and integration throughout the structural network, which is crucial for efficient communication between brain regions, may be triggered by cognitive training several years after pediatric TBI. While the results of these ample intervention studies are not consistent in terms of the extent to which structural changes may occur following a short-term intervention, important clinical implications for the

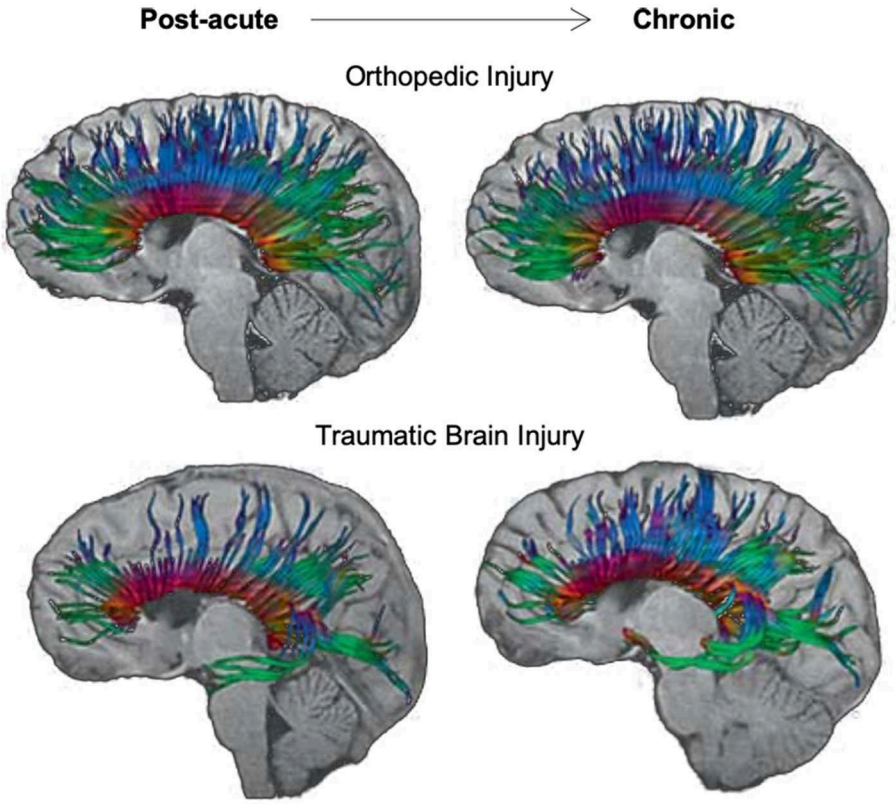

FIGURE 5 | Longitudinal changes in diffusion tensor imaging (DTI) tractography of the corpus callosum in an adolescent with orthopedic injury (OI) vs. an adolescent with moderate traumatic brain injury (TBI). DTI tractography is shown at post-acute (~3 months post-injury) and chronic (~18 months post-injury) periods. The top panel of images reflects the corpus callosum in a 16-year-old male with OI, and the bottom panel of images reflects the corpus callosum in a 15-year-old male with moderate TBI (GCS = 9). Note the subtle atrophy amidst development of the corpus callosum in the adolescent with moderate TBI over time. Adapted from Wu et al. (108).

effectiveness of cognitive rehabilitation long after pediatric TBI are nonetheless demonstrated. The results of these studies shed light on the potential benefit of restorative cognitive training for improving long-term outcome and recovery. However, future research is required to determine whether such effects reliably extend beyond functional restoration and contribute to the reorganization of underlying brain structure following pediatric TBI.

Magnetic Resonance Spectroscopy

Four longitudinal studies (see **Table 4**) used MRS to evaluate changes in metabolic levels following pediatric TBI. Participants were enrolled during the post-acute phase following injury and follow-up visits took place at 4-, 12-, or 18-months after TBIs sustained during childhood or adolescence (age at injury ranging from 4 to 18 years). Several analysis methods exist for MRS, however only two are used in the studies covered in the present review. Two of the four studies (119, 120) implemented multivariate (MV) single slice approaches through an automated spectra quantification method, whereas the other two studies utilized a whole-brain approach (110, 118).

Methodology and Outcome Measurement

MV single slice approaches involve the simultaneous acquisition of multiple spectroscopic voxels arranged in a grid across a predetermined volume of interest (VOI), from which the spectrum of metabolites can be mapped. The MV single slice approach has the advantage of simultaneous assessment of multiple tissues or multiple lesions present in a specified VOI. Furthermore, this approach is capable of showing changes in the composition of metabolites across the included voxels, which allows for good predictive value in determining the margins surrounding a lesion. Due to difficulties that arise in the shimming procedure that is required for the acquisition of a robust metabolic spectrum, the precision of voxels is degraded, and partial volume errors commonly occur. Such disadvantages have led researchers to use other approaches toward analyzing MRS data, and whole-brain approaches have recently been implemented as an alternative. Whole-brain approaches use similar processes as those used in TBM for structural MR data. The Metabolite Imaging and Data Analysis System [MIDAS; (138)] pipeline allows users to generate robust, spectrally fit data from Fourier transform reconstruction and automated spectral fitting. A water-reference MRS dataset is then used

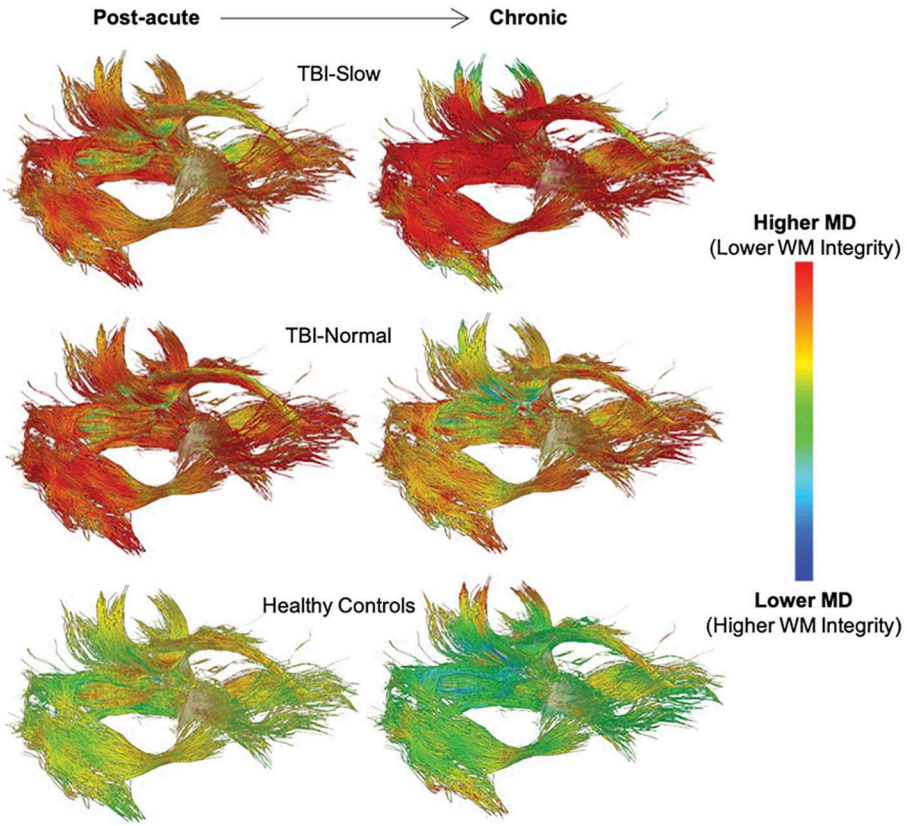

FIGURE 6 | Longitudinal changes in mean diffusivity (MD) along white matter tracts in traumatic brain injury (TBI) patients with slow interhemispheric transfer time (TBI-Slow), TBI patients with normal interhemispheric transfer time (TBI-Normal), and healthy controls. Tract-averaged maps are shown for each group at the post-acute (∼2–5 months post-injury) and chronic (∼13–19 months post-injury) periods, during which time ∼12 months passed. As indicated in the legend, areas with the lowest MD, and therefore the highest white matter integrity, are blue, whereas areas with the highest MD, and therefore the lowest white matter integrity, are red. The healthy controls ($n = 20$) show minimal decreases in MD, while widespread increases in MD are seen in the TBI-Slow group ($n = 11$), and a mixture of these patterns are seen in the TBI-Normal group ($n = 10$). Adapted from Dennis et al. (111).

to calibrate the spectrally fit data before it is normalized and registered to a common template space. This procedure is capable of maintaining the accuracy of the acquired neurochemical concentrations across the entire brain and includes a quality assurance check to correct for CSF partial-volume signal loss, which gives the whole-brain approach an advantage over MV single slice methods.

Key metabolites measured by MRS include *N*-acetyl aspartate (NAA), choline (Cho), creatine (Cr), and lactate. NAA is an amino acid produced by neuronal mitochondria that is believed to be an indicator of neuronal metabolism and integrity. In the developing brain, NAA is involved in myelin synthesis (139). In adults, NAA is involved in axonal repair, thus it is a good marker of axonal or neuronal integrity (140). Decreases in NAA are generally suggestive of neuronal death (141) and have been used as an indicator of disrupted myelin in damaged, developing brains (142). Cho levels are elevated postnatally, but decrease rapidly as the brain matures, and increased levels after birth are suggestive of inflammation, demyelination, or membrane synthesis/repair (140, 142). Both Cr and lactate are markers of energy metabolism. Imbalances in Cr concentration have been seen in mTBI (143, 144) and msTBI (145), although the directional nature is inconsistent in the literature. Furthermore, the causality of this imbalance has not been determined, though it has been suggested that changes in Cr concentrations are related to maintaining various equilibriums in the brain (146). Elevations in lactate, however, have been shown to indicate tissue damage due to ischemia, hypoxia, or inflammation (147). Increased Cho in white matter can result from cellular breakdown from shearing injuries or astrocytosis, suggesting DAI, and decreased NAA is typically the result of axonal damage. Further, an increased ratio of Cho/Cr commonly accompanies subarachnoid hemorrhage (148) and is related to poor long-term outcome after pediatric msTBI (149, 150).

Summary of Longitudinal Findings

Overall, the results of the four MRS studies reviewed here consistently demonstrate subacute decreases in NAA or NAA/Cr with simultaneous increases in Cho or Cho/Cr across white matter, gray matter, and subcortical regions, which likely reflects the primary injury-induced metabolic cascade that reduces the integrity of affected neurons and axons, leading to inflammation

or alterations in membrane metabolism. Likewise, studies consistently demonstrate that the initial metabolic changes generally return to normal levels during the chronic phase of recovery (between 6 and 12 months). Yeo et al. (120) evaluated recovery at 5-, 13-, and 24-weeks post-injury and found that this trajectory of metabolic recovery was only present in the subset of patients who followed up at 24-weeks, and no significant changes had yet occurred in those who followed-up at earlier time points. Similar results were reported by Holshouser et al. (119), where acutely altered metabolic levels returned to normal after 1 year across all gray and white matter regions in patients who had sustained early complicated mTBI or moderate TBI. In the severe TBI group, however, metabolic levels only returned to normal in cortical gray matter regions, whereas NAA/Cr and NAA/Cho ratios remained significantly lower in hemispheric white matter and, to a somewhat lesser extent, in subcortical regions. The authors suggest that these findings may be a reflection of neuroinflammation or an indication of recovery with cellular proliferation. Further investigation revealed that, when considered together, acute subcortical NAA/Cr ratios and length of hospital stay are accurate predictors of long-term neurological and neuropsychological recovery from early TBI ($R^2 = 47.6$) and can be used for the successful classification of TBI with 71.4% sensitivity and 96% specificity.

In addition to supporting the overall recovery of metabolic activity over the first year using a whole-brain approach, Babikian et al. (118) further employed a subgroup analysis in their TBI sample based on IHTT differences [see (124, 125)]. While the TBI-Normal group's metabolic levels of Cho returned to normal levels chronically, NAA levels in the corpus callosum were increased above those of the healthy control group, supporting a relationship between the recovery of metabolic activity in the commissural white matter and faster IHTT. In contrast, metabolic levels in the TBI-Slow group, who suffer from significantly slower IHTT, did not recover over a period of 3- to 18-month post-injury. Rather, the TBI-Slow group was shown to have lower levels of Cho globally and lower levels of NAA in the corpus callosum, relative to the TBI-Normal group. These findings suggest that the acute metabolic abnormalities, reflective of initial neuronal loss and impaired oligodendrocyte/myelin function, do not recover over time in those with functional impairments evidenced by slower IHTT; furthermore, the lower levels of Cho longitudinally in this group suggest a lack of ongoing membrane repair. These results are extended by Dennis et al. (110), who used multimodal MRI imaging to investigate the relationship between long-term metabolic differences in relation to white matter microstructure between the same IHTT subgroups of this pediatric TBI sample. Using MRS in combination with DTI tractography, the authors replicated the previous findings of Babikian et al. (118), but extended them by demonstrating that the specific white matter pathways with lower NAA in the TBI-Slow group also showed lower FA resulting from higher MD and/or RD, which is indicative of demyelination (134, 135). Such findings highlight the utility of multi-modal investigations of recovery from early TBI.

Functional Magnetic Resonance Imaging

Currently, only two longitudinal fMRI studies have been published in the pediatric TBI literature (see **Table 5**). Both studies investigated adolescents who were injured around four months prior to the initial visit, and follow-up visits occurred around 8- or 16-months post-injury. Cazalis et al. (121) implemented a spatial working memory paradigm in their task-based fMRI analysis of 6 adolescents with complicated mild-to-severe injuries, whereas Mutch et al. (122) used CO_2 stress testing and fMRI to assess whole-brain CVR in 6 adolescents with mild SRC relative to 24 healthy individuals between the ages of 13 and 25.

Methodology and Outcome Measurement

Functional MRI measures signal variations in the blood-oxygen-level-dependent (BOLD) hemodynamic response, which indicates active regions of the brain during task-based fMRI paradigms. Basic task-based fMRI designs include block and event-related designs. Block designs involve the constant presentation of some stimulus or task during a specific block of time, followed by a period of rest; this pattern is repeated several times in an alternating fashion. Event-related designs are similar, but the stimulus or task occurs at random intervals and varies in the duration of presentation time. While block designs are more powerful, event-related designs are more flexible and more sensitive to the shape of the hemodynamic response; for this reason, event-related designs are more commonly used in the present literature. Impairments in the system involved in the control and regulation of cerebral blood flow have been noted in TBI (151), and any change in cerebral blood flow in response to a vasodilatory stimulus, or cerebrovascular responsiveness (CVR), can be used to measure the functional status of this system (152, 153). Recent work by Mutch et al. (154) has led to the development of MR-based CO_2 stress testing, in which CO_2, a quantifiable and reliable vasoactive stimulus (155), is administered during BOLD fMRI, allowing for the standardized measurement of CVR longitudinally.

Summary of Longitudinal Findings

In line with the results of the majority of the studies using other imaging modalities that have been covered in this review, studies using fMRI have found general patterns of normalization in brain function over the course of time following pediatric TBI, although several factors appear to be involved in the degree and extent to which recovery occurs. Using task-based fMRI, Cazalis et al. (121) found that as patients with complicated mild-to-severe TBI progressed into the chronic phase of recovery, a partial normalization of acutely increased anterior cingulate cortex activity occurred along with a simultaneous increase in left sensorimotor cortex activity during participation in a difficult working memory task, which better represented the activations patterns seen in the healthy adolescents at the initial visit. These longitudinal changes in brain activity in the patients with TBI were accompanied by improvements in processing speed, although no improvements were seen in working memory ability. It is important to note that covarying for task performance is recommended if it differs between groups. Following an in-depth

discussion of conflicting models in the literature for the role of the anterior cingulate cortex after pediatric msTBI, the authors suggest that, based on the results of their study, the anterior cingulate cortex may play a compensatory role in recovery from pediatric TBI, where it is recruited when the executive system is overloaded during participation in a difficult task or when structural disconnection has occurred.

In their longitudinal investigation of whole-brain CVR following SRC, Mutch et al. (122) found predominantly increased patterns of CVR in the subacute phase; however, during the chronic phase, significantly decreased levels of CVR were seen in all adolescents with SRC, relative to healthy individuals. Interestingly, a stable pattern of decreased CVR was seen in two patients with chronic vestibulo-ocular and psychiatric symptoms, whereas slight improvements, that nevertheless remained persistently abnormal relative to healthy individuals, were seen in the remaining four patients, who either fully recovered or demonstrated relatively mild post-concussive symptomology. The findings of this pilot study highlight the potential utility of CVR as a marker of long-term recovery from SRC, in which the stability of CVR patterns during the chronic phase may be indicative of the degree of recovery that has occurred.

Methodological Considerations

A major challenge in studying the changes in brain structure following injury is characterizing how damage to pathway microstructure evolves over time and interacts with ongoing developmental changes. Unmyelinated axons are highly vulnerable to injury, and the rapid, ongoing myelination of most pathways may confer particular vulnerability when injury is sustained during the early stages of development (112). Age at the time of the injury and the amount of time that has elapsed post-injury interact, complicating the changing trajectories of anisotropy and diffusion. The trajectory of change over time must be compared to what is expected at different developmental stages, thus longitudinal studies are necessary to emphasize the dynamic and disruptive interplay of early brain injury and the subsequent development of neuronal processes, such as axonal thinning and increased myelination (19). Due to the initial increase and subsequent decrease in gray matter volume and the steady increase in white matter maturation that occurs during typical brain development across childhood and adolescence, the interpretation of longitudinal structural and functional changes after pediatric TBI is inherently more complex than that of recovery from adult TBI (156, 157). Care must be taken to ensure that appropriate factors, such as age at injury, age at enrollment, sex, time-since injury, and scan interval are considered in the longitudinal analysis of structural brain changes; differences in intracranial volume (ICV) are also necessary to control for when assessing morphometric changes. While all sMRI studies included ICV as a covariate, none of the 20 studies presently reviewed controlled for the effects of time-since-injury in their analyses. The effects of age at the time of injury were controlled for in one study (112), the effects of age at the time of enrollment were controlled for in six studies (103, 104, 110, 111, 113, 119), the effects of sex were controlled for in four studies (104, 110, 111, 113), and the effects of scan interval were controlled for in two studies (104, 111).

In addition to the necessity of controlling for the factors specified above, it is necessary that data is collected regarding other factors known to influence recovery and quantitative neuroimaging, *per se*; in particular, detailed documentation of SES, injury severity classification, mechanism of injury, and lesion characteristics for primary injuries found on initial neuroimaging should be obtained and reported when publishing pediatric TBI research. Although racial or ethnic background was not discussed as a factor influencing outcome, epidemiological studies suggest that disparities exist in the prevalence, severity, and mechanism of injuries sustained by children from different racial or ethnic groups. According to these studies, African American, Hispanic, and Native American children are more likely to be hit by motorized vehicle as a pedestrian or cyclist, experience msTBI, and have higher rates of mortality than Caucasian children, regardless of SES (158–160). For reasons such as these, it is important to report the racial or ethnic distribution of pediatric TBI samples in research (refer to the **Supplementary Material** for details regarding the reporting of such information in the included studies). While eleven studies included a measure of SES [e.g., parental education or SES composite indices; (104–109, 112–114, 116, 118)], two of these studies did not include SES results in their sample description (104, 107); however both studies reported no differences between SES of their TBI and control samples. The distribution of various injury mechanisms were reported for the pediatric TBI sample and orthopedic injury samples in all but four studies (117, 118, 120, 121), and specific information regarding the abnormal results found on day-of-injury neuroimaging was reported by all but eight studies (107–109, 115, 117–119). Additionally, one study reported complications seen on susceptibility weighted-imaging obtained at the initial evaluation, which occurred at least 12-months post-injury (103). While all studies provided the criteria used to classify injury severity, six studies did not comprehensively report the results of the measures (i.e., descriptive statistics) used to determine the injury severity in their pediatric TBI or SRC samples (103, 106, 107, 114, 115, 122). Finally, of the twenty longitudinal studies presently reviewed, only five provided information regarding the racial or ethnic distribution of their samples (108, 109, 112, 116, 117).

Several other methodological considerations must be addressed among the studies included the present review. In a field that often publishes findings from studies with small sample size, it is important that sample characteristics are reported in adequate detail so that meta-analytic studies can be performed, and meaningful results can be derived from the published data. Detailed descriptive statistics for all demographic characteristics across all samples, and for the injury characteristics of the injured samples, must be provided; this is especially true of longitudinal studies in children, in which attrition often leads to non-random differences in sample characteristics between initial and follow-up evaluations and samples continue to develop over time (known as "attrition bias"). For example, SES (including both educational and occupational attainment, level of income, and social class) has been cited as a contributing factor for

continued participation in long-term studies generally (161, 162) and in studies of pediatric TBI in particular (163). In studies of children, complex health, motivational, and lifestyle factors for both parent and child may also affect continued participation, and these factors may or may not change over long follow-up periods (162). Estimates of attrition are variably reported, but non-imaging studies of pediatric TBI have reported attrition estimates that range from 20% to over 60% (164–166).

Small sample sizes, the failure to report sufficient descriptive statistics, and attrition rates are sources of potential bias that may threaten internal and external validity, and necessary steps to avoid them must be undertaken during study design and data collection in future longitudinal research. Additionally, it is recommended that effect sizes and confidence intervals are reported along with *p*-values, as statistically significant differences are often misleading when reported alone (167), especially in underpowered studies, such as those with small sample sizes. Of the twenty longitudinal studies reviewed here, only eight provided detailed sample information, including sample size, sex distribution, and age-at-follow up visits (104, 109–111, 114–116, 121). While one study provided great detail on the sample characteristics of their longitudinal sample in their **Supplementary Material**, age at evaluation was not provided at the initial or follow-up visits (112). While all studies provided an approximate time interval between injury and MRI for the initial and follow-up visits, five studies did not specify details regarding average time-since-injury intervals for their pediatric TBI samples at the initial and/or follow-up visits (103–105, 111, 117). Finally, half of the studies reviewed presently included some measure of effect size with their results (103, 104, 106–108, 112–114, 117, 119).

It is important to note that, while these methodological considerations are meant to address areas that could be improved in future research, the studies included in this review are the first and only to address longitudinal outcome after pediatric TBI from a neuroimaging perspective and must be applauded for doing so. Furthermore, all of the studies reviewed here that included clinical assessments of neuropsychological or functional outcome included one or more measures recommended as basic or supplemental Common Data Elements (CDEs) by the Pediatric TBI Outcomes Working Group [see (168)]. The working groups within the TBI CDE project also suggest standardized reporting of MR image acquisition parameters (169), and all but four studies provided sufficient detail in this regard (refer to **Supplementary Material** for details).

GAPS IN THE LITERATURE

As reviewed in this paper, there have been a small number of studies published to date using neuroimaging to examine longitudinal changes after TBI in pediatric patients. Existing studies generally reveal dynamic changes in the months and years post-injury, but additional studies are needed to more comprehensively examine factors that may influence outcome. Severity plays an important role in outcome prediction but does not fully explain outcome heterogeneity. Additionally, the longitudinal neuroimaging studies that have been published to date are limited to investigations of pediatric TBI populations with injuries sustained no earlier than the early childhood stage of development (ages 4–6), which is likely due to difficulties associated with scanning infants and toddlers. The literature would greatly benefit from investigations of children who sustained accidental injuries at younger ages, however, and current efforts to develop multi-step procedures that ensure the comfort of young children in the MRI environment [see (170)]. The body of literature in this area is small but becomes even smaller when we consider how many individual cohorts have been examined: the tables included in this review indicate that 20 articles on 13 longitudinal cohorts have been published to date. There are a number of gaps in the literature that we hope will be addressed in the coming years.

Small sample size is the primary limitation of most neuroimaging studies of pediatric TBI. This substantially limits the ability of researchers to identify potential moderators of outcome. While the literature reviewed here suggests an effect of factors such as age, sex, and SES on outcome, these need to be examined in larger cohorts for reliability, and sources of attrition bias need to be carefully examined, disclosed and corrected for, particularly where there is a loss-to-follow up rate >20% (163, 171) or where the follow-up period is particularly long, as a relation between attrition and length of the study follow-up has been demonstrated (163). Large samples will allow for machine learning approaches to cluster demographic, clinical, and imaging variables and may reveal sub-populations within the larger patient population. There may be patterns of brain structural and functional disruption that are associated with particular cognitive, psychological, or somatic complaints. This has important implications for treatment and may help identify patients in need of more targeted treatment. The large amount of unexplained heterogeneity in post-injury outcome is a key gap in the field. There are also important outcomes that are relatively unexplored. Secondary psychiatric disorders are common post-injury but there have been very few investigations linking these to altered brain structure and function (172).

It is important to note that what constitutes an optimal comparison group for children with TBI remains an area of controversy within the field. While samples of healthy, typically-developing children are the most frequently utilized comparison group, some have argued that the use of such a comparison group fails to account for TBI-related risk factors, including predisposing neurobehavioral characteristics, such as attention-deficit/hyperactivity disorder (173) and associated impulsivity, risk-taking behavior, and substance use (174), or non-specific effects of traumatic injury, like posttraumatic stress (175, 176). Additionally, factors that may influence cognitive and functional assessment, including stress, pain, and medication effects, as well as prolonged absences from school are also not well-accounted for in TBI-related studies that use healthy comparison groups. Alternatively, other pediatric TBI studies have included children with extra-cranial or orthopedic injuries as a comparison group to account for some of the factors associated with the use of healthy children. In a recent DTI study of adolescents and

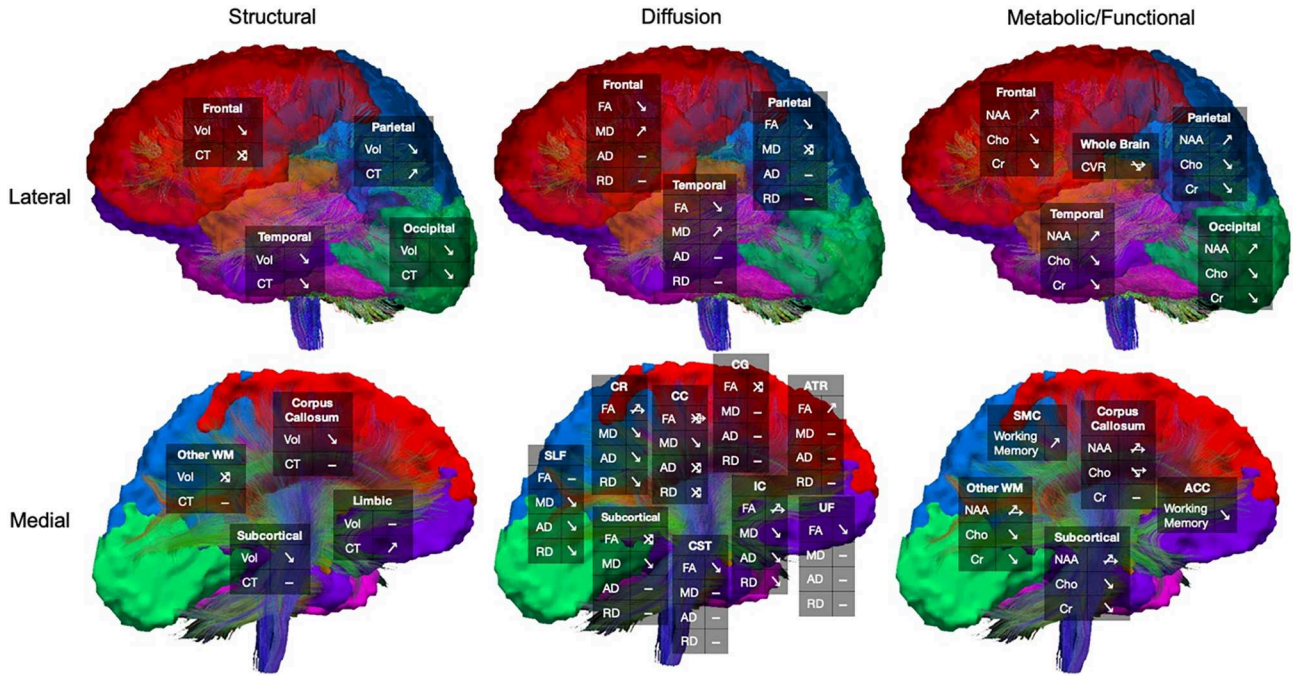

FIGURE 7 | Summary of longitudinal changes in pediatric traumatic brain injury (TBI) across magnetic resonance-based neuroimaging modalities. Results are organized according to general brain region or white matter pathway. Arrows reflect changes in TBI group over time (increase, decrease, or no change). Mixed changes across the TBI group, or mixed results reported across studies, are reflected in crossed arrows. Dashes indicate no reported differences. ACC, anterior cingulate cortex; AD, axial diffusivity; ATR, anterior thalamic radiation; CC, corpus callosum; CG, cingulum; Cho, choline; CR, corona radiata; Cr, creatine; CST, corticospinal tract; CT, cortical thickness; FA, fractional anisotropy; IC, internal capsule; MD, mean diffusivity (includes ADC results); NAA, *N*-acetyl aspartate; RD, radial diffusivity; SLF, superior longitudinal fasciculus; SMC, sensorimotor cortex; TBI, traumatic brain injury; UF, uncinate fasciculus; Vol, volume; WM, white matter.

young adults with mTBI (177), both typically-developing and orthopedically injured persons were included in comparison groups. Interestingly, the results of this study revealed that, relative to the typically-developing comparison group, both of the traumatically injured patient groups demonstrated similar patterns of altered white matter integrity at subacute and chronic post-injury periods, regardless of whether the injuries sustained occurred to the head. While acknowledging the strengths and limitations of each group, the authors conclude that the selection of a single comparison group may contribute to the inconsistency in dMRI findings reported in the literature. Wilde et al. (177) suggest that conclusions drawn from studies utilizing a typically-developing comparison group may be different if the studies had instead included an orthopedically-injured comparison group and therefore recommend the use of both comparison groups, if possible; however, further investigation of this issue is clearly warranted.

Advanced imaging methods and multi-modal approaches have the potential to yield important new information. Diffusion MRI is one of the most commonly used modalities in TBI neuroimaging studies, but DTI has a number of limitations. Crossing fibers can lead to inaccurate diffusion calculations when a single tensor model is used. Higher angular resolution partially addresses this, but more advanced modeling allowing for multiple fiber orientations within a voxel is also necessary. Multi-shell diffusion MRI sequences permits researchers to model both intracellular and extracellular diffusion, leading to more accurate modeling and allows for measurements of neurite density and orientation dispersion (178).

CONCLUSIONS

Here we review longitudinal neuroimaging studies of pediatric traumatic brain injury. See **Figure 7** for a summary of the results of all longitudinal neuroimaging studies. While there is considerable heterogeneity in post-injury outcome, the literature consistently shows that alterations in brain structure, function, and metabolism can persist for an extended period of time post-injury. Longitudinal studies are particularly important for assessing changes in a developing sample, but small sample sizes have limited most studies to date. With larger sample sizes and multi-site cooperation, future studies will be able to examine potential moderators of outcome, such as the quality of the pre-injury environment, and may identify clinically meaningful patient subtypes.

AUTHOR CONTRIBUTIONS

HL, EW, KC, and ED contributed the conception and design of the review. HL reviewed the literature for relevant articles to include and wrote the first draft of the manuscript. EW, ED, and KC wrote sections of the

manuscript. All authors contributed to the revision of the manuscript, and all authors read and approved the final submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.01296/full#supplementary-material

REFERENCES

1. Center for Disease Control and Prevention. *Report to Congress: The Management of Traumatic Brain Injury in Children*. Atlanta, GA: National Center for Injury Prevention and Control, Division of Unintentional Injury Prevention (2018).
2. Cunningham RM, Walton MA, Carter PM. The major causes of death in children and adolescents in the United States. *N Engl J Med.* (2018) 379:2468–75. doi: 10.1056/NEJMsr1804754
3. Taylor CA, Bell JM, Breiding MJ, Xu L. Traumatic brain injury–related emergency department visits, hospitalizations, and deaths — United States, 2007 and 2013. *MMWR Surveill Summar.* (2017) 66:1–16. doi: 10.15585/mmwr.ss6609a1
4. Daneshvar DH, Riley DO, Nowinski CJ, McKee AC, Stern RA, Cantu RC. Long-term consequences: effects on normal development profile after concussion. *Phys Med Rehabil Clin N Am.* (2011) 22:683–700. doi: 10.1016/j.pmr.2011.08.009
5. Giza CC, Prins ML. Is being plastic fantastic? Mechanisms of altered plasticity after developmental traumatic brain injury. *Dev Neurosci.* (2006) 28:364–79. doi: 10.1159/000094163
6. Königs M, van Heurn LWE, Bakx R, Vermeulen RJ, Goslings JC, Poll-The BT, et al. The structural connectome of children with traumatic brain injury. *Hum Brain Mapp.* (2017) 38:3603–14. doi: 10.1002/hbm.23614
7. Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, et al. Dynamic mapping of human cortical development during childhood through early adulthood. *Proc Natl Acad Sci USA.* (2004) 101:8174–9. doi: 10.1073/pnas.0402680101
8. Sowell ER, Thompson PM, Leonard CM, Welcome SE, Kan E, Toga AW. Longitudinal mapping of cortical thickness and brain growth in normal children. *J Neurosci.* (2004) 24:8223–31. doi: 10.1523/JNEUROSCI.1798-04.2004
9. Bigler ED. Anterior and middle cranial fossa in traumatic brain injury: relevant neuroanatomy and neuropathology in the study of neuropsychological outcome. *Neuropsychology.* (2007) 21:515–31. doi: 10.1037/0894-4105.21.5.515
10. Ganesalingam K, Yeates KO, Taylor HG, Walz NC, Stancin T, Wade S. Executive functions and social competence in young children 6 months following traumatic brain injury. *Neuropsychology.* (2011) 25:466–76. doi: 10.1037/a0022768
11. Lipszyc J, Levin H, Hanten G, Hunter J, Dennis M, Schachar R. Frontal white matter damage impairs response inhibition in children following traumatic brain injury. *Arch Clin Neuropsychol.* (2014) 29:289–99. doi: 10.1093/arclin/acu004
12. Lindsey HM, Lalani SJ, Mietchen J, Gale SD, Wilde EA, Faber J, et al. Acute pediatric traumatic brain injury severity predicts long-term verbal memory performance through suppression by white matter integrity on diffusion tensor imaging. *Brain Imaging Behav.* (2019). doi: 10.1007/s11682-019-00093-9. [Epub ahead of print].
13. Spitz G, Alway Y, Gould KR, Ponsford JL. Disrupted white matter microstructure and mood disorders after traumatic brain injury. *J Neurotrauma.* (2017) 34:807–15. doi: 10.1089/neu.2016.4527
14. Ryan NP, Reyes J, Crossley L, Beauchamp MH, Catroppa C, Anderson VA. Unraveling the association between pediatric traumatic brain injury and social dysfunction: the mediating role of self-regulation. *J Neurotrauma.* (2019) 36:2895–903. doi: 10.1089/neu.2018.6308
15. Degeilh F, Bernier A, Gravel J, Beauchamp MH. Developmental trajectories of adaptive functioning following early mild traumatic brain injury. *Dev Psychobiol.* (2018) 60:1037–47. doi: 10.1002/dev.21786
16. Anderson V, Godfrey C, Rosenfeld JV, Catroppa C. Predictors of cognitive function and recovery 10 years after traumatic brain injury in young children. *Pediatrics*. (2012) 129:e254–61. doi: 10.1542/peds.2011-0311
17. Anderson V, Spencer-Smith M, Wood A. Do children really recover better? Neurobehavioural plasticity after early brain insult. *Brain.* (2011) 134(Pt 8), 2197–2221. doi: 10.1093/brain/awr103
18. Ashwal S, Tong KA, Ghosh N, Bartnik-Olson B, Holshouser BA. Application of advanced neuroimaging modalities in pediatric traumatic brain injury. *J Child Neurol.* (2014) 29:1704–17. doi: 10.1177/0883073814538504
19. Bigler ED. Traumatic brain injury, neuroimaging, and neurodegeneration. *Front Hum Neurosci.* (2013) 7:395. doi: 10.3389/fnhum.2013.00395
20. Blackman JA, Rice SA, Matsumoto JA, Conaway MR, Elgin KM, Patrick PD, et al. Brain imaging as a predictor of early functional outcome following traumatic brain injury in children, adolescents, and young adults. *J Head Trauma Rehabil.* (2003) 18:493–503. doi: 10.1097/00001199-200311000-00003
21. Oni MB, Wilde EA, Bigler ED, McCauley SR, Wu TC, Yallampalli R, et al. Diffusion tensor imaging analysis of frontal lobes in pediatric traumatic brain injury. *J Child Neurol.* (2010) 25:976–84. doi: 10.1177/0883073809356034
22. Roberts RM, Mathias JL, Rose SE. Diffusion tensor imaging (DTI) findings following pediatric non-penetrating TBI: a meta-analysis. *Dev Neuropsychol.* (2014) 39:600–37. doi: 10.1080/87565641.2014.973958
23. Ashwal S, Holshouser BA, Tong KA. Use of advanced neuroimaging techniques in the evaluation of pediatric traumatic brain injury. *Dev Neurosci.* (2006) 28:309–26. doi: 10.1159/000094157
24. Niogi SN, Mukherjee P. Diffusion tensor imaging of mild traumatic brain injury. *J Head Trauma Rehabil.* (2010) 25:241–55. doi: 10.1097/htr.0b013e3181e52c2a
25. Catroppa C, Godfrey C, Rosenfeld JV, Hearps SS, Anderson VA. Functional recovery ten years after pediatric traumatic brain injury: outcomes and predictors. *J Neurotrauma.* (2012) 29:2539–47. doi: 10.1089/neu.2012.2403
26. Ryan NP, Noone K, Godfrey C, Botchway EN, Catroppa C, Anderson V. Young adults' perspectives on health-related quality of life after paediatric traumatic brain injury: a prospective cohort study. *Ann Phys Rehabil Med.* (2019) 62:342–50. doi: 10.1016/j.rehab.2019.06.014
27. Dennis EL, Babikian T, Giza CC, Thompson PM, Asarnow RF. Neuroimaging of the injured pediatric brain: methods and new lessons. *Neuroscientist.* (2018) 24:652–70. doi: 10.1177/1073858418759489
28. King DJ, Ellis KR, Seri S, Wood AG. A systematic review of cross-sectional differences and longitudinal changes to the morphometry of the brain following paediatric traumatic brain injury. *Neuroimage Clin.* (2019) 23:101844. doi: 10.1016/j.nicl.2019.101844
29. Dennis EL, Babikian T, Giza CC, Thompson PM, Asarnow RF. Diffusion MRI in pediatric brain injury. *Childs Nerv Syst.* (2017) 33:1683–92. doi: 10.1007/s00381-017-3522-y
30. Giza CC, Mink RB, Madikians A. Pediatric traumatic brain injury: not just little adults. *Curr Opin Crit Care.* (2007) 32:143–52. doi: 10.1097/MCC.0b013e32808255dc

31. Keenan HT, Bratton SL. Epidemiology and outcomes of pediatric traumatic brain injury. *Dev Neurosci.* (2006) 28:256–63. doi: 10.1159/000094152
32. Reitan RM, Wolfson D. *Traumatic Brain Injury: Pathophysiology and Neuropsychological Evaluation.* Tucson, AZ: Neuropsychology Press (1986).
33. Anderson V, Catroppa C, Morse S, Haritou F, Rosenfeld J. Functional plasticity or vulnerability after early brain injury? *Pediatrics.* (2005) 116:1374–82. doi: 10.1542/peds.2004-1728
34. Chapman SB, McKinnon L. Discussion of developmental plasticity. *J Commun Disord.* (2000) 33:333–44. doi: 10.1016/s0021-9924(00)00029-0
35. Howarth RA, Blackwell LS, Ono KE. Acute and long-term outcomes following pediatric traumatic brain injury. *J Pediatr Neuroradiol.* (2016) 5:26–31. doi: 10.1055/s-0036-1584285t
36. Wilde EA, Hunter, Bigler ED. Pediatric traumatic brain injury: neuroimaging and neurorehabilitation outcome. *NeuroRehabilitation.* (2012) 31:245–60. doi: 10.3233/nre-2012-0794
37. Chaudhury S, Sharma V, Kumar V, Nag TC, Wadhwa S. Activity-dependent synaptic plasticity modulates the critical phase of brain development. *Brain Dev.* (2016) 38:355–63. doi: 10.1016/j.braindev.2015.10.008
38. Kadis DS, Iida K, Kerr EN, Logan WJ, McAndrews MP, Ochi A, et al. Intrahemispheric reorganization of language in children with medically intractable epilepsy of the left hemisphere. *J Int Neuropsychol Soc.* (2007) 13:94–101. doi: 10.1017/s1355617707070397
39. Johnston MV. Plasticity in the developing brain: implications for rehabilitation. *Dev Disabil Res Rev.* (2009) 15:94–101. doi: 10.1002/ddrr.64
40. Johnston MV, Ishida A, Ishida WN, Matsushita HB, Nishimura A, Tsuji M. Plasticity and injury in the developing brain. *Brain Dev.* (2009) 31:1–10. doi: 10.1016/j.braindev.2008.03.014
41. Kennard MA. Reorganization of motor function in the cerebral cortex of monkeys deprived of motor and premotor areas in infancy. *J Neurophysiol.* (1938) 1:477–96.
42. Taylor HG, Alden J. Age-related differences in outcomes following childhood brain insults: an introduction and overview. *J Int Neuropsychol Soc.* (1997) 3:555–67.
43. Verger K, Junque C, Jurado MA, Tresserras P, Bartumeus F, Nogues P, et al. Age effects on long-term neuropsychological outcome in paediatric traumatic brain injury. *Brain Inj.* (2000) 14:495–503. doi: 10.1080/026990500120411
44. Anderson V, Spencer-Smith M, Leventer R, Coleman L, Anderson P, Williams J, et al. Childhood brain insult: can age at insult help us predict outcome? *Brain.* (2009) 132(Pt 1):45–56. doi: 10.1093/brain/awn293
45. Krasny-Pacini A, Chevignard M, Lancien S, Escolano S, Laurent-Vannier A, De Agostini M, et al. Executive function after severe childhood traumatic brain injury – Age-at-injury vulnerability periods: the TGE prospective longitudinal study. *Ann Phys Rehabil Med.* (2017) 60:74–82. doi: 10.1016/j.rehab.2016.06.001
46. Fuhrmann D, Knoll LJ, Blakemore SJ. Adolescence as a sensitive period of brain development. *Trends Cogn Sci.* (2015) 19:558–66. doi: 10.1016/j.tics.2015.07.008
47. Crowe LM, Catroppa C, Babl FE, Rosenfeld JV, Anderson V. Timing of traumatic brain injury in childhood and intellectual outcome. *J Pediatr Psychol.* (2012) 37:745–54. doi: 10.1093/jpepsy/jss070
48. Hebb DO. *The Organization of Behavior.* New York, NY: McGraw-Hill (1949).
49. Pascual-Leone A, Amedi A, Fregni F, Merabet LB. The plastic human brain cortex. *Annu Rev Neurosci.* (2005) 28:377–401. doi: 10.1146/annurev.neuro.27.070203.144216
50. Anderson V, Moore C. Age at injury as a predictor of outcome following pediatric head injury: a longitudinal perspective. *Child Neuropsychol.* (1995) 3:187–202.
51. Dennis M, Barnes M. Developmental aspects of neuropsychology. In: Zaidel DW, editor. *Neuropsychology.* Cambridge, MA: Academic Press (1994). p. 219–46.
52. Ewing-Cobbs L, Miner ME, Fletcher JM, Levin HS. Intellectual, motor, and language sequelae following closed head injury in infants and preschoolers. *J. Pediatr. Psychol.* (1989) 14:531–47. doi: 10.1093/jpepsy/14.4.531
53. Anderson V, Catroppa C. Recovery of executive skills following paediatric traumatic brain injury (TBI): A 2 year follow-up. *Brain Inj.* (2005) 19:459–70. doi: 10.1080/02699050400004823
54. Feldman HM, Holland AL, Kemp SS, Janosky JE. Language development after unilateral brain injury. *Brain Lang.* (1992) 42:89–102. doi: 10.1016/0093-934x(92)90058-m
55. Stiles J, Thal D. Linguistic and spatial cognitive development following early focal brain injury: patterns of deficit and recovery. In: Reader MH, editor. *Brain Development and Cognition.* Cambridge, MA: Blackwell (1993). p. 643–64.
56. Eslinger PJ, Biddle K, Pennington B, Page RB. Cognitive and behavioral development up to 4 years after early right frontal lobe lesion. *Dev Neuropsychol.* (1999) 15:157–91. doi: 10.1080/87565649909540744
57. Martin C, Falcone RA Jr. Pediatric traumatic brain injury: an update of research to understand and improve outcomes. *Curr Opin Pediatr.* (2008) 20:294–9. doi: 10.1097/MOP.0b013e3282ff0dfa
58. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet.* (1974) 2:81–4. doi: 10.1016/s0140-6736(74)91639-0
59. Simpson D, Reilly P. Pediatric coma scale. *Lancet.* (1982) 2:450. doi: 10.1016/s0140-6736(82)90486-x
60. Bigler ED, Jantz PB, Farrer TJ, Abildskov TJ, Dennis M, Gerhardt CA, et al. Day of injury CT and late MRI findings: cognitive outcome in a paediatric sample with complicated mild traumatic brain injury. *Brain Inj.* (2015) 29:1062–70. doi: 10.3109/02699052.2015.1011234
61. Bigler ED, Yeates KO, Dennis M, Gerhardt CA, Rubin KH, Stancin T, et al. Neuroimaging and social behavior in children after traumatic brain injury: findings from the Social Outcomes of Brain Injury in Kids (SOBIK) study. *NeuroRehabilitation.* (2013) 32:707–20. doi: 10.3233/NRE-130896
62. Rivara FP, Koepsell TD, Wang J, Temkin N, Dorsch A, Vavilala MS, et al. Disability 3, 12, and 24 months after traumatic brain injury among children and adolescents. *Pediatrics.* (2011) 128:e1129–38. doi: 10.1542/peds.2011-0840
63. Babikian T, Asarnow R. Neurocognitive outcomes and recovery after pediatric TBI: meta-analytic review of the literature. *Neuropsychology.* (2009) 23:283–96. doi: 10.1037/a0015268
64. Anderson V, Godfrey C, Rosenfeld JV, Catroppa C. 10 years outcome from childhood traumatic brain injury. *Int J Dev Neurosci.* (2012) 30:217–24. doi: 10.1016/j.ijdevneu.2011.09.008
65. Eierud C, Craddock RC, Fletcher S, Aulakh M, King-Casas B, Kuehl D, et al. Neuroimaging after mild traumatic brain injury: review and meta-analysis. *Neuroimage Clin.* (2014) 4:283–94. doi: 10.1016/j.nicl.2013.12.009
66. Catroppa C, Anderson V, Ditchfield M, Coleman L. Using magnetic resonance imaging to predict new learning outcome at 5 years after childhood traumatic brain injury. *J Child Neurol.* (2008) 23:486–96. doi: 10.1177/0883073807309773
67. Aram DM, Eisele JA. Intellectual stability in children with unilateral brain lesions. *Neuropsychologia.* (1994) 32:85–95. doi: 10.1016/0028-3932(94)90071-x
68. Levin HS, Zhang L, Dennis M, Ewing-Cobbs L, Schachar R, Max J, et al. Psychosocial outcome of TBI in children with unilateral frontal lesions. *J Int Neuropsychol Soc.* (2004) 10:305–16. doi: 10.1017/s1355617704102129
69. Anderson DP, Harvey AS, Saling MM, Anderson V, Kean M, Abbott DF, et al. FMRI lateralization of expressive language in children with cerebral lesions. *Epilepsia.* (2006) 47:998–1008. doi: 10.1111/j.1528-1167.2006.00572.x
70. Anderson SW, Damasio H, Tranel D, Damasio AR. Long-term sequelae of prefrontal cortex damage acquired in early childhood. *Dev Neuropsychol.* (2000) 18:281–96. doi: 10.1207/s1532694202anderson
71. Eslinger PJ, Biddle KR. Adolescent neuropsychological development after early right prefrontal cortex damage. *Dev Neuropsychol.* (2000) 18:297–329. doi: 10.1207/s1532694203eslinger
72. Power T, Catroppa C, Coleman L, Ditchfield M, Anderson V. Do lesion site and severity predict deficits in attentional control after preschool traumatic brain injury (TBI)? *Brain Inj.* (2007) 21:279–92. doi: 10.1080/02699050701253095
73. Chugani HT, Muller RA, Chugani DC. Functional brain reorganization in children. *Brain Dev.* (1996) 18:347–56.
74. Anderson VA, Catroppa C, Dudgeon P, Morse SA, Haritou F, Rosenfeld JV. Understanding predictors of functional recovery and outcome 30 months following early childhood head injury. *Neuropsychology.* (2006) 20:42–57. doi: 10.1037/0894-4105.20.1.42

75. Bigler ED. Neuropathology of mild traumatic brain injury: correlation to neurocognitive and neurobehavioral findings. In: Kobeissy FH, editor. *Brain Neurotrauma: Molecular, Neuropsychological, and Rehabilitation Aspects.* Boca Raton, FL: CRC Press/Taylor & Francis (2015). p. 1–9.
76. Margulies SS, Coats B. Biomechanics of pediatric TBI. In: Anderson V, Yeates KO, editors. *Pediatric Traumatic Brain Injury: New Frontiers in Clinical and Translational Research.* New York, NY: Cambridge University Press (2010). p. 7–17.
77. Pinto PS, Meoded A, Poretti A, Tekes A, Huisman TA. The unique features of traumatic brain injury in children. review of the characteristics of the pediatric skull and brain, mechanisms of trauma, patterns of injury, complications, and their imaging findings–part 2. *J Neuroimaging.* (2012) 22:e18–41. doi: 10.1111/j.1552-6569.2011.00690.x
78. Pinto PS, Poretti A, Meoded A, Tekes A, Huisman TA. The unique features of traumatic brain injury in children. Review of the characteristics of the pediatric skull and brain, mechanisms of trauma, patterns of injury, complications and their imaging findings–part 1. *J Neuroimaging.* (2012) 22:e1–17. doi: 10.1111/j.1552-6569.2011.00688.x
79. Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, et al. Brain development during childhood and adolescence: a longitudinal MRI study. *Nat Neurosci.* (1999) 2:861–3. doi: 10.1038/13158
80. Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW. Mapping cortical change across the human life span. *Nat Neurosci.* (2003) 6:309–15. doi: 10.1038/nn1008
81. Jacobs B, Schall M, Scheibel AB. A quantitative dendritic analysis of Wernicke's area in humans. II Gender, hemispheric, and environmental factors. *J Comp Neurol.* (1993) 327:97–111. doi: 10.1002/cne.903270108
82. Shaywitz BA, Shaywitz SE, Pugh KR, Constable RT, Skudlarski P, Fulbright RK, et al. Sex differences in the functional organization of the brain for language. *Nature.* (1995) 373:607–9. doi: 10.1038/373607a0
83. Wei J, Xiao GM. The neuroprotective effects of progesterone on traumatic brain injury: current status and future prospects. *Acta Pharmacol Sin.* (2013) 34:1485–90. doi: 10.1038/aps.2013.160
84. Deutsch ER, Espinoza TR, Atif F, Woodall E, Kaylor J, Wright DW. Progesterone's role in neuroprotection, a review of the evidence. *Brain Res.* (2013) 1530:82–105. doi: 10.1016/j.brainres.2013.07.014
85. De Nicola AF, Gonzalez SL, Labombarda F, Gonzalez Deniselle MC, Garay L, Guennoun R, et al. Progesterone treatment of spinal cord injury: effects on receptors, neurotrophins, and myelination. *J Mol Neurosci.* (2006) 28:3–15. doi: 10.1385/JMN:30:3:341
86. Labombarda F, Gonzalez S, Gonzalez Deniselle MC, Garay L, Guennoun R, Schumacher M, et al. Progesterone increases the expression of myelin basic protein and the number of cells showing NG2 immunostaining in the lesioned spinal cord. *J Neurotrauma.* (2006) 23:181–92. doi: 10.1089/neu.2006.23.181
87. Kolb B, Stewart J. Changes in the neonatal gonadal hormonal environment prevent behavioral sparing and alter cortical morphogenesis after early frontal cortex lesions in male and female rats. *Behav Neurosci.* (1995) 109:285–94.
88. Anderson V, Beauchamp MH, Yeates KO, Crossley L, Hearps SJ, Catroppa C. Social competence at 6 months following childhood traumatic brain injury. *J Int Neuropsychol Soc.* (2013) 19:539–50. doi: 10.1017/S1355617712001543
89. Max JE, Keatley E, Wilde EA, Bigler ED, Schachar RJ, Saunders AE, et al. Depression in children and adolescents in the first 6 months after traumatic brain injury. *Int J Dev Neurosci.* (2012) 30:239–45. doi: 10.1016/j.ijdevneu.2011.12.005
90. Schwartz L, Taylor HG, Drotar D, Yeates KO, Wade SL, Stancin T. Long-term behavior problems following pediatric traumatic brain injury: prevalence, predictors, and correlates. *J Pediatr Psychol.* (2003) 28:251–63. doi: 10.1093/jpepsy/jsg013
91. Scholten AC, Haagsma JA, Andriessen TM, Vos PE, Steyerberg EW, van Beeck EF, et al. Health-related quality of life after mild, moderate and severe traumatic brain injury: patterns and predictors of suboptimal functioning during the first year after injury. *Injury.* (2015) 46:616–24. doi: 10.1016/j.injury.2014.10.064
92. Diamond MC, Krech D, Rosenzweig MR. The effects of an enriched environment on the histology of the rat cerebral cortex. *J Comp Neurol.* (1964) 123:111–20.
93. Greenough WT, Volkmar FR, Juraska JM. Effects of rearing complexity on dendritic branching in frontolateral and temporal cortex of the rat. *Exp Neurol.* (1973) 41:371–8. doi: 10.1016/0014-4886(73)90278-1
94. Volkmar FR, Greenough WT. Rearing complexity affects branching of dendrites in the visual cortex of the rat. *Science.* (1972) 176:1445–7. doi: 10.1126/science.176.4042.1445
95. West RW, Greenough WT. Effect of environmental complexity on cortical synapses of rats: preliminary results. *Behav Biol.* (1972) 7:279–84.
96. Wade SL, Zhang N, Yeates KO, Stancin T, Taylor HG. Social environmental moderators of long-term functional outcomes of early childhood brain injurylong-term impairments associated with childhood traumatic brain injurylong-term impairments associated with childhood traumatic brain injury. *JAMA Pediatr.* (2016) 170:343–9. doi: 10.1001/jamapediatrics.2015.4485
97. McNally KA, Bangert B, Dietrich A, Nuss K, Rusin J, Wright M, et al. Injury versus noninjury factors as predictors of postconcussive symptoms following mild traumatic brain injury in children. *Neuropsychology.* (2013) 27:1–12. doi: 10.1037/a0031370
98. Yeates KO, Taylor HG, Rusin J, Bangert B, Dietrich A, Nuss K, et al. Premorbid child and family functioning as predictors of post-concussive symptoms in children with mild traumatic brain injuries. *Int J Dev Neurosci.* (2012) 30:231–7. doi: 10.1016/j.ijdevneu.2011.05.008
99. Brito NH, Noble KG. Socioeconomic status and structural brain development. *Front Neurosci.* (2014) 8:276. doi: 10.3389/fnins.2014.00276
100. Leijser LM, Siddiqi A, Miller SP. Imaging evidence of the effect of socio-economic status on brain structure and development. *Semin Pediatr Neurol.* (2018) 27:26–34. doi: 10.1016/j.spen.2018.03.004
101. Garcia D, Hungerford GM, Bagner DM. Topical review: negative behavioral and cognitive outcomes following traumatic brain injury in early childhood. *J Pediatr Psychol.* (2015) 40:391–7. doi: 10.1093/jpepsy/jsu093
102. Li L, Liu J. The effect of pediatric traumatic brain injury on behavioral outcomes: a systematic review. *Dev Med Child Neurol.* (2013) 55:37–45. doi: 10.1111/j.1469-8749.2012.04414.x
103. Verhelst H, Giraldo D, Vander Linden C, Vingerhoets G, Jeurissen B, Caeyenberghs K. Cognitive training in young patients with traumatic brain injury: a fixel-based analysis. *Neurorehabil Neural Repair.* (2019) 33:813–24. doi: 10.1177/1545968319868720
104. Dennis EL, Faskowitz J, Rashid F, Babikian T, Mink R, Babbitt C, et al. Diverging volumetric trajectories following pediatric traumatic brain injury. *Neuroimage Clin.* (2017) 15:125–35. doi: 10.1016/j.nicl.2017.03.014
105. Levin HS, Benavidez DA, Verger-Maestre K, Perachio N, Song J, Mendelsohn DB, et al. Reduction of corpus callosum growth after severe traumatic brain injury in children. *Neurology.* (2000) 54:647–53. doi: 10.1212/wnl.54.3.647
106. Mayer AR, Hanlon FM, Ling JM. Gray matter abnormalities in pediatric mild traumatic brain injury. *J Neurotrauma.* (2015) 32:723–30. doi: 10.1089/neu.2014.3534
107. Wu T, Merkley TL, Wilde EA, Barnes A, Li X, Chu ZD, et al. A preliminary report of cerebral white matter microstructural changes associated with adolescent sports concussion acutely and subacutely using diffusion tensor imaging. *Brain Imaging Behav.* (2018) 12:962–73. doi: 10.1007/s11682-017-9752-5
108. Wu TC, Wilde EA, Bigler ED, Li X, Merkley TL, Yallampalli R, et al. Longitudinal changes in the corpus callosum following pediatric traumatic brain injury. *Dev Neurosci.* (2010) 32:361–73. doi: 10.1159/000317058
109. Wilde EA, Merkley TL, Bigler ED, Max JE, Schmidt AT, Ayoub KW, et al. Longitudinal changes in cortical thickness in children after traumatic brain injury and their relation to behavioral regulation and emotional control. *Int J Dev Neurosci.* (2012) 30:267–76. doi: 10.1016/j.ijdevneu.2012.01.003
110. Dennis EL, Babikian T, Alger J, Rashid F, Villalon-Reina JE, Jin Y, et al. Magnetic resonance spectroscopy of fiber tracts in children with traumatic brain injury: a combined MRS - Diffusion MRI study. *Hum Brain Mapp.* (2018). doi: 10.1002/hbm.24209
111. Dennis EL, Rashid F, Ellis MU, Babikian T, Vlasova RM, Villalon-Reina JE, et al. Diverging white matter trajectories in children after traumatic brain injury: the RAPBI study. *Neurology.* (2017) 88:1392–9. doi: 10.1212/wnl.0000000000003808
112. Ewing-Cobbs L, Johnson CP, Juranek J, DeMaster D, Prasad M, Duque G, et al. Longitudinal diffusion tensor imaging after pediatric traumatic brain

injury: impact of age at injury and time since injury on pathway integrity. *Hum Brain Mapp.* (2016) 37:3929–45. doi: 10.1002/hbm.23286
113. Genc S, Anderson V, Ryan NP, Malpas CB, Catroppa C, Beauchamp MH, et al. Recovery of white matter following pediatric traumatic brain injury depends on injury severity. *J Neurotrauma.* (2017) 34:798–806. doi: 10.1089/neu.2016.4584
114. Mayer AR, Ling JM, Yang Z, Pena A, Yeo RA, Klimaj S. Diffusion abnormalities in pediatric mild traumatic brain injury. *J Neurosci.* (2012) 32:17961–9. doi: 10.1523/jneurosci.3379-12.2012
115. Van Beek L, Vanderauwera J, Ghesquiere P, Lagae L, De Smedt B. Longitudinal changes in mathematical abilities and white matter following paediatric mild traumatic brain injury. *Brain Inj.* (2015) 29:1701–10. doi: 10.3109/02699052.2015.1075172
116. Wilde EA, Ayoub KW, Bigler ED, Chu ZD, Hunter JV, Wu TC, et al. Diffusion tensor imaging in moderate-to-severe pediatric traumatic brain injury: changes within an 18 month post-injury interval. *Brain Imaging Behav.* (2012) 6:404–16. doi: 10.1007/s11682-012-9150-y
117. Yuan W, Treble-Barna A, Sohlberg MM, Harn B, Wade SL. Changes in structural connectivity following a cognitive intervention in children with traumatic brain injury. *Neurorehabil Neural Repair.* (2017) 31:190–201. doi: 10.1177/1545968316675430
118. Babikian T, Alger JR, Ellis-Blied MU, Giza CC, Dennis E, Olsen A, et al. Whole brain magnetic resonance spectroscopic determinants of functional outcomes in pediatric moderate/severe traumatic brain injury. *J Neurotrauma.* (2018) 35:1637–45. doi: 10.1089/neu.2017.5366
119. Holshouser B, Pivonka-Jones J, Nichols JG, Oyoyo U, Tong K, Ghosh N, et al. Longitudinal metabolite changes after traumatic brain injury: a prospective pediatric magnetic resonance spectroscopic imaging study. *J Neurotrauma.* (2019) 36:1352–60. doi: 10.1089/neu.2018.5919
120. Yeo RA, Phillips JP, Jung RE, Brown AJ, Campbell RC, Brooks WM. Magnetic resonance spectroscopy detects brain injury and predicts cognitive functioning in children with brain injuries. *J Neurotrauma.* (2006) 23:1427–35. doi: 10.1089/neu.2006.23.1427
121. Cazalis F, Babikian T, Giza C, Copeland S, Hovda D, Asarnow RF. Pivotal role of anterior cingulate cortex in working memory after traumatic brain injury in youth. *Front Neurol.* (2011) 1:158. doi: 10.3389/fneur.2010.00158
122. Mutch WA, Ellis MJ, Ryner LN, Morissette MP, Pries PJ, Dufault B, et al. Longitudinal brain magnetic resonance imaging CO_2 stress testing in individual adolescent sports-related concussion patients: a pilot study. *Front Neurol.* (2016) 7:107. doi: 10.3389/fneur.2016.00107
123. Kim J, Avants B, Patel S, Whyte J, Coslett BH, Pluta J, et al. Structural consequences of diffuse traumatic brain injury: a large deformation tensor-based morphometry study. *Neuroimage.* (2008) 39:1014–26. doi: 10.1016/j.neuroimage.2007.10.005
124. Dennis EL, Ellis MU, Marion SD, Jin Y, Moran L, Olsen A, et al. Callosal function in pediatric traumatic brain injury linked to disrupted white matter integrity. *J Neurosci.* (2015) 35:10202–11. doi: 10.1523/JNEUROSCI.1595-15.2015
125. Ellis MU, DeBoard Marion S, McArthur DL, Babikian T, Giza C, Kernan CL, et al. The UCLA study of children with moderate-to-severe traumatic brain injury: event-related potential measure of interhemispheric transfer time. *J Neurotrauma.* (2016) 33:990–6. doi: 10.1089/neu.2015.4023
126. Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage.* (2006) 31:1487–505. doi: 10.1016/j.neuroimage.2006.02.024
127. Raffelt DA, Smith RE, Ridgway GR, Tournier JD, Vaughan DN, Rose S, et al. Connectivity-based fixel enhancement: whole-brain statistical analysis of diffusion MRI measures in the presence of crossing fibres. *Neuroimage.* (2015) 117:40–55. doi: 10.1016/j.neuroimage.2015.05.039
128. Raffelt DA, Tournier JD, Smith RE, Vaughan DN, Jackson G, Ridgway GR, et al. Investigating white matter fibre density and morphology using fixel-based analysis. *Neuroimage.* (2017) 144(Pt A), 58–73. doi: 10.1016/j.neuroimage.2016.09.029
129. He Y, Evans A. Graph theoretical modeling of brain connectivity. *Curr Opin Neurol.* (2010) 23:341–50. doi: 10.1097/WCO.0b013e32833aa567
130. Rubinov M, Sporns O. Complex network measures of brain connectivity: uses and interpretations. *Neuroimage.* (2010) 52:1059–69. doi: 10.1016/j.neuroimage.2009.10.003
131. Alexander AL, Lee JE, Lazar M, Field AS. Diffusion tensor imaging of the brain. *Neurotherapeutics.* (2007) 4:316–29. doi: 10.1016/j.nurt.2007.05.011
132. Budde MD, Kim JH, Liang HF, Russell JH, Cross AH, Song SK. Axonal injury detected by *in vivo* diffusion tensor imaging correlates with neurological disability in a mouse model of multiple sclerosis. *NMR Biomed.* (2008) 21:589–97. doi: 10.1002/nbm.1229
133. Budde MD, Xie M, Cross AH, Song SK. Axial diffusivity is the primary correlate of axonal injury in the experimental autoimmune encephalomyelitis spinal cord: a quantitative pixelwise analysis. *J Neurosci.* (2009) 29:2805–13. doi: 10.1523/JNEUROSCI.4605-08.2009
134. Song SK, Sun SW, Ju WK, Lin SJ, Cross AH, Neufeld AH. Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. *Neuroimage.* (2003) 20:1714–22. doi: 10.1016/j.neuroimage.2003.07.005
135. Song SK, Yoshino J, Le TQ, Lin SJ, Sun SW, Cross AH, et al. Demyelination increases radial diffusivity in corpus callosum of mouse brain. *Neuroimage.* (2005) 26:132–40. doi: 10.1016/j.neuroimage.2005.01.028
136. Harsan LA, Poulet P, Guignard B, Steibel J, Parizel N, de Sousa PL, et al. Brain dysmyelination and recovery assessment by noninvasive *in vivo* diffusion tensor magnetic resonance imaging. *J Neurosci Res.* (2006) 83:392–402. doi: 10.1002/jnr.20742
137. Sun SW, Liang HF, Trinkaus K, Cross AH, Armstrong RC, Song SK. Noninvasive detection of cuprizone induced axonal damage and demyelination in the mouse corpus callosum. *Magn Reson Med.* (2006) 55:302–8. doi: 10.1002/mrm.20774
138. Maudsley AA, Darkazanli A, Alger JR, Hall LO, Schuff N, Studholme C, et al. Comprehensive processing, display and analysis for *in vivo* MR spectroscopic imaging. *NMR Biomed.* (2006) 19:492–503. doi: 10.1002/nbm.1025
139. Huppi PS, Inder TE. Magnetic resonance techniques in the evaluation of the perinatal brain: recent advances and future directions. *Semin Neonatol.* (2001) 6:195–210. doi: 10.1053/siny.2001.0039
140. Croall I, Smith FE, Blamire AM. Magnetic resonance spectroscopy for traumatic brain injury. *Top Magn Reson Imaging.* (2015) 24:267–74. doi: 10.1097/RMR.0000000000000063
141. Moffett JR, Ross B, Arun P, Madhavarao CN, Namboodiri AM. N-Acetylaspartate in the CNS: from neurodiagnostics to neurobiology. *Prog Neurobiol.* (2007) 81:89–131. doi: 10.1016/j.pneurobio.2006.12.003
142. McKenna MC, Scafidi S, Robertson CL. Metabolic alterations in developing brain after injury: knowns and unknowns. *Neurochem Res.* (2015) 40:2527–43. doi: 10.1007/s11064-015-1600-7
143. Gasparovic C, Yeo R, Mannell M, Ling J, Elgie R, Phillips J, et al. Neurometabolite concentrations in gray and white matter in mild traumatic brain injury: an 1H-magnetic resonance spectroscopy study. *J Neurotrauma.* (2009) 26:1635–43. doi: 10.1089/neu.2009-0896
144. Govindaraju V, Gauger GE, Manley GT, Ebel A, Meeker M, Maudsley AA. Volumetric proton spectroscopic imaging of mild traumatic brain injury. *AJNR Am J Neuroradiol.* (2004) 25:730–7.
145. Vagnozzi R, Signoretti S, Tavazzi B, Floris R, Ludovici A, Marziali S, et al. Temporal window of metabolic brain vulnerability to concussion: a pilot 1H-magnetic resonance spectroscopic study in concussed athletes–part III. *Neurosurgery.* (2008) 62:1286–95; discussion: 1295–86. doi: 10.1227/01.neu.0000333300.34189.74
146. Ross B, Bluml S. Magnetic resonance spectroscopy of the human brain. *Anat Rec.* (2001) 265:54–84. doi: 10.1002/ar.1058
147. Panigrahy A, Nelson MD Jr, Bluml S. Magnetic resonance spectroscopy in pediatric neuroradiology: clinical and research applications. *Pediatr Radiol.* (2010) 40:3–30. doi: 10.1007/s00247-009-1450-z
148. Macmillan CS, Wild JM, Wardlaw JM, Andrews PJ, Marshall I, Easton VJ. Traumatic brain injury and subarachnoid hemorrhage: *in vivo* occult pathology demonstrated by magnetic resonance spectroscopy may not be "ischaemic". A primary study and review of the literature. *Acta Neurochir.* (2002) 144:853–62; discussion: 862. doi: 10.1007/s00701-002-0966-x
149. Ashwal S, Holshouser BA, Shu SK, Simmons PL, Perkin RM, Tomasi LG, et al. Predictive value of proton magnetic resonance spectroscopy

in pediatric closed head injury. *Pediatr Neurol.* (2000) 23:114–25. doi: 10.1016/S0887-8994(00)00176-4
150. Holshouser BA, Tong KA, Ashwal S. Proton MR spectroscopic imaging depicts diffuse axonal injury in children with traumatic brain injury. *AJNR Am J Neuroradiol.* (2005) 26:1276–85.
151. Len TK, Neary JP. Cerebrovascular pathophysiology following mild traumatic brain injury. *Clin Physiol Funct Imaging.* (2011) 31:85–93. doi: 10.1111/j.1475-097X.2010.00990.x
152. Bhogal AA, Philippens ME, Siero JC, Fisher JA, Petersen ET, Luijten PR, et al. Examining the regional and cerebral depth-dependent BOLD cerebrovascular reactivity response at 7T. *Neuroimage.* (2015) 114:239–48. doi: 10.1016/j.neuroimage.2015.04.014
153. Leung J, Kosinski PD, Croal PL, Kassner A. Developmental trajectories of cerebrovascular reactivity in healthy children and young adults assessed with magnetic resonance imaging. *J Physiol.* (2016) 594:2681–9. doi: 10.1113/JP271056
154. Mutch WA, Ellis MJ, Graham MR, Wourms V, Raban R, Fisher JA, et al. Brain MRI CO2 stress testing: a pilot study in patients with concussion. *PLoS ONE.* (2014) 9:e102181. doi: 10.1371/journal.pone.0102181
155. Fierstra J, Sobczyk O, Battisti-Charbonney A, Mandell DM, Poublanc J, Crawley AP, et al. Measuring cerebrovascular reactivity: what stimulus to use? *J Physiol.* (2013) 591:5809–21. doi: 10.1113/jphysiol.2013.259150
156. Bigler ED, Abildskov TJ, Petrie J, Farrer TJ, Dennis M, Simic N, et al. Heterogeneity of brain lesions in pediatric traumatic brain injury. *Neuropsychology*. (2013) 27:438–51. doi: 10.1037/a0032837
157. Bigler ED, Zielinski BA, Goodrich-Hunsaker N, Black GM, Huff BS, Christiansen Z, et al. The relation of focal lesions to cortical thickness in pediatric traumatic brain injury. *J Child Neurol.* (2016) 31:1302–11. doi: 10.1177/0883073816654143
158. Coronado VG, Xu L, Basavaraju SV, McGuire LC, Wald MM, Faul M, et al. Surveillance for traumatic brain injury-related deaths; United States, 1997–2007 *MMWR Surveill Summ.* (2011) 60:1–32.
159. Falcone RA Jr, Martin C, Brown RL, Garcia VF. Despite overall low pediatric head injury mortality, disparities exist between races. *J Pediatr Surg.* (2008) 43:1858–64. doi: 10.1016/j.jpedsurg.2008.01.058
160. Howard I, Joseph JG, Natale JE. Pediatric traumatic brain injury: do racial/ethnic disparities exist in brain injury severity, mortality, or medical disposition? *Ethn Dis.* (2005) 15(4 Suppl 5):S5–56.
161. Cameron, CM, Osborne JM, Spinks AB, Davey TM, Sipe N, McClure RJ. Impact of participant attrition on child injury outcome estimates: a longitudinal birth cohort study in Australia. *BMJ Open.* (2017) 7:e015584. doi: 10.1136/bmjopen-2016-015584
162. Launes J, Hokkanen L, Laasonen M, Tuulio-Henriksson A, Virta M, Lipsanen J, et al. Attrition in a 30-year follow-up of a perinatal birth risk cohort: factors change with age. *PeerJ.* (2014) 2:e480. doi: 10.7717/peerj.480
163. Blaha RZ, Arnett AB, Kirkwood MW, Taylor HG, Stancin T, Brown TM, et al. Factors influencing attrition in a multisite, randomized, clinical trial following traumatic brain injury in adolescence. *J Head Trauma Rehabil.* (2015) 30:E33–40, doi: 10.1097/HTR.0000000000000059
164. Catroppa C, Anderson VA, Morse SA, Haritou F, Rosenfeld JV. Outcome and predictors of functional recovery 5 years following pediatric traumatic brain injury (TBI). *J Pediatr Psychol.* (2008) 33:707–18. doi: 10.1093/jpepsy/jsn006
165. Anderson V, Catroppa C, Morse S, Haritou F, Rosenfeld JV. Intellectual outcome from preschool traumatic brain injury: a 5-year prospective, longitudinal study. *Pediatrics*. (2009) 124:e1064–1071. doi: 10.1542/peds.2009-0365
166. Fletcher JM, Ewing-Cobbs L, Miner ME, Levin HS, Eisenberg HM. Behavioral changes after closed head injury in children. *J Consult Clin Psychol.* (1990) 58:93–8. doi: 10.1037//0022-006x.58.1.93
167. Nicholls N. The insignificance of significance testing. *Bull Am Meteorol Soc.* (2001) 82:981–6. doi: 10.1175/1520-0477(2001)082<0981:CAATIO>2.3.CO;2
168. McCauley SR, Wilde EA, Anderson VA, Bedell G, Beers SR, Campbell TF, et al. Recommendations for the use of common outcome measures in pediatric traumatic brain injury research. *J Neurotrauma.* (2012) 29:678–705. doi: 10.1089/neu.2011.1838
169. Duhaime AC, Holshouser B, Hunter JV, Tong K. Common data elements for neuroimaging of traumatic brain injury: pediatric considerations. *J Neurotrauma.* (2012) 29:629–33. doi: 10.1089/neu.2011.1927
170. Dennis EL, Caeyenberghs K, Asarnow RF, Babikian T, Bartnik-Olson B, Bigler ED, et al. Brain imaging in young brain-injured patients: a coordinated effort towards individualized predictors from the ENIGMA pediatric msTBI group. *PsyArXiv.* (2019). doi: 10.31234/osf.io/y2txh. [Epub ahead of print].
171. Kristman V, Manno M, Cote P. Loss to follow-up in cohort studies: how much is too much? *Eur J Epidemiol.* (2004) 19:751–760. doi: 10.1023/b:ejep.0000036568.02655.f8
172. Max JE, Wilde EA, Bigler ED, Hanten G, Dennis M, Schachar RJ, et al. Personality change due to traumatic brain injury in children and adolescents: neurocognitive correlates. *J Neuropsychiatry Clin Neurosci.* (2015) 27:272–9. doi: 10.1176/appi.neuropsych.15030073
173. Stancin T, Taylor HG, Thompson GH, Wade S, Drotar D, Yeates KO. Acute psychosocial impact of pediatric orthopedic trauma with and without accompanying brain injuries. *J Trauma.* (1998) 45:1031–8. doi: 10.1097/00005373-199812000-00010
174. Gerring JP, Brady KD, Chen A, Vasa R, Grados M, Bandeen-Roche KJ, et al. Premorbid prevalence of ADHD and development of secondary ADHD after closed head injury. *J Am Acad Child Adolesc Psychiatry.* (1998) 37:647–54. doi: 10.1097/00004583-199806000-00015
175. Basson MD, Guinn JE, McElligott J, Vitale R, Brown W, Fielding LP. Behavioral disturbances in children after trauma. *J Trauma.* (1991) 31:1363–8. doi: 10.1097/00005373-199110000-00008
176. Hajek CA, Yeates KO, Gerry Taylor H, Bangert B, Dietrich A, Nuss KE, et al. Relationships among post-concussive symptoms and symptoms of PTSD in children following mild traumatic brain injury. *Brain Inj.* (2010) 24:100–9. doi: 10.3109/02699050903508226
177. Wilde EA, Ware AL, Li X, Wu TC, McCauley SR, Barnes A, et al. Orthopedic injured versus uninjured comparison groups for neuroimaging research in mild traumatic brain injury. *J Neurotrauma.* (2019) 36:239–49. doi: 10.1089/neu.2017.5513
178. Zhang H, Schneider T, Wheeler-Kingshott CA, Alexander DC. NODDI: practical *in vivo* neurite orientation dispersion and density imaging of the human brain. *Neuroimage.* (2012) 61:1000–16. doi: 10.1016/j.neurdoimage.2012.03.072

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REVIEW
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Monitoring and Measurement of Intracranial Pressure in Pediatric Head Trauma

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Purpose of Review: Monitoring of intracranial pressure (ICP) is an important and integrated part of the treatment algorithm for children with severe traumatic brain injury (TBI). Guidelines often recommend ICP monitoring with a treatment threshold of 20 mmHg. This focused review discusses; (1) different ICP technologies and how ICP should be monitored in pediatric patients with severe TBI, (2) existing evidence behind guideline recommendations, and (3) how we could move forward to increase knowledge about normal ICP in children to support treatment decisions.

Summary: Current reference values for normal ICP in adults lie between 7 and 15 mmHg. Recent studies conducted in "pseudonormal" adults, however, suggest a normal range below this level where ICP is highly dependent on body posture and decreases to negative values in sitting and standing position. Despite obvious physiological differences between children and adults, no age or body size related reference values exist for normal ICP in children. Recent guidelines for treatment of severe TBI in pediatric patients recommend ICP monitoring to guide treatment of intracranial hypertension. Decision on ICP monitoring modalities are based on local standards, the individual case, and the clinician's choice. The recommended treatment threshold is 20 mmHg for a duration of 5 min. Both prospective and retrospective observational studies applying different thresholds and treatment strategies for intracranial hypertension were included to support this recommendation. While some studies suggest improved outcome related to ICP monitoring (lower rate of mortality and severe disability), most studies identify high ICP as a marker of worse outcome. Only one study applied age-differentiated thresholds, but this study did not evaluate the effect of these different thresholds on outcome. The quality of evidence behind ICP monitoring and treatment thresholds in severe pediatric TBI is low and treatment can potentially be improved by knowledge about normal ICP from observational studies in healthy children and cohorts of pediatric "pseudonormal" patients expected to have normal ICP. Acceptable levels of ICP – and thus also treatment thresholds—probably vary with age, disease and whether the patient has intact cerebral autoregulation. Future treatment algorithms should reflect these differences and be more personalized and dynamic.

Keywords: intracranial pressure (ICP), age-dependent, reference values, traumatic brain injury (TBI), head trauma, children, pediatric, guidelines

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INTRODUCTION

Traumatic brain injury (TBI) is one of the leading causes of mortality among children and adolescents, and a great contributor to morbidity (1, 2). The annual incidence of reported TBI cases per 100.000 people (due to all causes) is higher in high-income countries than in low—and middle-income countries (3), with an annual incidence of children with a TBI related emergency department visit estimated to 691 per 100.000, hospitalization due to TBI to 74 per 100.000 and TBI related death to 9 per 100.000 (4). These numbers may also reflect differences in reference and reporting patterns in different geographical areas (5, 6). However, the total burden of TBI cases are nearly three times higher in low-income countries, with road traffic accidents being the leading cause (3). The risk of road traffic deaths in low-income countries are by WHO reported three times higher than in high-income countries, and the leading cause of all deaths in age group 5–29 years (7).

Although the number of pediatric patients sustaining a severe TBI is increasing, the understanding of pathophysiology and long-term outcome remains limited. Most clinicians argue that therapy strategies should be based on high-quality research, conducted either as randomized clinical trials (RCT) or observational studies with high-quality body of evidence. Where an RCT aims to eliminate as many confounding variables as possible, a high-quality observational study aims to clarify those variables. In the last decades, only ten RCTs in pediatric patients with severe TBI have been conducted and the level of evidence in observational studies is reported as low or moderate (8–10). This affects both international guidelines for management of severe pediatric TBI and treatment algorithms at individual TBI centers. A survey from 2013 conducted at 32 American and European pediatric TBI centers revealed high variability in treatment algorithms, particularly for topics with limited evidence (11). However, both monitoring of intracranial pressure (ICP) and treatment of intracranial hypertension were an integral part of TBI management despite the lack of evidence, and all centers unanimously reported the use of an ICP threshold of 20 mmHg. Eight centers further reported age-specific ICP threshold values with slightly lower values in younger patients (10 mmHg at one center, 15 mmHg at four centers and 18 mmHg at three centers) (11).

In this focused review we discuss the use of different ICP monitoring modalities in the treatment of pediatric TBI. Furthermore, the existing evidence behind the Brain Trauma Foundation guidelines for ICP (10) are evaluated, and it is discussed how ICP treatment in severe pediatric TBI can potentially be improved by improved knowledge about normal ICP in children and age-specific threshold values.

ICP MONITORING TECHNOLOGY

The first data on invasive measurement of ICP were published by Guillaume and Janny in 1951 (12), and the first comprehensive analysis of ICP curve morphology was performed in patients with probable space occupying lesions by Lundberg in 1960 (13) and in patients with TBI in 1965 (14). The measurements were obtained through a transducer coupled to an external ventricular drain (EVD). Today, in continuous monitoring of ICP in patients admitted to neuro-intensive care unit, ICP is often measured using a parenchymal sensor. In infants, there are two additional possibilities to indirectly evaluate ICP; (1) by palpating the open anterior fontanelle and cranial sutures, and (2) by serial measurements of head circumference. Although palpation of the anterior fontanelle can be used for screening of patients for further investigations, neither palpation nor head circumference are used in management of acute severe pediatric TBI (15). Other non-invasive methods of ICP estimation (e.g., contrast-enhanced ultrasonography, magnetic resonance imaging, near-infrared spectroscopy, optic nerve sheath diameter, otoacoustic emission, quantitative pupillometry, transcranial doopler) are constantly being improved, but have not yet achieved quantitation of absolute ICP values or reached a level of accuracy sufficient for treatment decisions in clinical practice (16–19).

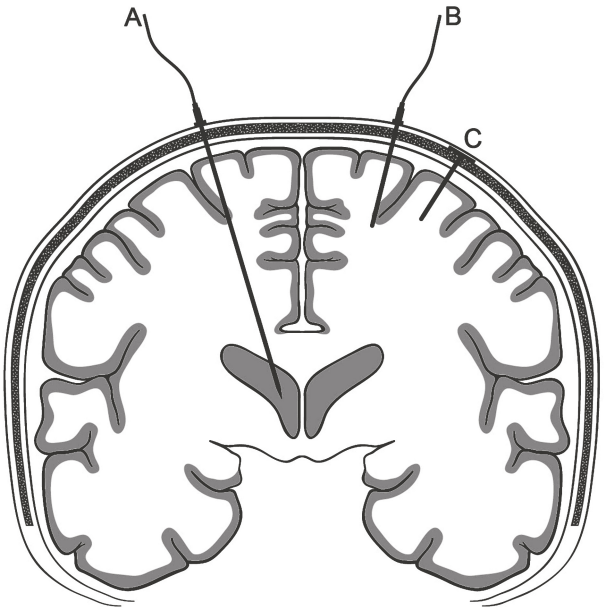

FIGURE 1 | ICP monitoring technologies. The figure is a schematic drawing of different ICP monitoring devices in a coronal plane. The placement of an EVD (corresponding to Kocher's point) **(A)**, a parenchymal ICP sensor **(B)**, and a telemetric ICP sensor **(C)** are shown.

Measurement of ICP Through an External Ventricular Drain

The gold standard to measure ICP is through an EVD coupled to an external fluid-filled transducer (**Figure 1A**) with the draining end closed for an exact ICP measurement (17). An EVD is often placed at the non-dominant side through a burr hole at Kocher's point. No recommendations on drain placement exits, if the patient has focal lesions in the non-dominant hemisphere.

The overall complication rate to EVD treatment in the pediatric population is around 20–25% including infection, misplacement, hemorrhage, and malfunction (occlusion with cellular debris or collapse of the ventricular system around the

drain tip) (20). The most common complication is infection, estimated to occur in around 10% of the patients (20, 21), which is comparable to the rate in adult populations (22). The rate of EVD related infections may be lowered using prophylactic antibiotics, including antimicrobial impregnated catheters, although this might increase the rate of infections with more resistant bacteria, such as methicillin resistant Staphylococcus Aureus (23, 24). Secondly, the pediatric patient often has a very narrow ventricular system, which makes the placement of the ventricular catheter difficult and may increase the risk of malfunction. Correct placement can be aided by guide (e.g., the Ghajar guide or the Thomale guide) (25, 26), surgical navigation (27) and maybe in the future, holographic visualization of the ventricular system (28). Finally, placement of the external transducer/choice of reference point strongly influences measurement levels and is a source of potential error. EVDs with integrated ICP sensors at the tip inside the ventricular system (Raumedic Neurovent) or in the parenchyma (Spiegelberg ventricular probe) eliminate this source of error. In addition, these devices also allow both drainage and continuous ICP measurements.

Measurement of ICP Using a Parenchymal ICP Sensor

Several parenchymal ICP monitoring devices exist, using different technologies including fiber optic sensors (e.g., Camino ICP Monitor), strain gauge devices (e.g., Codman MicroSensor and Raumedic Neurovent-P ICP sensor) and pneumatic sensors (Spiegelberg) (**Figure 1B**) (17). A parenchymal ICP sensor is often placed in the non-dominant frontal region. The placement can be modified if focal lesions are verified or suspected. There is, however, no consensus whether "true" ICP is measured in the healthy hemisphere or the damaged hemisphere. An interhemispheric supratentorial pressure gradient in patients with head trauma and focal lesions has been documented suggesting that such patients could benefit from bilateral ICP monitors (29). However, in a setup with bilateral measurement a concern would be the risk of a pressure gradient between the two sensors due to technical issues and not resulting from biological causes (30, 31). Other sensor locations aside from the brain parenchyma such as the subdural or epidural spaces have been investigated, but are less used in daily clinical practice (32–35).

The complications using parenchymal sensors are infection and hemorrhage (17). Technical errors, with a particular risk of baseline-drift with time, might be especially relevant in the neuro-intensive care setting due to the frequent occurrence of electrostatic discharges (30). Such baseline-drifts can be sudden ("baseline-shifts") or gradual and can sometimes be identified by a discrepancy between the pulse wave amplitude and the ICP value, as the amplitude will increase parallel to increasing ICP. A review comparing technical aspects and complication rate of the different sensor types was published in 2012 (17).

For nearly a decade, telemetric ICP monitoring has been possible through the Raumedic Neurovent-P-tel, which is a parenchymal strain gauge sensor coupled to a wireless transcutaneous data transmitter (**Figure 1C**) (36). So far, telemetric ICP monitoring has been applied only in severe adult TBI (37). In previous investigations (38, 39), complication rates were similar to those of cabled ICP sensors (40–42). Another telemetric device (Miethke/Aesculap Sensor Reservoir) has also been developed to measure ICP through an implanted ventricular shunt system (43, 44). In principle, this could also be coupled to an EVD, but so far there are no reports testing the device in a neuro-intensive care setting.

Comparison of The Different Techniques

The Brain Trauma Foundation guidelines recommend the use of ICP monitoring to determine if intracranial hypertension is present, while drainage of cerebrospinal fluid (CSF) through an EVD is suggested to manage intracranial hypertension (45). The decisions on how to monitor ICP and where to monitor ICP are still based on local standards, the individual case, and the clinician's choice.

ICP monitoring through an EVD provides the possibility to perform intermittent or continuous ICP measurement as well as therapeutic interventions such as treatment of elevated ICP through drainage of CSF, and intrathecal administration of medicine (e.g., antibiotics) (17). Another advantage of ICP measurement through an EVD is the possibility to directly measure water column height and recalibrate the transducer, which is not possible for most parenchymal ICP sensors (except for the Spiegelberg sensor). Lack of recalibration can cause a risk of treatment decisions made on incorrect ICP values. In a recently published systematic review, no differences in mortality or functional outcome in patients with TBI could be detected comparing ICP measurement through an EVD to a parenchymal sensor. The overall complication rate was, however, higher in EVDs, mainly due to infections (46).

In summary, both measurement sites (intraventricular vs. parenchymal) have advantages in clinical decision making in children with severe TBI. Though the parenchymal ICP sensors have equal accuracy and probably a slightly lower complication rate compared to intraventricular ICP monitoring, the latter remains gold standard (41, 42, 47–49). This may be explained by; (1) a historical perspective, (2) a less significant intercompartment pressure gradient, and (3) validation of measured ICP through an external fluid column (23).

ICP IN CHILDREN

ICP treatment in TBI aims at reducing an elevated ICP in order to improve outcome. The treatment threshold is 20 mmHg in children and 22 mmHg in adults (10, 50). However, it can be questioned how close the current threshold is to normal ICP (**Figure 2**). Güiza et al. (51) showed that outcome measured using the Glasgow Outcome Scale in patients with TBI depends on the cumulated duration of episodes with elevated ICP and that the tolerated burden is less in children than in adults. The tolerance for ICP $>$ 20 mmHg is only 7 min in children (vs. 37 min in adults), and for an ICP of 10 mmHg it is 180 min (**Figure 3**). As the tolerance for normal ICP levels should be indefinite, this could indicate that normal ICP in children is $<$10 mmHg. However, if cerebral autoregulation is intact, the tolerance level for 'indefinite duration' is shifted to 15 mmHg (51).

FIGURE 2 | ICP and pulse wave amplitude. The two pressure curves illustrate ICP tracings at mean ICP 5 mmHg **(A)** and mean ICP 20 mmHg **(B)**. At 20 mmHg (recommended treatment threshold), the amplitude is higher consistent with increased pulsatility and decreased compliance. The probability of abnormal ICP patterns (A waves and tall B waves) also occur frequently ≥20 mmHg, but are not seen at 5 mmHg, where the signal is much more uniform and stable.

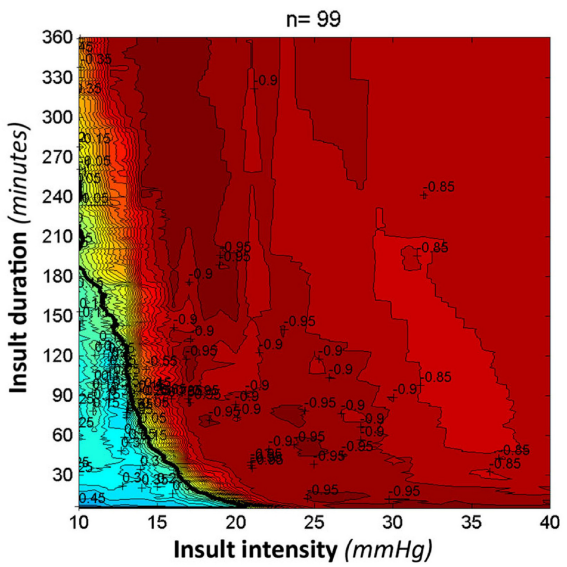

FIGURE 3 | ICP tolerance. This figure was adapted and used with permission from Intensive Care Medicine Journal. It visualizes the correlation between outcome on the Glasgow Outcome Scale and the time burden of intracranial hypertension in a pediatric population with traumatic brain injury. Red episodes illustrate a low score on the Glasgow Outcome Scale (worse outcome), while blue episodes illustrate a high score (good outcome). The black curve is named the transition curve and illustrates zero correlation (51).

Normal ICP Reference Values

Obtaining reliable, quantitative ICP values still involves performing invasive intracranial measurements, which is the straightforward explanation behind the lack of reference values for normal ICP. Currently, ICP in "pseudonormal" subjects; i.e., patients in whom ICP/CSF related pathology is absent or unlikely, provides an insight into ICP ranges which are probably normal. This kind of documentation indicates that normal ICP is considerably lower than previously assumed and strongly dependent on postural changes. Values obtained in this way in adults range between approximately 0 to 5 mmHg in supine position and −5 to 0 mmHg in upright position (52, 53). Interestingly, Lundberg's ground-breaking work from 1960 included just one patient, who was retrospectively considered to have normal ICP, and in whom the supine intraventricular pressure recorded continuously was around 0 mmHg (13). In children, the evidence for normal ICP values is even more scarce, and most studies are conducted in children with TBI, cranial synostosis or shunt-managed hydrocephalus, i.e., situations from which normal ICP cannot be extrapolated. In a series on shunted pediatric patients, the ICP range in children with functional shunts (neither under nor overdrainage) was −1.6 to 16.9 mmHg, but the range overlapped the overdrainage group (54), and as shunt treatment directly affects ICP, normal ICP levels cannot be inferred from shunted cohorts even if ICP is "well-managed".

We have examined a "pseudonormal" mixed pediatric and adult cohort undergoing ICP monitoring which was considered normal, and in whom there was no further suspicion of increased ICP or need for pressure relieving treatment during a minimum follow-up period of 3 years following the measurement (55). Mean daytime ICP in children was 2.8 mmHg ± 2.2 vs. 1.9 mmHg ± 4.2 in adults. Mean night-time ICP was 6 mmHg higher in both children and adults. Surprisingly, this study also showed an inverse relationship between age and ICP with a decrement of 1 mmHg per decade. This is in obvious

disagreement with the generally accepted perception that ICP is lower in children than in adults. However, the same age-related ICP pattern was shown in a mixed diagnostic cohort from age 16 to 85 years (56). Studies examining the lumbar puncture opening pressure (CSF_{op}) specify a diagnostic cut-off at 25–28 cm H_2O (18–21 mmHg) (57, 58). CSF_{op} could be an ethically more acceptable way of documenting truly normal ICP values, but there are limitations extrapolating these values to reference values for intracranially measured ICP. CSF_{op} is a momentary measurement and the body position necessary for performing the lumbar puncture will itself increase the measured value (52).

In summary, little is known about "normal" ICP in children and reference values are either extrapolated from adults or from pediatric patients in whom ICP must be considered abnormal. Since children differ from adults in both anatomy and physiology (59) reference values including treatment threshold in severe pediatric TBI should reflect this.

EVIDENCE BEHIND GUIDELINE RECOMMENDATIONS REGARDING ICP MONITORING AND TREATMENT THRESHOLD OF ICP

ICP monitoring in pediatric TBI relates to the 10% who suffer a moderate or severe head trauma with a higher risk of intracranial complications (60). The updated guidelines provides recommendations for clinical decisions and treatment algorithms including evidence—and consensus-based suggestions for both first and second tier treatment (10, 45). Despite a systematic review of the literature, only low-quality studies and few moderate-quality studies have been found, leaving no level I recommendation, few level II recommendations and a majority of level III recommendations to guide the clinician.

The Use of ICP Monitoring

A total of 19 studies examining if treatment decisions based on ICP monitoring improves outcome were included in the 3rd edition of the guidelines (10). Three large retrospective multicenter studies [one using hospitals as unit of measurement (61) and two using patients as unit of measurement (62, 63)] were added since the 2nd edition and provides evidence that ICP monitoring and treatment of increased ICP improves clinical outcome. Based on the included studies, the guidelines recommend ICP monitoring in severe pediatric TBI (level III recommendation) (10). However, it is noteworthy that the three studies do not provide a unanimous conclusion.

Alkhoury et al. (62) aimed to determine the effect of ICP monitoring on mortality in pediatric patients with severe TBI and found that ICP monitoring only reduced mortality in patients with a Glasgow Coma Scale (GCS) score of 3. The two groups (ICP monitor vs. no ICP monitor) were comparable in age, sex, GCS and Trauma and Injury Severity Score, but differed in Injury Severity Score (higher in the ICP monitoring group) and Revised Trauma Score (lower in the ICP monitoring group). Patients who underwent ICP monitoring were found to have longer hospital admissions, including a longer stay in the neuro-intensive care unit and more ventilator days. This could either indicate a selection bias with more severe injuries in patients with an ICP monitor (not explained in the paper), that ICP monitoring itself keeps the patient in the neuro-intensive care setting or an increased risk of complications following ICP monitoring and potentially aggressive pressure relieving treatment.

To assess whether hospital factors (e.g., trauma level center, patient admissions) and ICP monitoring are associated with outcome Bennet et al. (61) included pediatric TBI patients admitted to 31 centers. They reported that hospitals with higher patient volumes and pediatric trauma level I centers were more likely to use ICP monitoring and that a higher patient volume was associated with a more standardized ICP management and an overall better patient outcome. Conclusively ICP guided management results in a more favorable outcome; it is however also possible that hospitals with more patient admissions and standardized ICP management provide an overall better patient care.

A subsequent study by Bennet et al. (63) found no evidence that ICP monitoring in pediatric patients with severe TBI improved outcome. However, unlike the groups formed by Alkhoury et al. (62), the initial assessment of patients in the ICP monitoring group revealed poorer Injury Severity Scores, head Abbreviated Injury Scale scores and GCS scores and a higher risk of an intracranial hemorrhage. In accordance with Alkhoury et al., patients with an ICP monitor had longer hospital admissions and received more treatment to manage intracranial hypertension. Further they had higher odds of mortality, discharge to hospice and to receive either a tracheostomy or a gastrostomy tube. If patients receiving an ICP monitor had a more severe injury, such a selection bias could explain why no association was found between ICP monitoring and improved outcome.

In summary, the ambiguous conclusions can be a result of inadequate control for statistically confounding factors (e.g., severity of injuries, different treatment algorithms for insertion of an ICP monitor, different standards of patient care in different centers). Interestingly, the retrospective multicenter studies revealed that only 7.7% (62), 32.5% (63), and 55.0% (61) of the included patients underwent ICP monitoring, although the use of ICP monitoring has been suggested since the initial guidelines in 2003. In both 2012 and 2017 Bennet et al. reported a high inter-hospital variation in the use of ICP monitoring [14–83% (61) and 6-50% (63), respectively] and over a 10-year period (2001-2011) the rate of ICP monitoring was decreasing, seemingly in contrast to the initial guidelines (61).

The Threshold for Treatment of Intracranial Hypertension

Treatment threshold for ICP in the pediatric patient is based on 12 retrospective and prospective studies examining target values for lowering ICP to improve clinical outcome (10). Most studies applied an ICP threshold of 20 mmHg and reported lower ICP values in patients with a favorable outcome compared to those with an unfavorable outcome (64–70). Few studies

examined if different threshold values resulted in different outcome [respectively 14/20/30 mmHg (69) and 15/20 mmHg (71)]. ICP values > 20 mmHg were found to be associated with an unfavorable outcome (64, 67, 69, 70), but no difference in outcome across the different threshold values could be detected (69, 71). Two studies even applied thresholds of 35 and 40 mmHg and found, not surprisingly, that values higher than the applied threshold were associated with an unfavorable outcome (72, 73). Based on these findings, the guidelines suggest a treatment threshold of 20 mmHg for 5 min (level III recommendation) (10).

Though age itself does not affect outcome (74), the definition of childhood (due to differences in anatomy and physiology between infants, children and adolescents) is extremely important in comparison of pediatric patients (59). None of the included studies examine comparable patient populations. One study includes infants from age 0–24 months (71), while others exclude the youngest patients (66, 68, 70, 72, 73, 75). Furthermore, the definition of a pediatric patient varies from 1–12 years of age (66), 0–13 years of age (64), 3 months to 14 years of age (73), 0–15 years of age (67), 1 month to 16 years (70), 3 months to 16 years of age (72), to 17 years of age (68), 2.4 months to 18 years of age (75) and 0–19 years of age (65). Furthermore, only one of 12 studies applied age-specific treatment thresholds (15 mmHg at age 0–24 months, ICP > 18 mmHg at age 25–96 months and ICP > 20 mmHg at age 97–214 months). However, it was not examined if age-differentiated thresholds were correlated with improved outcome (64).

Even though the guideline committee speculates in individualized ICP management and lack of existing normal values for ICP, the same treatment threshold is recommended across all age-groups. Interestingly, threshold values for CPP are suggested to be age-dependent with lowest values in infants (10). A well-documented age-dependent blood pressure (84) and the correlation between ICP, CPP and mean arterial blood pressure (MAP) (CPP = MAP-ICP) is not further addressed.

In summary, the lack of consistence in age of childhood and the differing contribution of extracranial injuries, challenges the threshold-comparison and emphasizes the need for greater consistency in pediatric research. The currently used treatment threshold is considerably higher than ICP reference values proposed in studies examining "normal" ICP (52, 55, 56, 76, 77), which could be one of the reasons for the still ambiguous benefit of ICP monitoring and regulation in pediatric patients with severe TBI.

FUTURE PERSPECTIVES

High-quality research in ICP monitoring and regulation in severe pediatric TBI is still limited. Limitations may be due to the heterogeneity in pathology, patient populations (as previously mentioned), treatment algorithms including threshold values and sensitivity and specificity in outcome measurements (8). Further research must be conducted for future guidelines to provide level I or level II recommendations. Studies can still add evidence by examining smaller, but more homogenous patient groups (8), as such studies can also be collected into meta-analysis protocols. The multicenter cohort observational study SYNAPSE-ICU is being conducted with the aim to describe worldwide current practices of ICP monitoring and ICP management in neuro-intensive care setting; unfortunately, this study only enrolls patients >18 years (78). The ADAPT trial describes the correlation between outcome and treatment approaches and decisions for pediatric TBI already used in clinical practice, aiming to provide evidence for new level II recommendations (9). The observational cohort study includes 51 centers and approximately 1,000 study subjects. Few preliminary results have been published, but to our knowledge data form this study to guide management of intracranial hypertension are still awaiting.

It is important to remember that outcome is not affected by ICP monitoring in itself, but only by the clinical consequences and actions based on it, and ICP control alone does thus not necessary lead to a good outcome (71). ICP is only one component in a complex cerebral homeostasis, which also includes CPP, autoregulation, oxygenation, and preservation of metabolism/blood flow index. An intact cerebral autoregulation protects the brain from inadequate blood flow despite changes in CPP. TBI can however affect the autoregulation and autoregulation in pediatric patients with severe TBI are reported impaired in 29–50% of the patients (79, 80). Several surrogate measurements for cerebral autoregulation exist (81), one being the pressure reactivity index (PRx) first described in 1997 (82). The PRx is the Pearson correlation between the slow waves of ICP and MAP and can be used to determine the individual optimal CPP and thus the maintenance of an efficient autoregulation level (83). High PRx values (indicating an impaired autoregulation) have within recent years found to be associated with higher mortality/unfavorable outcome in pediatric TBI (80, 83). Multimodal neuromonitoring of pediatric TBI patients covering several of these physiological interactions would potentially improve clinical management and may facilitate a more individualized treatment strategy. Comprehensive guidelines thus must be based on complex physiological algorithms. However, a very basic and simple first line challenge is to provide truly normal pediatric ICP reference values.

Determining the normal reference range for ICP in healthy children requires a patient cohort with no suspicion of CSF pathology. Due to its invasive nature, it is not ethically acceptable to measure ICP intracranially in a healthy child. A normal reference range with good statistical confidence requires measurements in large numbers in different age groups, and can therefore only be obtained through non-invasive ICP measurements; alternatively by extrapolating data from measurements in "pseudonormal" patient populations. Since ICP is strongly affected by body posture, the ICP monitoring technology must allow the child a free range of motion during measurement. As discussed, non-invasive methods for ICP estimation are improving, but still lack accuracy and are not suitable for continuous monitoring during daily activities. The telemetric ICP sensor can be used in the neuro-intensive care unit and can be left implanted for 3 months permitting ICP monitoring sessions both during recovery and during follow-up with return of daily life activities. This facilitates a useful ICP

monitoring technology which can be used in a "pseudonormal" population with an initial need of ICP measurement, and a subsequent complete cerebral recovery.

Due to human physiology and established age-dependent values in both CPP and MAP, it may be assumed that ICP is also affected by age and body growth. An RCT including age-defined subgroups with three different ICP threshold values applied in each group could clarify if threshold values should differ between age-groups. The pediatric patient cohort (age 0–18) could be divided into subgroups corresponding to physiological milestones (e.g., cranial suture closure, change in CSF production, change in general body growth rate), while applied treatment thresholds in each group could be 20, 15, and 10 mmHg (and thus corresponding to/lower than recommended values).

CONCLUSION

ICP monitoring and treatment of intracranial hypertension is a central part of the Brain Trauma Foundation guidelines for management of severe pediatric TBI. Due to the heterogeneity in TBI pathology, variation in patient populations, treatment algorithms, and outcome measures between centers/studies, the clinician is left with no high-level recommendations to guide the treatment of a child with a severe head trauma. Specifically regarding ICP monitoring and ICP treatment thresholds, evidence of a normal ICP range in children is lacking. No studies have evaluated the effect of different treatment thresholds on outcome. We therefore recommend that normal ICP reference values for infants, children and adolescents and age-specific treatment thresholds are established through further studies.

AUTHOR CONTRIBUTIONS

SP have been responsible for the primary drafting and revision of the paper. All authors (SP, AL-C, RA, and MJ) have been contributing to the drafting and revising of the paper, giving their approval for publication and agree to be accountable for all aspects of the work.

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REFERENCES

1. Atike Ongun E. Prediction of mortality in pediatric traumatic brain injury: implementations from a tertiary pediatric intensive care facility. *Turkish J Trauma Emerg Surg.* (2017) 24:199–206. doi: 10.5505/tjtes.2017.37906
2. Parslow RC. Epidemiology of traumatic brain injury in children receiving intensive care in the UK. *Arch Dis Child.* (2005) 90:1182–7. doi: 10.1136/adc.2005.072405
3. Dewan MC, Rattani A, Gupta S, Baticulon RE, Hung Y-C, Punchak M, et al. Estimating the global incidence of traumatic brain injury. *J Neurosurg.* (2019) 130:1080–97. doi: 10.3171/2017.10.JNS17352
4. Thurman DJ. The epidemiology of traumatic brain injury in children and youths: a review of research since 1990. *J Child Neurol.* (2014) 31:20–7. doi: 10.1177/0883073814544363
5. Iaccarino C, Carretta A, Nicolosi F, Morselli C. Epidemiology of severe traumatic brain injury. *J Neurosurg Sci.* (2018) 62:535–541. doi: 10.23736/S0390-5616.18.04532-0
6. Tropeano MP, Spaggiari R, Ileyassoff H, Park KB, Kolias AG, Hutchinson PJ, et al. A comparison of publication to TBI burden ratio of low- and middle-income countries versus high-income countries: how can we improve worldwide care of TBI? *Neurosurg Focus.* (2019) 47:E5. doi: 10.3171/2019.8.FOCUS19507
7. Global Status Report on Road Safety (2018). Available online at: https://www.who.int/violence_injury_prevention/road_safety_status/2018/en/
8. Appavu B, Foldes ST, Adelson PD. Clinical trials for pediatric traumatic brain injury: definition of insanity? *J Neurosurg Pediatr.* (2019) 23:661–9. doi: 10.3171/2019.2.PEDS18384
9. Bell MJ, Adelson PD, Wisniewski SR. Challenges and opportunities for pediatric severe TBI—review of the evidence and exploring a way forward. *Child's Nerv Syst.* (2017) 33:1663–7. doi: 10.1007/s00381-017-3530-y
10. Kochanek PM, Tasker RC, Carney N, Totten AM, Adelson PD, Selden NR, et al. Guidelines for the management of pediatric severe traumatic brain injury, third edition. *Pediatr. Crit. Care Med.* (2019) 20:S1–82. doi: 10.1097/PCC.0000000000001735
11. Bell MJ, Adelson PD, Hutchison JS, Kochanek PM, Tasker RC, Vavilala MS, et al. Differences in medical therapy goals for children with severe traumatic brain injury—an international study. *Pediatr Crit Care Med.* (2013) 14:811–8. doi: 10.1097/PCC.0b013e3182975e2f
12. Guillaume J, Janny P. Continuous intracranial manometry; importance of the method and first results. *Rev. Neurol.* (1951) 84:131–42.
13. Lundberg, N. Continuous recording and control of ventricular fluid pressure in neurosurgical practice. *Acta Psychiatr Scand.* (1960) 36:1–193.
14. Lundberg N, Troupp H, Lorin H. Continuous recording of the ventricular-fluid pressure in patients with severe acute traumatic brain injury. A preliminary report. *J Neurosurg.* (1965) 22:581–90. doi: 10.3171/jns.1965.22.6.0581
15. Narayan V, Mohammed N, Savardekar AR, Patra DP, Notarianni C, Nanda A. Noninvasive intracranial pressure monitoring for severe traumatic brain injury in children: a concise update on current methods. *World Neurosurg.* (2018) 114:293–300. doi: 10.1016/j.wneu.2018.p02.159
16. Cardim D, Robba C, Bohdanowicz M, Donnelly J, Cabella B, Liu X, et al. Non-invasive monitoring of intracranial pressure using transcranial doppler ultrasonography: is it possible? *Neurocrit Care.* (2016) 25:473–91. doi: 10.1007/s12028-016-0258-6
17. Raboel PH, Bartek J, Andresen M, Bellander BM, Romner B. Intracranial pressure monitoring: invasive versus non-invasive methods-a review. *Crit Care Res Pract.* (2012) 2012:950393. doi: 10.1155/2012/950393
18. Ringstad G, Lindstrøm EK, Vatnehol SAS, Mardal K-A, Emblem KE, Eide PK. Non-invasive assessment of pulsatile intracranial pressure with phase-contrast magnetic resonance imaging. *PLoS ONE.* (2017) 12:e0188896. doi: 10.1371/journal.pone.0188896
19. Robba C, Bacigaluppi S, Cardim D, Donnelly J, Bertuccio A, Czosnyka M. Non-invasive assessment of intracranial pressure. *Acta Neurol Scand.* (2016) 134:4–21. doi: 10.1111/ane.12527
20. Ngo QN, Ranger A, Singh RN, Kornecki A, Seabrook JA, Fraser DD. External ventricular drains in pediatric patients. *Pediatr Crit Care Med.* (2009) 10:346–51. doi: 10.1097/PCC.0b013e3181a320cd
21. Miller C, Guillaume D. Incidence of hemorrhage in the pediatric population with placement and removal of external ventricular drains. *J Neurosurg Pediatr.* (2015) 16:662–7. doi: 10.3171/2015.5.PEDS1563

22. Jamjoom AAB, Joannides AJ, Poon MT-C, Chari A, Zaben M, Abdulla MAH, et al. Prospective, multicentre study of external ventricular drainage-related infections in the UK and Ireland. *J Neurol Neurosurg Psychiatry.* (2018) 89:120–6. doi: 10.1136/jnnp-2017-316415
23. Chau CYC, Craven CL, Rubiano AM, Adams H, Tülü S, Czosnyka M, et al. The evolution of the role of external ventricular drainage in traumatic brain injury. *J Clin Med.* (2019) 8:1422. doi: 10.3390/jcm8091422
24. Konstantelias AA, Vardakas KZ, Polyzos KA, Tansarli GS, Falagas ME. Antimicrobial-impregnated and -coated shunt catheters for prevention of infections in patients with hydrocephalus: a systematic review and meta-analysis. *J Neurosurg.* (2015) 122:1096–112. doi: 10.3171/2014.12.JNS14908
25. O'Leary ST, Kole MK, Hoover DA, Hysell SE, Thomas A, Shaffrey CI. Efficacy of the Ghajar Guide revisited: a prospective study. *J Neurosurg.* (2000) 92:801–3. doi: 10.3171/jns.2000.92.5.0801
26. Thomale UW, Schaumann A, Stockhammer F, Giese H, Schuster D, Kästner S, et al. GAVCA study: randomized, multicenter trial to evaluate the quality of ventricular catheter placement with a mobile health assisted guidance technique. *Clin Neurosurg.* (2018) 83:252–62. doi: 10.1093/neuros/nyx420
27. Shtaya A, Roach J, Sadek A-R, Gaastra B, Hempenstall J, Bulters D. Image guidance and improved accuracy of external ventricular drain tip position particularly in patients with small ventricles. *J Neurosurg.* (2019) 130:1268–73. doi: 10.3171/2017.11.JNS171892
28. Li Y, Chen X, Wang N, Zhang W, Li D, Zhang L, et al. A wearable mixed-reality holographic computer for guiding external ventricular drain insertion at the bedside. *J Neurosurg.* (2018). doi: 10.3171/2018.4.JNS18124. [Epub ahead of print].
29. Sahuquillo J, Poca M-A, Arribas M, Garnacho A, Rubio E. Interhemispheric supratentorial intracranial pressure gradients in head-injured patients: are they clinically important? *J Neurosurg.* (1999) 90:16–26. doi: 10.3171/jns.1999.90.1.0016
30. Andresen M, Juhler M, Thomsen OC. Electrostatic discharges and their effect on the validity of registered values in intracranial pressure monitors. *J Neurosurg.* (2013) 119:1119–24. doi: 10.3171/2013.7.JNS13506
31. Eide P, Holm S, Sorteberg W. Simultaneous monitoring of static and dynamic intracranial pressure parameters from two separate sensors in patients with cerebral bleeds: comparison of findings. *Biomed Eng.* (2012) 11:66. doi: 10.1186/1475-925X-11-66
32. Bruder N, N'Zoghe P, Graziani N, Pelissier D, Grisoli F, François G. A comparison of extradural and intraparenchymatous intracranial pressures in head injured patients. *Intensive Care Med.* (1995) 21:850–2. doi: 10.1007/BF01700971
33. Eide PK. Comparison of simultaneous continuous intracranial pressure (ICP) signals from ICP sensors placed within the brain parenchyma and the epidural space. *Med Eng Phys.* (2008) 30:34–40. doi: 10.1016/j.medengphy.2007.01.005
34. Poca MA, Sahuquillo J, Topczewski T, Peñarrubia MJ, Muns A. Is intracranial pressure monitoring in the epidural space reliable? *Fact Fiction J Neurosurg.* (2007) 106:548–56. doi: 10.3171/jns.2007.106.4.548
35. Weinstabl C, Richling B, Plainer B, Czech T, Spiss CK. Comparative analysis between epidural (Gaeltec) and subdural (Camino) intracranial pressure probes. *J Clin Monit.* (1992) 8:116–20. doi: 10.1007/BF01617429
36. Welschehold S, Schmalhausen E, Dodier P, Vulcu S, Oertel J, Wagner W, et al. First clinical results with a new telemetric intracranial pressure-monitoring system. *Neurosurgery.* (2012) 70:44–9; discussion 49. doi: 10.1227/NEU.0b013e31822dda12
37. Lilja-Cyron A, Kelsen J, Andresen M, Fugleholm KK, Juhler M. Feasibility of telemetric intracranial pressure monitoring in the neuro intensive care unit. *J Neurotrauma.* (2018) 35:1578–86. doi: 10.1089/neu.2017.5589
38. Antes S, Tschan CA, Kunze G, Ewert L, Zimmer A, Halfmann A, et al. Clinical and radiological findings in long-term intracranial pressure monitoring. *Acta Neurochir.* (2014) 156:1009–19; discussion 1019. doi: 10.1007/s00701-013-1991-7
39. Lilja A, Andresen M, Hadi A, Christoffersen D, Juhler M. Clinical experience with telemetric intracranial pressure monitoring in a Danish neurosurgical center. *Clin Neurol Neurosurg.* (2014) 120:36–40. doi: 10.1016/j.clineuro.2014.02.010
40. Citerio G, Piper I, Chambers IR, Galli D, Enblad P, Kiening K, et al. Multicenter clinical assessment of the Raumedic Neurovent-P intracranial pressure sensor: a report by the BrainIT group. *Neurosurgery.* (2008) 63, 1152–8; discussion 1158. doi: 10.1227/01.NEU.0000335148.87042.D7
41. Gelabert-González M, Ginesta-Galan V, Sernamito-García R, Allut AG, Bandin-Diéguez J, Rumbo RM. The Camino intracranial pressure device in clinical practice. Assessment in a 1000 cases. *Acta Neurochir.* (2006) 148:435–41. doi: 10.1007/s00701-005-0683-3
42. Koskinen L-OD, Grayson D, Olivecrona M. The complications and the position of the Codman MicroSensor^{TM} ICP device: an analysis of 549 patients and 650 Sensors. *Acta Neurochir.* (2013) 155:2141–8; discussion 2148. doi: 10.1007/s00701-013-1856-0
43. Antes S, Stadie A, Müller S, Linsler S, Breuskin D, Oertel J. Intracranial pressure-guided shunt valve adjustments with the Miethke sensor reservoir. *World Neurosurg.* (2018) 109:e642–50. doi: 10.1016/j.wneu.2017.10.044
44. Norager NH, Lilja-Cyron A, Hansen TS, Juhler M. Deciding on appropriate telemetric intracranial pressure monitoring system. *World Neurosurg.* (2019) 126:564–9. doi: 10.1016/j.wneu.2019.03.077
45. Kochanek PM, Tasker RC, Bell MJ, Adelson PD, Carney N, Vavilala MS, et al. Management of pediatric severe traumatic brain injury: 2019 consensus and guidelines-based algorithm for first and second tier therapies. *Pediatr Crit Care Med.* (2019) 20:269–79. doi: 10.1097/PCC.0000000000001737
46. Volovici V, Huijben JA, Ercole A, Stocchetti N, Dirven CMF, van der Jagt M, et al. Ventricular drainage catheters versus intracranial parenchymal catheters for intracranial pressure monitoring-based management of traumatic brain injury: a systematic review and meta-analysis. *J Neurotrauma.* (2019) 36:988–95. doi: 10.1089/neu.2018.6086
47. Kasotakis G, Michailidou M, Bramos A, Chang Y, Velmahos G, Alam H, et al. Intraparenchymal vs extracranial ventricular drain intracranial pressure monitors in traumatic brain injury: less is more? *J Am Coll Surg.* (2012) 214:950–7. doi: 10.1016/j.jamcollsurg.2012.03.004
48. Tavakoli S, Peitz G, Ares W, Hafeez S, Grandhi R. Complications of invasive intracranial pressure monitoring devices in neurocritical care. *Neurosurg Focus.* (2017) 43:E6. doi: 10.3171/2017.8.FOCUS17450
49. Zacchetti L, Magnoni S, Di Corte F, Zanier ER, Stocchetti N. Accuracy of intracranial pressure monitoring: systematic review and meta-analysis. *Crit Care.* (2015) 19:420. doi: 10.1186/s13054-015-1137-9
50. Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GWJ, Bell MJ, et al. Guidelines for the management of severe traumatic brain injury, Fourth Edition. *Neurosurgery.* (2017) 80:6–15. doi: 10.1227/NEU.0000000000001432
51. Güiza F, Depreitere B, Piper I, Citerio G, Chambers I, Jones PA, et al. Visualizing the pressure and time burden of intracranial hypertension in adult and paediatric traumatic brain injury. *Intensive Care Med.* (2015) 41:1067–76. doi: 10.1007/s00134-015-3806-1
52. Andresen M, Hadi A, Petersen LG, Juhler M. Effect of postural changes on ICP in healthy and ill subjects. *Acta Neurochir.* (2015) 157:109–13. doi: 10.1007/s00701-014-2250-2
53. Andresen M, Hadi A, Juhler M. Evaluation of intracranial pressure in different body postures and disease entities. *Acta Neurochir Suppl.* (2016) 122:45–7. doi: 10.1007/978-3-319-22533-3_9
54. Sæhle T, Eide PK. Intracranial pressure monitoring in pediatric and adult patients with hydrocephalus and tentative shunt failure: a single-center experience over 10 years in 146 patients. *J Neurosurg.* (2015) 122:1076–86. doi: 10.3171/2014.12.JNS141029
55. Pedersen SH, Lilja-Cyron A, Andresen M, Juhler M. The relationship between intracranial pressure and age—chasing age-related reference values. *World Neurosurg.* (2017) 110:e119–23. doi: 10.1016/j.wneu.2017.10.086
56. Chari A, Dasgupta D, Smedley A, Craven C, Dyson E, Matloob S, et al. Intraparenchymal intracranial pressure monitoring for hydrocephalus and cerebrospinal fluid disorders. *Acta Neurochir.* (2017) 159:1967–78. doi: 10.1007/s00701-017-3281-2
57. Avery RA, Shah SS, Licht DJ, Seiden JA, Huh JW, Boswinkel J, et al. Reference range for cerebrospinal fluid opening pressure in children. *N Engl J Med.* (2010) 363:891–3. doi: 10.1056/NEJMc1004957
58. Mollan SP, Davies B, Silver NC, Shaw S, Mallucci CL, Wakerley BR, et al. Idiopathic intracranial hypertension: consensus guidelines on management. *J Neurol Neurosurg Psychiatry.* (2018) 89:1088–100. doi: 10.1136/jnnp-2017-317440

59. Figaji AA. Anatomical and physiological differences between children and adults relevant to traumatic brain injury and the implications for clinical assessment and care. *Front Neurol.* (2017) 8:685. doi: 10.3389/fneur.2017.00685
60. Astrand R, Rosenlund C, Undén J. Scandinavian guidelines for initial management of minor and moderate head trauma in children. *BMC Med.* (2016) 14:33. doi: 10.1186/s12916-016-0574-x
61. Bennett TD, Riva-Cambrin J, Keenan HT, Korgenski EK, Bratton SL. Variation in intracranial pressure monitoring and outcomes in pediatric traumatic brain injury. *Arch Pediatr Adolesc Med.* (2012) 166:641–7. doi: 10.1001/archpediatrics.2012.322
62. Alkhoury F, Kyriakides TC. Intracranial pressure monitoring in children with severe traumatic brain injury: national trauma data bank-based review of outcomes. *JAMA Surg.* (2014) 149:544–8. doi: 10.1001/jamasurg.2013.4329
63. Bennett TD, DeWitt PE, Greene TH, Srivastava R, Riva-Cambrin J, Nance ML, et al. Functional outcome after intracranial pressure monitoring for children with severe traumatic brain injury. *JAMA Pediatr.* (2017) 171:965–71. doi: 10.1001/jamapediatrics.2017.2127
64. Adelson PD, Ragheb J, Muizelaar JP, Kanev P, Brockmeyer D, Beers SR, et al. Phase II clinical trial of moderate hypothermia after severe traumatic brain injury in children. *Neurosurgery.* (2005) 56:740–53. doi: 10.1227/01.NEU.0000156471.50726.26
65. Alberico AM, Ward JD, Choi SC, Marmarou A, Young HF. Outcome after severe head injury. *J Neurosurg.* (2009) 67:648–56. doi: 10.3171/jns.1987.67.5.0648
66. Cruz J, Nakayama P, Imamura JH, Rosenfeld KGW, De Souza HS, Giorgetti GVF, et al. Cerebral extraction of oxygen and intracranial hypertension in severe, acute, pediatric brain trauma: preliminary novel management strategies. *Neurosurgery.* (2002) 50:774–80. doi: 10.1097/00006123-200204000-00017
67. Downard C, Hulka F, Mullins RJ, Piatt J, Chesnut R, Quint P, et al. Relationship of cerebral perfusion pressure and survival in pediatric brain-injured patients. *J Trauma - INJ Infect Crit Care.* (2000) 49:654–9. doi: 10.1097/00005373-200010000-00012
68. Kasoff SS, Lansen TA, Holder D, Filippo JS. Aggressive physiologic monitoring of pediatric head trauma patients with elevated intracranial pressure. *Pediatr Neurosci.* (1988) 14:241–9. doi: 10.1159/000120397
69. Miller Ferguson N, Shein SL, Kochanek PM, Luther J, Wisniewski SR, Clark RSB, et al. Intracranial hypertension and cerebral hypoperfusion in children with severe traumatic brain injury: thresholds and burden in accidental and abusive insults. *Pediatr Crit Care Med.* (2016) 17:444–50. doi: 10.1097/PCC.0000000000000709
70. Pfenninger J, Santi A. Severe traumatic brain injury in children–are the results improving? *Swiss Med Wkly.* (2002) 132:116–20. doi: 10.1016/j.pedhc.2014.09.003
71. Mehta A, Kochanek M, Tyler-kabara E, Bell RL, Clark SB, Bell J. Relationship of intracranial pressure and cerebral perfusion pressure with outcome in young children after severe traumatic brain injury. *Dev Neurosci.* (2010) 32:413–9. doi: 10.1159/000316804
72. Chambers IR, Treadwell L, Mendelow AD. Determination of threshold levels of cerebral perfusion pressure and intracranial pressure in severe head injury by using receiver operating—characteristic curves: an observational study in 291 patients. *J Neurosurg.* (2009) 94:412–6. doi: 10.3171/jns.2001.94.3.0412
73. Pfenninger J, Kaiser G, Lütschg J, Sutter M. Treatment and outcome of the severely head injured child. *Intensive Care Med.* (1983) 9:13–6. doi: 10.1007/BF01693699
74. Sarnaik A, Ferguson NM, O'Meara AI, Agrawal S, Deep A, Buttram S, et al. Age and mortality in pediatric severe traumatic brain injury: results from an international study. *Neurocrit Care.* (2018) 28:302–13. doi: 10.1007/s12028-017-0480-x
75. Grinkeviciute DE, Kevalas R, Matukevicius A, Ragaisis V, Tamasauskas A. Significance of intracranial pressure and cerebral perfusion pressure in severe pediatric traumatic brain injury. *Medicina.* (2008) 44:119–25. doi: 10.3390/medicina44020015
76. Andresen M, Juhler M. Intracranial pressure following complete removal of a small demarcated brain tumor: a model for normal intracranial pressure in humans. *J Neurosurg.* (2014) 121:1–5. doi: 10.3171/2014.2.JNS132209
77. Chapman PH, Cosman ER, Arnold MA. The relationship between ventricular fluid pressure and body position in normal subjects and subjects with shunts. *Neurosurgery.* (1990) 181. doi: 10.1097/00006123-199002000-00001
78. Citerio G, Prisco L, Oddo M, Meyfroidt G, Helbok R, Stocchetti N, et al. International prospective observational study on intracranial pressure in intensive care (ICU): the SYNAPSE-ICU study protocol. *BMJ Open.* (2019) 9:1–5. doi: 10.1136/bmjopen-2018-026552
79. Figaji AA, Zwane E, Fieggen AG, Argent AC, Le Roux PD, Siesjo P, et al. Pressure autoregulation, intracranial pressure, and brain tissue oxygenation in children with severe traumatic brain injury. *J Neurosurg Pediatr.* (2009) 4:420–8. doi: 10.3171/2009.6.PEDS096
80. Nagel C, Diedler J, Gerbig I, Heimberg E, Schuhmann MU, Hockel K. State of cerebrovascular autoregulation correlates with outcome in severe infant/pediatric traumatic brain injury. *Acta Neurochir.* (2016) 122:239–244. doi: 10.1007/978-3-319-22533-3_48
81. Armstead WM. Cerebral blood flow autoregulation and dysautoregulation. *Anesthesiol Clin.* (2016) 34:465–77. doi: 10.1016/j.anclin.2016.04.002
82. Czosnyka M, Smielewski P, Kirkpatrick P, Laing RJ, Menon D, Pickard JD. Continuous assessment of the cerebral vasomotor reactivity in head injury. *Neurosurgery.* (1997) 41:11–9. doi: 10.1097/00006123-199707000-00005
83. Young AMH, Donnelly J, Czosnyka M, Jalloh I, Liu X, Aries MJ, et al. Continuous multimodality monitoring in children after traumatic brain injury—preliminary experience. *PLoS ONE.* (2016) 11:e0148817. doi: 10.1371/journal.pone.0148817
84. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (2004). The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics* 114:555–76. doi: 10.1542/peds.114.2.S2.555

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Epidemiology of Pediatric Traumatic Brain Injury and Hypothalamic-Pituitary Disorders in Arizona

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Traumatic brain injury (TBI) in children can result in long-lasting social, cognitive, and neurological impairments. In adults, TBI can lead to endocrinopathies (endocrine system disorders), but this is infrequently reported in children. Untreated endocrinopathies can elevate risks of subsequent health issues, such that early detection in pediatric TBI survivors can initiate clinical interventions. To understand the risk of endocrinopathies following pediatric TBI, we identified patients who had experienced a TBI and subsequently developed a new-onset hypothalamic regulated endocrinopathy ($n = 498$). We hypothesized that pediatric patients who were diagnosed with a TBI were at higher risk of being diagnosed with a central endocrinopathy than those without a prior diagnosis of TBI. In our epidemiological assessment, we identified pediatric patients enrolled in the Arizona Health Care Cost Containment System (AHCCCS) from 2008 to 2014 who were diagnosed with one of 330 TBI International Classification of Diseases (ICD)-9 codes and subsequently diagnosed with one of 14 central endocrinopathy ICD-9 codes. Additionally, the ICD-9 code data from over 600,000 Arizona pediatric patients afforded an estimate of the incidence, prevalence, relative risk, odds ratio, and number needed to harm, regarding the development of a central endocrinopathy after sustaining a TBI in Arizona Medicaid pediatric patients. Children with a TBI diagnosis had 3.22 times the risk of a subsequent central endocrine diagnosis compared with the general population (±0.28). Pediatric AHCCCS patients with a central endocrine diagnosis had 3.2-fold higher odds of a history of a TBI diagnosis than those without an endocrine diagnosis (±0.29). Furthermore, the number of patients with a TBI diagnosis for one patient to receive a diagnosis of a central endocrine diagnosis was 151.2 (±6.12). Female subjects were more likely to present with a central endocrine diagnosis after a TBI diagnosis compared to male subjects (64.1 vs. 35.9%). These results are the first state-wide epidemiological study conducted to determine the risk of developing a

hypothalamic-pituitary disorder after a TBI in the pediatric population. Our results contribute to a body of knowledge demonstrating a TBI etiology for idiopathic endocrine disorders, and thus advise physicians with regard to TBI follow-up care that includes preventive screening for endocrine disorders.

Keywords: traumatic brain injury, pediatrics, endocrine dysfunction, concussion, adolescence, hypopituitarism, puberty, head injury

INTRODUCTION

In children, traumatic brain injuries (TBIs) account for over 812,000 emergency department visits every year and are a leading cause of childhood mortality and morbidity in the United States (1). A TBI can be defined as a non-degenerative, non-congenital insult to the brain from an external mechanical force, potentially leading to permanent or temporary impairment of cognitive, physical, and psychosocial functions, with an associated diminished or altered state of consciousness. Those who survive pediatric TBI are at risk for poor developmental and functional outcomes later in life. Very young children may be particularly vulnerable to the effects of TBI as the brain is under continuous development throughout childhood (2). Pediatric survivors of TBI are at increased risk for worse behavioral, social, and academic outcomes compared to their peers (3–6). Moreover, pediatric survivors of TBI show high incidence of health issues including pain, cardiovascular, and metabolic disorders (2). In particular, TBI precede the development of endocrinopathies, or dysfunction of the endocrine system, as reported in adults (7–11). Furthermore, both early and late endocrine changes can occur after TBI in pediatric patients (12). These alterations include acute alterations in the hypothalamic-pituitary-adrenal axis, antidiuretic hormone regulation, growth hormone (GH) deficiency, disturbances in puberty, central hypothyroidism [hypothyroidism due to insufficient stimulations by thyroid stimulating hormone (TSH) of an otherwise normal thyroid gland], and elevated prolactin, which can each be temporary or permanent (12, 13). The goal of this study was to better understand the epidemiology of TBI and subsequent endocrinopathy in the pediatric population. We hypothesized that pediatric patients who were diagnosed with a TBI were at greater risk of being diagnosed with a hypothalamic-pituitary disorder than those without a prior diagnosis of TBI.

In adults, the prevalence of endocrinopathy following TBI is common, with the most prevalent disorder being GH deficiency (7, 10, 14, 15). A recent meta-analysis that included data from 2,756 adult TBI patients reported a 32% overall prevalence of at least one endocrine diagnosis after TBI (8). Similarly, a previous meta-analysis that included data of 1,203 adult TBI patients, reported a 27.8% overall prevalence of at least one endocrine dysfunction, with 6.2% of patients having more than one endocrine dysfunction post-TBI (16). However, the prevalence of endocrine dysfunction after TBI in the pediatric population is less clear. Between 1977 and 2004, only a total of 20 pediatric cases of hypopituitarism after TBI were reported. Across these reports, the interval between TBI and endocrine diagnosis ranged from 1 to 42 years (17), which highlights the lack of recorded data in this domain. The prevalence of endocrine dysfunction following a TBI in pediatric studies ranged from 5 to 57% and up to 86% in studies including hyperprolactinemia as an abnormality (17). However, more recent studies show that endocrine dysfunction may be a common occurrence following pediatric TBI (18–23). These existing reports differ in the eligible pediatric population, inclusion criteria, and methodological design, in addition to varied hormonal assessment, baseline profile, and dynamic tests, sometimes in subsets of subjects (24–30), which compromise the ability to compare between studies. Thus, there is a need to better understand whether a TBI diagnosis is a risk factor for a subsequent endocrine diagnosis in the pediatric population. Here, we present the epidemiology of central endocrine diagnoses following a patient's first TBI diagnosis in the Arizona pediatric population, with a focus on male/female patients and time between TBI and endocrine diagnoses.

METHODS

Inclusion and Exclusion Criteria

We used de-identified patient records from the Arizona Health Care Cost Containment System (AHCCCS), the Medicaid program for the state of Arizona. We queried the AHCCCS database for patients ($\leq$18 years old) with a TBI diagnosis followed by a central endocrine diagnosis after the initial TBI diagnosis (see **Appendices 1, 2** for International Classification of Diseases (ICD)-9 diagnoses codes for TBI and endocrinopathies, respectively). Based on clinical relevance and inputs from care providers, TBI diagnoses were restricted to a total of 330 diagnoses of concussion, skull fracture, cerebral injury or hemorrhage, and head injury; cerebrovascular diseases were excluded. Central endocrine diagnoses were restricted to 14 diagnoses of the pituitary, the hypothalamus, diabetes insipidus, and puberty, excluding premorbid diabetes, toxic exposure, and circadian rhythm disorders. Inclusion/exclusion criteria for the research study primarily identified cases of TBI followed by an endocrine diagnosis, with both diagnoses having occurred before or at the age of 18. In addition, we included only patients who were continuously enrolled in AHCCCS with no more than a 30-day gap in coverage per year, in order to assure that missed diagnoses were minimized. The number of patients found in these records was sufficient to conduct an epidemiological study to determine the relationships between age and gender (only male and female) of patients with a TBI diagnosis and subsequent endocrine diagnosis. The inclusion/exclusion criteria for the population is presented in **Table 1**. The study protocol was reviewed and approved by the

TABLE 1 | Inclusion/exclusion criteria for the sample population.

Inclusion criteria
Age 0 ≤ 18 years
Located in Arizona
Enrolled in AHCCCS Medicaid from 2008 to 2014 without a lapse >30 days
Diagnosis of TBI
Diagnosis of an endocrine disorder after the TBI diagnosis
All diagnoses prior to or at the age of 18
Patients diagnosed with a TBI prior to or at the age of 18, without an endocrine disorder
Patients diagnosed with an endocrine disorder prior to or at the age of 18, without a TBI
Exclusion criteria
Diagnosis of an endocrine disorder prior to TBI

AHCCCS, Arizona Health Care Cost Containment Service; TBI, Traumatic Brain Injury.

Phoenix Children's Hospital Institutional Review Board (IRB 15-021) and deferred by the University of Arizona and Arizona State University.

Data Analysis

To evaluate the risk of endocrine diagnosis after TBI diagnosis, a limited data set with ICD-9 diagnosis and billing codes was extracted for individual patients in the sample. Demographic data and care delivery dates populated four cohorts (see contingency matrix in **Table 2**): patients diagnosed with TBI and subsequent endocrine disorder (TBI+, Endo+; A), with TBI and without endocrine disorder (TBI+, Endo–; B), without TBI and with endocrine disorder (TBI–, Endo+; C), and with neither TBI nor endocrine diagnoses (TBI–, Endo–; D). Based on the contingency table and demographic data, calculations produced the prevalence, incidence, relative risk, odds ratio, attributable risk, and number needed to harm of endocrine diagnosis after TBI diagnosis stratified by age and male/female patients. Data pre-processing and analyses were performed using Python (version 3.7.3). Prevalence was calculated as the number of TBI patients with an endocrine diagnosis divided by those TBI patients without an endocrine diagnosis for each year (A/C). Incidence rate was calculated as the number of new cases per year of endocrine diagnoses in TBI patients divided by the cumulative population of TBI patients $\left(A/(A+B)\right)$. Relative risk was calculated as the ratio of endocrine diagnoses in subjects with and without TBI $\left(\frac{A}{(A+B)}/\frac{C}{(C+D)}\right)$. Odds ratio was calculated as the ratio of patients with endocrine diagnoses and TBI to those without TBI as a fraction of patients without endocrine diagnoses and TBI to those without TBI $\left(\frac{A}{C}/\frac{B}{D}\right)$. Attributable risk was calculated as the difference in risk between patients with TBI and those without TBI $\left(\frac{A}{A+B}-\frac{C}{C+D}\right)$. Number needed to harm was calculated as the inverse of the attributable risk $\left(\frac{1}{Attributable\ Risk}\right)$. Epidemiological calculations were performed for each year, averaged over the 7 years. Prevalence of TBI and endocrine dysfunction are reported as mean and 90% confidence interval.

TABLE 2 | Contingency table of sample populations for 2008–2014.

	TBI+		TBI–	
Year	**Endo+**	**Endo–**	**Endo+**	**Endo–**
2008	144	15,238	1,334	568,645
2009	154	16,919	1,585	646,008
2010	191	20,389	1,945	606,738
2011	220	20,906	2,024	622,756
2012	221	22,597	2,168	629,391
2013	223	22,153	2,237	616,052
2014	232	22,353	2,137	657,512

Contingency table of the sample populations used in this study. The table shows the database population for each year included in the analysis. TBI+, traumatic brain injury diagnosis present; TBI–, TBI diagnosis absent; Endo+, central endocrine diagnosis present; Endo–, central endocrine diagnosis absent.

TABLE 3 | Prevalence of hypothalamic-pituitary disorder after a TBI diagnosis for male subjects and female subjects and across age ranges.

	TBI+, Endo+	
	Percent (*n*)	**Prevalence**
Total	100.00% (498)	0.103
Male	35.94% (179)	0.278
Female	64.06% (319)	0.758
Age range	**Prevalence**	
0–0.9 years	0.042	
1–1.9 years	0.046	
2–2.9 years	0.061	
3–3.9 years	0.072	
4–4.9 years	0.104	
5–5.9 years	0.153	
6–6.9 years	0.151	
7–7.9 years	0.213	
8–8.9 years	0.203	
9–9.9 years	0.188	
10–10.9 years	0.167	
11–11.9 years	0.163	
12–12.9 years	0.128	
13–13.9 years	0.109	
14–14.9 years	0.152	
15–15.9 years	0.104	
16–16.9 years	0.091	
17–17.9 years	0.069	

RESULTS

Prevalence of TBI and Endocrine Dysfunction Stratified by Age

The AHCCCS provided care for an average of 643,212 (±19,097 at CI of 90%) pediatric patients per year for analysis. From the 275,781 unique patients with either a TBI or central endocrine diagnosis, there were 498 unique patients who were diagnosed with a TBI and a subsequent endocrine diagnosis between 2008

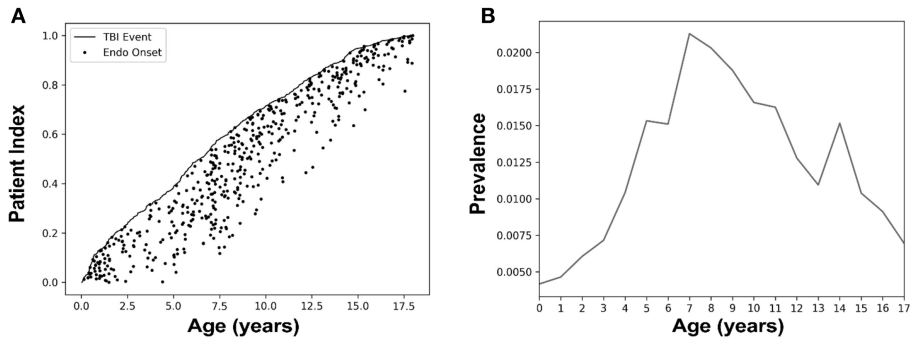

FIGURE 1 | Pediatric patients with a traumatic brain injury (TBI) who were diagnosed with a hypothalamic-pituitary disorder showed the highest prevalence in ages 7–11. **(A)** Patients ($n = 498$) with a TBI and subsequent endocrine diagnosis were indexed by age. Here, we sorted all patients of our group of interest by age with patient index referring to the fraction of the total. The black line represents the age of each patient when they were diagnosed with a TBI, and the dot tracking along the x-axis from the line indicates the subsequent onset of their first endocrine diagnosis. **(B)** Prevalence of an endocrine diagnosis after a TBI stratified by age at the endocrine diagnosis. Here, prevalence was calculated as the number of TBI patients with an endocrine diagnosis divided by those TBI patients without an endocrine. Children aged 7–11 years had the highest prevalence of an endocrine disorder diagnosis after a TBI diagnosis compared to other age groups.

and 2014, with an annual average of 197.9 (±22.3 at CI of 90%) unique patients within each year. A total of 107,458 children were diagnosed with a TBI before or at the age of 18 years.

The 498 patients with a TBI and subsequent endocrine diagnosis were indexed by age to show age at TBI and age at endocrine diagnosis (**Figure 1A**). The 18-year upper age limit for both TBI and endocrine diagnosis sets an arbitrary ceiling effect on the data. The overall prevalence for an endocrine diagnosis after TBI was 0.103 (±0.003 at CI of 90%), with the highest prevalence of an endocrine disorder diagnosis after a TBI diagnosis occurring in the age range of 7–11 years old (**Figure 1B**). The overall incidence was 0.0014 (±0.0002 at CI of 90%). We calculated a relative risk of 3.22 (±0.29 at CI of 90%), and an odds ratio of 3.24 (±0.29 at CI of 90%), indicating that patients exposed to pediatric TBI had about 3 times the risk of a central endocrine diagnosis compared to the general population. We observe an average number needed to harm of 151.19 (±6.12 at CI of 90%), meaning that for every 151 children diagnosed with a TBI, one would have a hypothalamic-pituitary disorder.

Male/Female Differences With Age

The AHCCCS dataset contained binary entries for male and female as entered by the health care facility, which were used to calculate prevalence and incidence. **Table 3** shows the prevalence of hypothalamic-pituitary disorder after a TBI diagnosis for male subjects and female subjects across age ranges. In the sample of children with a TBI diagnosis followed by an endocrine diagnosis, female individuals ($n = 319$) outnumbered male individuals ($n = 179$). However, the prevalence of an endocrine diagnosis after a TBI diagnosis in female patients (0.758) was almost three times the prevalence in male patients (0.278; **Table 3**). The greatest number of TBIs with subsequent endocrine diagnoses in female patients occurred at <2 and 5–8 years of age, whereas male patients had the most between 8 and 12 years of age (**Figure 2A**). Regardless, both male subjects and female subjects had a high rate of endocrine diagnoses between 7 and 15 years of age (**Figure 2A**). By 4-year age band, the incidence associated with the age of an endocrine diagnosis differed between female subjects and male subjects, where female subjects showed higher overall incidence and at younger ages than male subjects (**Figure 2B**). The time gap between TBI diagnosis and endocrine diagnosis differed between male and female patients (**Figure 2C**). Both male and female patients were weighted toward an endocrine diagnosis within 2 years of TBI, with the bulk of female patients receiving the diagnosis early.

Predominant ICD-9 Codes Used and Diagnoses Over the Years

Table 4 shows the frequency and the number of patients for each of the 14 endocrine-related ICD-9 codes analyzed in the study, and for the 10 most frequent TBI-related ICD-9 codes reported in the database. The predominant TBI diagnosis code identified in the sample was 959.01 (Head Injury: Unspecified) which comprised ∼64% of the subjects. Of note, 15% of subjects had concussion (850.X) TBI diagnosis codes. The predominant endocrine disorder code, based on the number of subjects, found in the current study were 259.1 (Precocious sexual development and puberty; not elsewhere classified) which comprised ∼59% of the subjects followed by 253.3 (Pituitary dwarfism/GH deficiencies) which comprised 9% of subjects. The substantial number of unspecified head injury diagnostic codes (959.01) prevented a meaningful analysis between TBI and endocrine disorder diagnoses.

DISCUSSION

This is the first study to determine the epidemiology of new-onset central endocrinopathies after TBI in the pediatric population in Arizona. Our analyses indicated an increased risk of a hypothalamic-pituitary disorder for patients with a history of pediatric TBI diagnosis. We observed important male/female differences, where female patients exhibited a higher incidence peaking at an earlier age range compared to male patients, and with female subjects displaying a higher prevalence of endocrine diagnosis after a TBI diagnosis compared to male subjects.

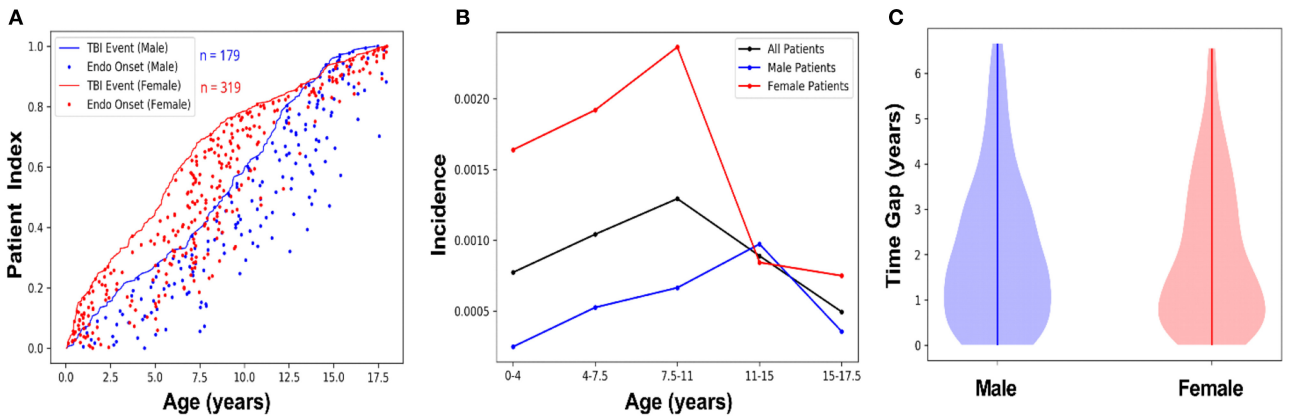

FIGURE 2 | Female subjects show a higher incidence, and an early age of onset, of hypothalamic-pituitary disorder following TBI compared to male subjects. **(A)** Male and female patients with a TBI diagnosis and subsequent endocrine diagnosis were indexed by age, as a fraction of the total number of subjects in each group. The lines represent male ($n = 179$; blue) and female ($n = 319$; red) age of each patient when they were diagnosed with a TBI, and the dots tracking along the x-axis from the line indicate male (blue) and female (red) age at the time of their first endocrine diagnosis. **(B)** Endocrine diagnosis incidence rates after TBI were calculated for male/female patients in blocks of 4-year age groups, with children older than 0 and ≤4 years old in the first block, followed by children >4 years old and ≤7.5 years old in the second block, etc. Female subjects diagnosed with a TBI (red line) were more likely to have a central endocrine diagnosis at an earlier age compared with male subjects diagnosed with a TBI (blue line). The overall incidence of endocrine dysfunction peaked between ages 7 and 11. This is driven by the higher overall incidence of post-TBI endocrine diagnoses in female patients, compared to male patients, whose incidence peaks between ages 11 and 15. Incidence rate was calculated as the number of new cases per year of endocrine diagnoses in TBI patients divided by the cumulative population of TBI patients. **(C)** Data stratified by male/female indicated female patients showed a shorter time gap between diagnosis of TBI and subsequent endocrine diagnosis compared with male subjects, but not necessarily reflect the onset of undiagnosed symptoms.

Overall, both incidence and prevalence of endocrine diagnosis following a TBI diagnosis peaked between ages 7–11, roughly within 2 years of the initial TBI diagnosis. Additionally, by using data from over 600,000 Arizona pediatric patients per year, we are the first to successfully estimate the epidemiology, relative risk, odds ratio, and number needed to harm of developing a central endocrinopathy after sustaining a TBI in Arizona Medicaid pediatric patients.

Mechanisms of Endocrine Dysfunction

The exact mechanisms behind endocrine dysfunction following pediatric TBI are unknown, but may be attributed to direct damage to the hypothalamus or pituitary gland. Together, the hypothalamus and pituitary are an integral system in regulating neuronal and hormonal function. The pituitary gland is regulated by a centrally located collection of neurons in the hypothalamus. The hypothalamus secretes precursors and hormones that travel through the hypophyseal portal blood system to act on receptors in the pituitary. The pituitary gland is a major endocrine gland that secretes hormones necessary for normal physiologic functioning such as growth hormone (GH), thyroid stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), prolactin (PRL), luteinizing hormone (LH), follicle stimulating hormone (FSH), anti-diuretic hormone (ADH), and oxytocin. Injury to either the hypothalamus or pituitary gland due to TBI has been shown, in both pre-clinical and clinical studies, to promote endocrine dysfunction due to imbalance in the hormones regulated by these structures (14, 31–35).

Mechanically, the forces of a TBI can selectively damage the hypothalamus and/or the pituitary gland due to their location close to the base of the skull. The pituitary sits at the base of the brain, encapsulated by the hypophyseal fossa, the innermost aperture of the sella turcica, a small cavity within the sphenoid bone of the human skull. It is because of this position in the skull that the pituitary is susceptible to mechanical injury from the impact of blunt force head trauma. Indeed, early studies assessing pituitary damage following TBI found that necrosis in the pituitary gland occurred after injury in patients that had died from TBI (36). More recent studies confirmed that cell death, vascular compromise/hemorrhage, and diffuse axonal injury can result from TBI and lead to damage of the pituitary [reviewed in (37)]. Moreover, a recent study found that individuals who sustained a skull fracture as a result of TBI had the highest rate of pituitary dysfunction after a 1-year follow up (38). As such, the impact forces that occur during a TBI event may directly damage the pituitary or hypothalamus. Without case details on the type and severity of injury, compounded by the majority of TBI diagnosis codes as head injury—unspecified, the relationship between mode of TBI and pituitary or hypothalamus damage cannot be determined. Future population studies with access to imaging findings could uncover this important relationship.

Prevalence of Endocrine Diagnosis Following a TBI Diagnosis in the Literature

Studies have reported long-term hypopituitarism in the range of 11–69% for TBI survivors, and endocrinopathies have become increasingly recognized over the past couple decades as a consequence of TBI (7, 20, 39). In 2005, the International Consensus Guidelines published screening guidelines for hypopituitarism after TBI in adults, recommending pituitary

TABLE 4 | Top 10 reported ICD-9 codes for TBI-related diagnoses, and 14 ICD-9 codes for endocrine related diagnoses.

ICD-9 code	Description	Number of patients	Frequency (%)
TBI-RELATED			
959.01	Head injury; unspecified	96,421	66.4
850.00	Concussion with no loss of consciousness	10,446	7.2
850.90	Concussion; unspecified	7,850	5.4
850.50	Concussion with loss of consciousness of unspecified duration	3,865	2.7
802.00	Fracture of face bones	3,822	2.6
850.11	Concussion; with loss of consciousness of 30 min or less	3,562	2.5
854.01	Intracranial injury of other and unspecified nature without mention of open intracranial wound; with no loss of consciousness	2,392	1.6
800.01	Closed fracture of vault of skull without mention of intracranial injury; with no loss of consciousness	1,489	1.0
802.80	Closed fracture of other facial bones	1,109	0.8
801.01	Closed fracture of base of skull without mention of intra cranial injury; with no loss of consciousness	943	0.6
ENDOCRINE-RELATED			
259.10	Precocious sexual development and puberty; not elsewhere classified	5,334	59.4
253.30	Pituitary dwarfism	856	9.5
259.00	Delay in sexual development and puberty; not elsewhere classified	731	8.1
253.50	Diabetes Insipidus	407	4.5
253.20	Panhypopituitarism	405	4.5
253.10	Other and unspecified anterior pituitary hyperfunction	319	3.6
253.80	Other disorders of the pituitary and other syndromes of diencephalohypophyseal origin	244	2.7
253.40	Other anterior pituitary disorders	177	2.0
253.90	Unspecified disorder of the pituitary gland and its hypothalamic control	172	1.9
253.60	Other disorders of neurohypophysis	147	1.6
256.39	Other ovarian failure	118	1.3
253.70	Latrogenic pituitary disorders	64	0.7
256.31	Premature menopause	5	0.05
628.1	Infertility; female; of pituitary hypothalamic origin	0	0

function screening for all patients with moderate (Glasgow coma score 9–12) to severe TBI (Glasgow coma score 3–8) (20). Although the hypothalamic-pituitary axis regulates normal childhood development, relatively few studies focus on pediatric patients, and no endocrine dysfunction screening guidelines exist for children diagnosed with a TBI. Retrospective and prospective studies report variable rates of hypopituitarism after childhood TBI (18, 19, 21–23). Among retrospective cohort studies that have investigated new-onset endocrine dysfunction after TBI in children (20, 22, 23), our study is unique in that it contains the largest number of patients in the analysis, and it is also the only study to investigate post-TBI endocrine dysfunction in a large state-wide dataset. Regardless, the prevalence of endocrine dysfunction in the first 6 months after TBI [4–86%; (21, 22, 24)], and at 1–5 years after TBI [10–38%; (18, 19, 23, 37)] in children as currently reported in the literature is not instructive due to the large variability in prevalence. The variability in overall prevalence of pituitary dysfunction after TBI may be due to under recognition by caregivers and health-care providers due to protracted, subtle, and non-specific signs, as well as a broad differential diagnosis (40). Also, more than one endocrine pathway may be disrupted after TBI, further confounding the symptomatology and presentation of these patients.

The majority of endocrine dysfunction post-TBI in pediatric patients are GH deficiencies (21–31%), but children can also experience central adrenal deficiency, diabetes insipidus, central hypothyroidism, hypogonadotropic hypogonadism, and elevated prolactin reported between 6 months to a year after TBI (41). It is known that in adults, endocrine dysfunction may present up to 5 years after the initial TBI, suggesting the need for continuous endocrine monitoring of TBI survivors (42, 43). Moreover, recovery of pituitary function can occur in up to 50% of adult patients with major hormonal deficiencies diagnosed at 3 months post-injury (7, 20, 44).

Importantly, unrecognized hypopituitarism can elevate risk for diabetes, delayed or absent puberty, short stature, metabolic syndrome, adrenal insufficiency, and other endocrine dysfunctions, that can significantly affect patients' quality of life. Screening for endocrine deficiencies in susceptible patients and initiating appropriate hormone replacement therapy may prevent these sequelae and improve the prognosis for recovery. For TBI patients, endocrine dysfunction may be prevented, or the prospect for recovery may be improved, through the application of a systematic screen for endocrine dysfunction and the administration of appropriate, well-studied, and well-tolerated hormone replacement therapy. If TBI occurs near period of elevated growth velocity (10–12 years of age for girls; 13–15 years of age for boys), then patients may risk short stature throughout life. Thus, childhood TBI should initiate regular endocrine surveillance, with accurate height and weight measurements, and blood tests and symptom monitoring every 6 months in the first year and yearly thereafter.

Risk factors of hypothalamic-pituitary disorders after TBI are controversial, without definitive relationships between injury factors and hypopituitarism (26, 45, 46). Importantly, TBI need not be severe to lead to endocrine dysfunction, since repeated less severe TBIs disrupt endocrine function (47). In the current study, the dataset lacked indicators of injury severity and a limited number of TBI ICD-9 codes were used, which prevented analysis of a relationship between TBI severity and hypothalamic-pituitary disorder.

Overall, individuals that suffer pediatric and adult TBI may experience hormonal deficits for many years, with a wide range of symptom expression in these patients. Post-TBI

endocrinopathies and hypothalamic-pituitary disorders must be considered in the differential diagnosis of any patient with a history of head trauma, regardless of age at injury, mechanism, or severity. Additional large cohort studies, such as ours, are needed to detail the prevalence of endocrine dysfunction following TBI in order to guide clinical decisions.

Benefits and Limitations of Health Care Terminologies

For this study, we used ICD-9 diagnostic codes associated with TBI and central endocrine disorders to develop inclusion criteria. ICD-9 and Current Procedural Terminology (CPT) billing codes for reimbursement are a vital part of health-care operations (48, 49). These terminologies or codes are generally specific to a particular disease, syndrome, or diagnosis of each patient. These codes are entered into hospital records for every patient visit, regardless of acuity. For example, a patient at her 11th office visit for GH deficiency will have the relevant diagnostic code entered, despite it being the 11th visit for this chronic condition. The physician will also submit a billing code along with the diagnostic code for GH deficiency. Billing codes are coupled with diagnostic codes to help health insurance companies determine the reason for the visit as well as the appropriate reimbursement rate. ICD-9 codes have inherent flaws both with the level of detail and selection of codes by the physician. Selection bias is demonstrated by the predominant TBI ICD-9 code in AHCCCS as 959.01 (Head Injury: unspecified), when there are over 400 other codes to select. It is suspected that the ICD-9 code for "Head Injury: unspecified" and the code for "concussion" may represent a mix of all TBI types which limited our ability in the current study to stratify data and analyze if a specific mechanism of TBI was associated with a higher frequency of central endocrinopathies. Moreover, the use of ICD-9 codes limits interpretation and access to information regarding previous neurological disorders and/or prescribed medications, where steroids and medication for attention deficit hyperactivity disorder may increase risk for endocrine disorders.

Another limitation of our sample is that our data are derived from the Medicaid population of Arizona. Medicaid is the Federal and State program within the United States that subsidizes the cost of medical care for individuals and families with low income and limited resources. In Arizona, the Arizona Health Care Cost Containment Service (AHCCCS) is the Medicaid program, funded by both the Federal and State government, which provides medical insurance coverage for individuals and families. In the year 2011, a half-way point of the years sampled in our study (2008–2014), in order to qualify for this Medicaid program (AHCCCS) individuals were required to meet the following requirements: must be an Arizona resident, must be a United States citizen or qualified immigrant, must have or have applied for a social security number, and must be under the income limit. In 2011, the income limit of a family's income was required to be at or below 133% of the federal poverty level of $22,350/year for a family of four. As such, this sample population represents a unique group of individuals and may not generalize to the entire population. These shortcomings are inherent in any large database, however they are recognized and assumed to be equal among age and male/female patients.

Other limitations of the study include patients who were missed due to the nature of data collection in AHCCCS, due to underreporting of symptoms of endocrine disorders, and due to the large number of patients who do not report TBI. Our data show that most endocrine diagnoses occur in the 2 years following a TBI diagnosis. As such, there is a large cohort of individuals who experience a TBI event from the ages of 15–18 and possibly later go on to develop an endocrine disorder in the next years, but the AHCCCS database does not include children over the age of 18 years. As such, we may have missed patients who suffered a TBI in their late teens and later developed an endocrine disorder over the 18-year-old exclusion criteria. Moreover, some studies report that endocrine disorders during this age range may be underreported or not recognized as a TBI-induced endocrinopathy (50). Additionally, TBI can often go unreported (51, 52), especially when they are mild injuries. However, in the adult literature it has been shown that even mild injuries can lead to dysfunctions of the endocrine system (37, 53). Therefore, these patients may also have been missed in our cohort analysis.

Significance and Rational for the Research Question

Despite the wide-ranging reports on pediatric TBIs affecting endocrine function, there is little published epidemiological data analyzing large cohorts of patients to identify correlations with male and female patients and age. Additionally, assessing endocrine function is not commonly considered in a clinician's differential diagnosis for a patient presenting to the office after TBI, nor is a history of TBI routinely asked for in a patient presenting with fatigue, weight gain, obesity, delayed puberty, and growth stunting. Our study, and others like it, help emphasize the importance of screening for endocrine dysfunction through diligent history taking and serum endocrine analysis in all patients with a history of pediatric TBI. Moreover, predictive measures are needed in order to better determine which children should undergo further endocrine evaluation after TBI. In order to better care for patients, it is of high importance to develop standard protocols to accurately diagnosis endocrine dysfunction following TBI. Results from this project will help to increase awareness among pediatricians, pediatric endocrinologists, pediatric neurologists, and other clinicians treating children with TBIs, of the incidence and risks of endocrine disorders among TBI survivors. Patients can present with central, new-onset endocrinopathies days to years after TBI, and further assessments of risk-factors and characteristics that contribute to endocrine dysfunction after TBI are critical. Physicians must be aware of endocrine symptoms after TBI and add TBI-induced central endocrinopathies to their differential diagnosis when treating a patient with a history of TBI.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Phoenix Children's Hospital Institutional Review Board. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

AS and JL initiated the worked and developed an experimental plan. GH was consulted and developed the algorithms for data extraction from CHiR with AS and JL. AS, BB, JO, RR, JL, and VS worked to analyze the data, develop the data tables, and figures. BB and VS drafted a technical report to summarize the results, from which AS and JO wrote the manuscript. PA, KL, and OO are consulting physicians with expertise in TBI and/or endocrine disorders and helped frame the research questions, develop the inclusion/exclusion criteria, select ICD-9 codes, and reviewed the manuscript. All authors contributed to the interpretation of results and provided critical feedback on the manuscript prior to submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.01410/full#supplementary-material

REFERENCES

1. Faul M, Wald MM, Xu L, Coronado VG. *Traumatic Brain Injury in the United States; Emergency Department Visits, Hospitalizations, and Deaths 2002–2006*. Atlanta, GA: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control (2010).
2. Babikian T, Merkley T, Savage RC, Giza CC, Levin H. Chronic aspects of pediatric traumatic brain injury: review of the literature. *J Neurotrauma.* (2015) 32:1849–60. doi: 10.1089/neu.2015.3971
3. Catroppa C, Anderson VA, Morse SA, Haritou F, Rosenfeld JV. Outcome and predictors of functional recovery 5 years following pediatric traumatic brain injury (TBI). *J Pediatr Psychol.* (2008) 33:707–18. doi: 10.1093/jpepsy/jsn006
4. Catroppa C, Godfrey C, Rosenfeld JV, Hearps SS, Anderson VA. Functional recovery ten years after pediatric traumatic brain injury: outcomes and predictors. *J Neurotrauma.* (2012) 29:2539–47. doi: 10.1089/neu.2012.2403
5. Currie J, Widom CS. Long-term consequences of child abuse and neglect on adult economic well-being. *Child Maltreat.* (2010) 15:111–20. doi: 10.1177/1077559509355316
6. Keenan HT, Presson AP, Clark AE, Cox CS, Ewing-Cobbs L. Longitudinal developmental outcomes after traumatic brain injury in young children: are infants more vulnerable than toddlers? *J Neurotrauma.* (2018) 36:282–92. doi: 10.1089/neu.2018.5687
7. Aimaretti G, Ambrosio MR, Benvenga S, Borretta G, De Marinis L, De Menis E, et al. Hypopituitarism and growth hormone deficiency (GHD) after traumatic brain injury (TBI). *Growth Horm IGF Res.* (2004) 14 (Suppl. A):S114–7. doi: 10.1016/j.ghir.2004.03.025
8. Emelifeonwu JA, Flower H, Loan J, McGivern K, Andrews PJ. Prevalence of anterior pituitary dysfunction 12 months or more following traumatic brain injury in adults-a systematic review and meta-analysis. *J Neurotrauma.* (2020) 37:217–26. doi: 10.1089/neu.2018.6349
9. Fernandez-Rodriguez E, Bernabeu I, Castro AI, Casanueva FF. Hypopituitarism after traumatic brain injury. *Endocrinol Metab Clin North Am.* (2015) 44:151–9. doi: 10.1016/j.ecl.2014.10.012
10. Leal-Cerro A, Flores JM, Rincon M, Murillo F, Pujol M, Garcia-Pesquera F, et al. Prevalence of hypopituitarism and growth hormone deficiency in adults long-term after severe traumatic brain injury. *Clin Endocrinol.* (2005) 62:525–32. doi: 10.1111/j.1365-2265.2005.02250.x
11. Srinivas R, Brown SD, Chang YF, Garcia-Fillion P, Adelson PD. Endocrine function in children acutely following severe traumatic brain injury. *Childs Nerv Syst.* (2010) 26:647–53. doi: 10.1007/s00381-009-1038-9
12. Rose SR, Auble BA. Endocrine changes after pediatric traumatic brain injury. *Pituitary.* (2012) 15:267–75. doi: 10.1007/s11102-011-0360-x
13. Auble BA, Bollepalli S, Makoroff K, Weis T, Khoury J, Colliers T, et al. Hypopituitarism in pediatric survivors of inflicted traumatic brain injury. *J Neurotrauma.* (2014) 31:321–6. doi: 10.1089/neu.2013.2916
14. Schneider HJ, Samann PG, Schneider M, Croce CG, Corneli G, Sievers C, et al. Pituitary imaging abnormalities in patients with and without hypopituitarism after traumatic brain injury. *J Endocrinol Invest.* (2007) 30:RC9–12. doi: 10.1007/BF03346291
15. Tanriverdi F, Kelestimur F. Pituitary dysfunction following traumatic brain injury: clinical perspectives. *Neuropsychiatr Dis Treat.* (2015) 11:1835–43. doi: 10.2147/NDT.S65814
16. Tanriverdi F, Schneider HJ, Aimaretti G, Masel BE, Casanueva FF, Kelestimur F. Pituitary dysfunction after traumatic brain injury: a clinical and pathophysiological approach. *Endocr Rev.* (2015) 36:305–42. doi: 10.1210/er.2014-1065
17. Lieberman SA, Oberoi AL, Gilkison CR, Masel BE, Urban RJ. Prevalence of neuroendocrine dysfunction in patients recovering from traumatic brain injury. *J Clin Endocrinol Metab.* (2001) 86:2752–6. doi: 10.1210/jc.86.6.2752
18. Casano-Sancho P, Suarez L, Ibanez L, Garcia-Fructuoso G, Medina J, Febrer A. Pituitary dysfunction after traumatic brain injury in children: is there a need for ongoing endocrine assessment? *Clin Endocrinol.* (2013) 79:853–8. doi: 10.1111/cen.12237
19. Einaudi S, Matarazzo P, Peretta P, Grossetti R, Giordano F, Altare F, et al. Hypothalamo-hypophysial dysfunction after traumatic brain injury in children and adolescents: a preliminary retrospective and prospective study. *J Pediatr Endocrinol Metab.* (2006) 19:691–703. doi: 10.1515/JPEM.2006.19.5.691
20. Ghigo E, Masel B, Aimaretti G, Leon-Carrion J, Casanueva FF, Dominguez-Morales MR, et al. Consensus guidelines on screening for

hypopituitarism following traumatic brain injury. *Brain Inj.* (2005) 19:711–24. doi: 10.1080/02699050400025315
21. Kaulfers AM, Backeljauw PF, Reifschneider K, Blum S, Michaud L, Weiss M, et al. Endocrine dysfunction following traumatic brain injury in children. *J Pediatr.* (2010) 157:894–9. doi: 10.1016/j.jpeds.2010.07.004
22. Niederland T, Makovi H, Gal V, Andreka B, Abraham CS, Kovacs J. Abnormalities of pituitary function after traumatic brain injury in children. *J Neurotrauma.* (2007) 24:119–27. doi: 10.1089/neu.2005.369ER
23. Poomthavorn P, Maixner W, Zacharin M. Pituitary function in paediatric survivors of severe traumatic brain injury. *Arch Dis Child.* (2008) 93:133–7. doi: 10.1136/adc.2007.121137
24. Agha A, Rogers B, Sherlock M, O'Kelly P, Tormey W, Phillips J, et al. Anterior pituitary dysfunction in survivors of traumatic brain injury. *J Clin Endocrinol Metab.* (2004) 89:4929–36. doi: 10.1210/jc.2004-0511
25. Crompton MR. Hypothalamic lesions following closed head injury. *Brain.* (1971) 94:165–72. doi: 10.1093/brain/94.1.165
26. Heather NL, Jefferies C, Hofman PL, Derraik JG, Brennan C, Kelly P, et al. Permanent hypopituitarism is rare after structural traumatic brain injury in early childhood. *J Clin Endocrinol Metab.* (2012) 97:599–604. doi: 10.1210/jc.2011-2284
27. Kelly DF, Gonzalo IT, Cohan P, Berman N, Swerdloff R, Wang C. Hypopituitarism following traumatic brain injury and aneurysmal subarachnoid hemorrhage: a preliminary report. *J Neurosurg.* (2000) 93:743–52. doi: 10.3171/jns.2000.93.5.0743
28. Khadr SN, Crofton PM, Jones PA, Wardhaugh B, Roach J, Drake AJ, et al. Evaluation of pituitary function after traumatic brain injury in childhood. *Clin Endocrinol.* (2010) 73:637–43. doi: 10.1111/j.1365-2265.2010.03857.x
29. Kokshoorn NE, Wassenaar MJ, Biermasz NR, Roelfsema F, Smit JW, Romijn JA, et al. Hypopituitarism following traumatic brain injury: prevalence is affected by the use of different dynamic tests and different normal values. *Eur J Endocrinol.* (2010) 162:11–8. doi: 10.1530/EJE-09-0601
30. Popovic V, Pekic S, Pavlovic D, Maric N, Jasovic-Gasic M, Djurovic B, et al. Hypopituitarism as a consequence of traumatic brain injury (TBI) and its possible relation with cognitive disabilities and mental distress. *J Endocrinol Invest.* (2004) 27:1048–54. doi: 10.1007/BF03345308
31. Greco T, Hovda D, Prins M. The effects of repeat traumatic brain injury on the pituitary in adolescent rats. *J Neurotrauma.* (2013) 30:1983–90. doi: 10.1089/neu.2013.2990
32. Greco T, Hovda DA, Prins ML. Adolescent TBI-induced hypopituitarism causes sexual dysfunction in adult male rats. *Dev Neurobiol.* (2015) 75:193–202. doi: 10.1002/dneu.22218
33. Maiya B, Newcombe V, Nortje J, Bradley P, Bernard F, Chatfield D, et al. Magnetic resonance imaging changes in the pituitary gland following acute traumatic brain injury. *Intensive Care Med.* (2008) 34:468–75. doi: 10.1007/s00134-007-0902-x
34. Rowe RK, Rumney BM, May HG, Permana P, Adelson PD, Harman SM, et al. Diffuse traumatic brain injury affects chronic corticosterone function in the rat. *Endocr Connect.* (2016) 5:152–66. doi: 10.1530/EC-16-0031
35. Sundaram NK, Geer EB, Greenwald BD. The impact of traumatic brain injury on pituitary function. *Endocrinol Metab Clin North Am.* (2013) 42:565–83. doi: 10.1016/j.ecl.2013.05.003
36. Daniel PM, Prichard MM, Treip CS. Traumatic infarction of the anterior lobe of the pituitary gland. *Lancet.* (1959) 2:927–31. doi: 10.1016/S0140-6736(59)91583-1
37. Reifschneider K, Auble BA, Rose SR. Update of endocrine dysfunction following pediatric traumatic brain injury. *J Clin Med.* (2015) 4:1536–60. doi: 10.3390/jcm4081536
38. Yang WH, Chen PC, Wang TC, Kuo TY, Cheng CY, Yang YH. Endocrine dysfunction following traumatic brain injury: a 5-year follow-up nationwide-based study. *Sci Rep.* (2016) 6:32987. doi: 10.1038/srep32987
39. Popovic V. GH deficiency as the most common pituitary defect after TBI: clinical implications. *Pituitary.* (2005) 8:239–43. doi: 10.1007/s11102-006-6047-z
40. Bistritzer T, Theodor R, Inbar D, Cohen BE, Sack J. Anterior hypopituitarism due to fracture of the sella turcica. *Am J Dis Child.* (1981) 135:966–8. doi: 10.1001/archpedi.1981.02130340070022
41. Keenan HT, Bratton SL. Epidemiology and outcomes of pediatric traumatic brain injury. *Dev Neurosci.* (2006) 28:256–63. doi: 10.1159/000094152
42. Bondanelli M, De Marinis L, Ambrosio MR, Monesi M, Valle D, Zatelli MC, et al. Occurrence of pituitary dysfunction following traumatic brain injury. *J Neurotrauma.* (2004) 21:685–96. doi: 10.1089/0897715041269713
43. Michaud LJ, Rivara FP, Grady MS, Reay DT. Predictors of survival and severity of disability after severe brain injury in children. *Neurosurgery.* (1992) 31:254–64. doi: 10.1227/00006123-199208000-00010
44. McCarthy ML, MacKenzie EJ, Durbin DR, Aitken ME, Jaffe KM, Paidas CN, et al. Health-related quality of life during the first year after traumatic brain injury. *Arch Pediatr Adolesc Med.* (2006) 160:252–60. doi: 10.1001/archpedi.160.3.252
45. Personnier C, Crosnier H, Meyer P, Chevignard M, Flechtner I, Boddaert N, et al. Prevalence of pituitary dysfunction after severe traumatic brain injury in children and adolescents: a large prospective study. *J Clin Endocrinol Metab.* (2014) 99:2052–60. doi: 10.1210/jc.2013-4129
46. Salomon-Estebanez MA, Grau G, Vela A, Rodriguez A, Morteruel E, Castano L, et al. Is routine endocrine evaluation necessary after paediatric traumatic brain injury? *J Endocrinol Invest.* (2014) 37:143–8. doi: 10.1007/s40618-013-0020-2
47. Sezgin Caglar A, Tanriverdi F, Karaca Z, Unluhizarci K, Kelestimur F. Sports-related repetitive traumatic brain injury: a novel cause of pituitary dysfunction. *J Neurotrauma.* (2019) 36:1195–202. doi: 10.1089/neu.2018.5751
48. Eberhardt J, Harb W. Current procedural terminology codes - why are they important? *Dis Colon Rectum.* (2018) 61:1128–9. doi: 10.1097/DCR.0000000000001190
49. King MS, Sharp L, Lipsky MS. Accuracy of CPT evaluation and management coding by family physicians. *J Am Board Fam Pract.* (2002) 14:184–92.
50. Acerini CL, Tasker RC, Bellone S, Bona G, Thompson CJ, Savage MO. Hypopituitarism in childhood and adolescence following traumatic brain injury: the case for prospective endocrine investigation. *Eur J Endocrinol.* (2006) 155:663–9. doi: 10.1530/eje.1.02284
51. McCrea M, Hammeke T, Olsen G, Leo P, Guskiewicz K. Unreported concussion in high school football players: implications for prevention. *Clin J Sport Med.* (2004) 14:13–7. doi: 10.1097/00042752-200401000-00003
52. Meier TB, Brummel BJ, Singh R, Nerio CJ, Polanski DW, Bellgowan PS. The underreporting of self-reported symptoms following sports-related concussion. *J Sci Med Sport.* (2015) 18:507–11. doi: 10.1016/j.jsams.2014.07.008
53. Cernak I, Savic VJ, Lazarov A, Joksimovic M, Markovic S. Neuroendocrine responses following graded traumatic brain injury in male adults. *Brain Inj.* (1999) 13:1005–15. doi: 10.1080/026990599121016

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REVIEW
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Advances and Future Directions of Diagnosis and Management of Pediatric Abusive Head Trauma: A Review of the Literature

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Abusive head trauma (AHT) is broadly defined as injury of the skull and intracranial contents as a result of perpetrator-inflicted force and represents a persistent and significant disease burden in children under the age of 4 years. When compared to age-matched controls with typically single occurrence accidental traumatic brain injury (TBI), mortality after AHT is disproportionately high and likely attributable to key differences between injury phenotypes. This article aims to review the epidemiology of AHT, summarize the current state of AHT diagnosis, treatment, and prevention as well as areas for future directions of study. Despite neuroimaging advances and an evolved understanding of AHT, early identification remains a challenge for contemporary clinicians. As such, the reported incidence of 10–30 per 100,000 infants per year may be a considerable underestimate that has not significantly decreased over the past several decades despite social campaigns for public education such as "Never Shake a Baby." This may reflect caregivers in crisis for whom education is not sufficient without support and intervention, or dangerous environments in which other family members are at risk in addition to the child. Acute management specific to AHT has not advanced beyond usual supportive care for childhood TBI, and prevention and early recognition remain crucial. Moreover, AHT is frequently excluded from studies of childhood TBI, which limits the precise translation of important brain injury research to this population. Repeated injury, antecedent abuse or neglect, delayed medical attention, and high rates of apnea and seizures on presentation are important variables to be considered. More research, including AHT inclusion in childhood TBI studies with comparisons to age-matched controls, and translational models with clinical fidelity are needed to better elucidate the pathophysiology of AHT and inform both clinical care and the development of targeted therapies. Clinical prediction rules, biomarkers, and imaging modalities hold promise, though these have largely been developed and validated in patients after clinically evident AHT has already occurred. Nevertheless, recognition of warning signs and intervention before irreversible harm occurs remains the current best strategy for medical professionals to protect vulnerable infants and toddlers.

Keywords: non-accidental head injury, abusive head trauma (AHT), child abuse, TBI, children, intimate partner violence (IPV), subdural hematoma (SDH), inflicted brain injury

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INTRODUCTION

As defined by the American Academy of Pediatrics (AAP), abusive head trauma (AHT) is a "well-recognized constellation of brain injuries caused by the directed application of force (shaking or direct impact) to an infant or young child, resulting in physical injury to the head and/or its contents." (1, 2). The focus of this article is to review the advances and future directions in the diagnosis, treatment, and prevention of pediatric abusive head trauma. AHT encompasses a range of injury mechanisms and clinical outcomes, from subtle presentations requiring a high index of clinical suspicion to moribund infants with lethal injuries. There is ample evidence to support the existence and diagnosis of AHT, from clinical observation and study, multi-specialty expert consensus, multi-species animal models, and perpetrator confession (3–10). A 2009 policy statement from the AAP recommended that pediatricians use AHT rather than a term that implies a single injury mechanism, such as the previous moniker "shaken baby syndrome." (2). AHT is characterized by an aggregate of physical, radiographic, and laboratory evidence that cannot be explained by the provided history or is incongruent with the developmental stage of the child. Children suffering from AHT generally benefit from advances in traumatic brain injury (TBI) care, but there remain disproportionate mortality and poor outcomes in survivors of AHT as compared to accidental traumatic brain injury (TBI), making prevention and early identification paramount (11–14).

While there remains some controversy in the legal community surrounding the diagnosis of AHT and the intensity and/or mechanical forces that are necessary to cause the spectrum of associated injuries, there is no scientific controversy regarding the clinical diagnosis of AHT (15–20). Defense strategies have historically relied upon undermining the diagnosis of AHT and "inappropriate use of scientifically unsupported alternative theories." (20). Our understanding of AHT has evolved and coincided with developments in the field of radiology that have facilitated the identification of hemorrhages, parenchymal injuries, and fractures that could only be attributed to physical abuse. Formally named "The Battered Child Syndrome" by C. Henry Kempe in 1962, the term described a series of symptoms and findings that should prompt practitioners to suspect harm by caregivers (21). Further research in the 1970s posed shaking or whiplash injury as an important mechanism of subdural hemorrhage (SDH) in these patients (22, 23). There is contemporary literature as well as perpetrator confession to support that not only is whiplash-shaking alone sufficient to cause SDH, but retinal hemorrhages as well (5–7, 24). Acceleration-deceleration impact and rotational force injuries are also better understood in recent years, with data indicating that comparatively mild non-accidental head trauma can result in significant injury, particularly when repetitive, or when medical care is delayed (25).

EPIDEMIOLOGY OF AHT

Incidence and Risk Factors

Current estimates place the incidence of abusive head trauma between 10 and 30 per 100,000 infants per year, with the highest incidence in the first 2 years of life (26–28). Historically, there has been a male predominance in diagnosed AHT cases, but a few recent studies suggest that females may be equally represented, if not more (29, 30). Low socioeconomic status and domestic violence have been cited as risk factors, and recent epidemiologic studies have further identified young maternal age, male caregivers, and caregiver substance abuse or mental health disorders as additional risk factors for AHT (8, 26, 31). This data is likely incomplete, as there is not a "gold standard" diagnostic for AHT. Additionally, under-reporting and delayed recognition remain significant issues.

Impact/Outcome

AHT presents a significant chronic societal burden, not only in direct costs but also in lost potential and productivity. Beyond the already exceedingly high cost of treating a child with AHT from injury through convalescence lies the debilitating strain placed on families and society (32). Miller et al. estimated the overall impact of the estimated 4824 AHT (fatal and non-fatal) cases in 2010 at ∼$13.5 billion, factoring in medical expenses, long-term care, and social intervention (child protective services and criminal justice costs). A large portion of this estimated cost comes from the work loss cost. Interestingly, even a "mild" case with a reasonable outcome has an average estimated loss of 15% of health-related quality of life (33). Attempts to objectively measure the degree of impairment have met with difficulty, as this can be a fairly subjective term. However, using self-report surveys of disability like the Health Utilities Index (HUI), it is estimated that over the lifespan of a survivor of AHT, overall quality of life may range from 80% for mild AHT, all the way down to 40% for severe AHT survivors (HUI score represents percentage of quality of life someone has compared to person in perfect health) (34). Disease burden in terms of disability has also proven to be extremely problematic in AHT. Disability-adjusted life-years (DALYs) are calculated by summing years of productive life that survivors lose to disability plus years lost to premature death. In the case of severe AHT, annual DALY per surviving child averaged 0.555 years, with an estimated average lifetime DALY burden of 24.1 years. Put in perspective, even mild AHT poses a DALY burden that exceeds that of a severe burn (34, 35).

Given perceptions of the neuroplasticity of youth and implied recovery potential, it may be counterintuitive at first that typical brain injury patterns and ultimate outcomes are worse in AHT than those following accidental TBI (such as motor vehicle collisions and witnessed falls) (36–40). When adjusted for age, it has been demonstrated a nearly 10-fold higher incidence of neurosurgical intervention in AHT patients compared to their accidental trauma counterparts (12). Studies indicate mortality rates ranging from 18 to 25% (8, 27, 29, 41). For those that survive, 20–40% will do so with severe disability, defined as gross neurologic impairment requiring full assistance in activities of daily living. For the remainder, longitudinal studies report high rates of neuromotor, psychiatric, and cognitive deficits (31, 37, 38, 42). Poor outcomes are multifactorial, likely attributable to the age and neurodevelopmental state of these patients, chronicity of abuse, the type and timing of injury, as well as delayed presentation

leading to additional insults known to worsen outcomes after TBI (43).

Injury Mechanisms/Pathophysiology

AHT patients tend to experience a high burden of secondary insults before presenting to medical care, including apnea with consequent hypoxemia and hypotension, and seizures (29, 44, 45). Coinciding systemic polytrauma with fractures and intra-abdominal injury can exacerbate marked anemia, coagulopathy, systemic inflammatory responses, and shock. Furthermore, even mild TBI is recognized to cause persistent perturbations in not only cerebrovascular autoregulation, but also autonomic regulation and inflammatory and apoptotic cascades such that every subsequent injury is not simply additive, but the consequences are exponential (46, 47). Vavilala et al. found in a small cohort of AHT that all had impaired cerebral autoregulation, either unilateral or bilateral hemispheric dysfunction (48). Studied most heavily in contact-sport athletes, "second-hit syndrome" is not elucidated in AHT, but given transcranial doppler evidence of altered vascular tone early after acute pediatric TBI, the repetitive concussion of contact-sports presents an interesting parallel in terms of the pathophysiology of neuronal and glial injury with sustained vulnerability and represents an area that might inform further study (49–51).

The immature brain requires an inherently different balance of neurotransmission, blood flow, and energy requirements that, while important for early neurodevelopment, may predispose to a poorer injury phenotype (52). There are two major pathologic mechanisms for secondary damage and cell death after trauma that have been identified- excitotoxicity and apoptosis. An overabundance of actively developing and immature dendrites and synapses is vital in early childhood but may potentiate excitotoxicity which occurs within the first few hours after the primary insult. Additionally, microglia play an important role in regulating dendritosynaptogenesis, and may be primed in a manner that exacerbates the neuroinflammatory response after injury. Animal models have shown that apoptosis appears to be the more devastating event in producing significantly higher rates of cell death than excitotoxicity in immature rodents (53, 54). These studies also have shown an age-dependent effect on apoptotic cell death, with younger rodents (3, 7 day old) demonstrating increased vulnerability for trauma-induced apoptosis. An intrinsic need to cull extraneous neurons and synapses through apoptosis and pruning during normal developmental remodeling appear to negatively sway the cell survival balance after injury, as interestingly the highest proportion of apoptotic cells after trauma were found in areas that had the highest densities of cells undergoing physiologic apoptosis in sham animals (53, 54). If the injury involves areas of the brain with a narrow developmental window or interdependent connectivity with non-contiguous regions, functional outcomes in survivors can be impacted dramatically. Additionally, trauma during this period may also interfere with ongoing developmental events such as neuronal migration, and axonal and dendritic growth by altering the proteins that guide these processes (55).

DIAGNOSING AHT

Clinical Features

Presenting history is important in identifying AHT, as is a physical examination with a high index of suspicion when indicators are present. While caregiver histories are frequently not forthcoming, the incongruity of an explanation with presentation is a hallmark of AHT. In the prehospital phase of care, children with AHT are nearly twice as likely to have been transported from home, often by private vehicle with little to no resuscitation (29). Apnea has been shown in several studies to be significantly associated with AHT as compared to accidental TBI, as are seizures, with studies finding 28–50% of AHT with seizures upon presentation (29, 44, 45). History of developmental or growth delay should raise concern, as should a history of vomiting (without diarrhea), increased head circumference, and/or excessive irritability (44). Rib, long bone, and complex skull fractures support a diagnosis of AHT, and retinal and subdural hemorrhages have historically been the most relied on indicators of an abusive injury. While not required for diagnosis, retinal hemorrhages have been reported in up to 85% of AHT victims, and tend to be diffuse and bilateral, involving all layers of the retina (56). Subdural hemorrhages have been reported in >70% of AHT victims (45, 57, 58). Specific neuroimaging patterns were further described by Kemp et al. in 2011: multiple SDH over the convexity, interhemispheric hemorrhages, posterior fossa SDH, hypoxic-ischemic injury (HII), and cerebral edema were significantly associated with AHT (59). Chronic SDH appears to be specific for AHT, if not particularly sensitive, with less than half of identified AHT cases presenting with chronic SDH (vs. the far more common acute SDH) (60).

Imaging

Non-contrast head computed tomography (CT) is generally the first imaging modality for acute traumatic or unexplained encephalopathy, as it rapidly informs the need for urgent neurosurgical interventions such as hematoma evacuation or cerebrospinal fluid (CSF) diversion. Ideally, initial head CT should include 3D calvarial reconstruction for the accurate representation of skull fractures, as depicted in **Figures 1A, B** (61). Thereafter, additional complementary magnetic resonance imaging (MRI) is more sensitive for parenchymal injuries, diffuse axonal injury, injury to bridging veins, and early evidence of HII and cerebral edema, all of which can be seen in AHT and contribute to high morbidity and mortality. Additionally, MRI may be used to differentiate subdural hemorrhage from benign enlargement of the subarachnoid space (BESS) as chronic SDH may be difficult to distinguish on CT. Neuroimaging should not be solely relied upon for precisely pinpointing the age of SDH due to variability of hematoma appearance and evolution when combined with less dense CSF, a consequence of traumatic violation of the arachnoid membrane and leakage of CSF into the subdural space (62). Mixed-density SDH, as shown in **Figures 1C,D**, is more frequently observed in AHT than simple hyperdensity typical of acute hematoma blood products (58 vs. 28%, respectively, with 14% appearing hypodense in a

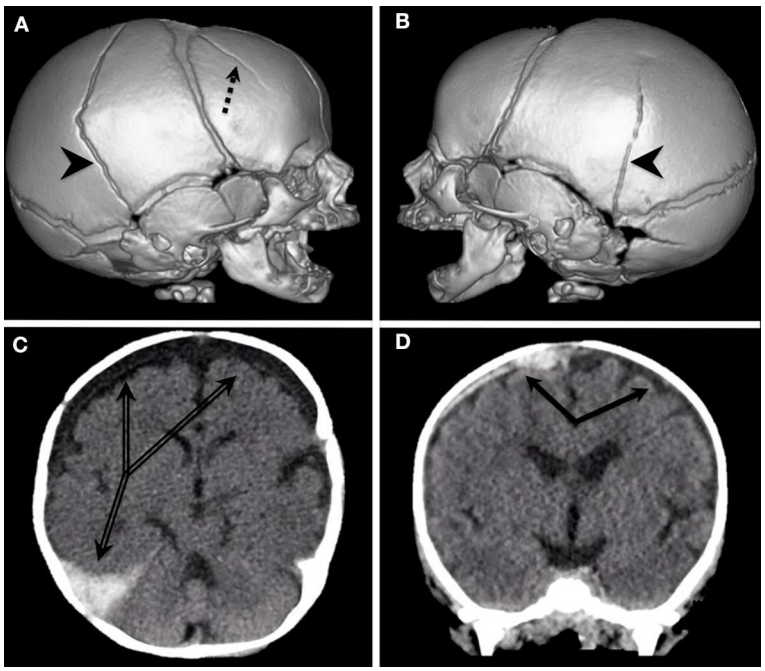

FIGURE 1 | (A,B) Multiple, bilateral skull fractures as a result of AHT depicted with 3D calvarial reconstruction. Right posterior temporal fracture extending obliquely over the vertex to the left posterior temporal region (arrowheads) with additional fracture anterior to the right coronal suture (dashed arrow). **(C,D)** Mixed density subdural collections resulting from AHT. Image C demonstrates neomembranes in chronic subdural hygromas over the bifrontotemporal convexities with a newer hyperdensity in the right temporo-occipital convexity extending into the cerebral falx (double line arrows).

series of 105 confirmed AHT) (63). Additionally, mixed-density SDH is more frequently observed in AHT than accidental TBI (63). This may be related to the presence of co-mingled CSF, but could also result from an antecedent subacute injury or acute-on-chronic collection. It can be challenging to differentiate on a single imaging study in isolation, as hyperdense blood product resolution varies in its timeline from 48 h to 40 days (9). Heterogeneous mixed-density SDH with distinct regional differences (hypodense in one area and hyperdense in another) may or may not be suggestive of separate injury events, but the development of intradural neomembranes is consistent with an injury at least 10 days to several weeks old, as seen in **Figure 1C**. With caveats regarding the variability in SDH appearance and hematoma evolution, there may be a role for neuroimaging in establishing an injury timeline when combined with other clinical, historical, and radiographic findings, particularly in the exclusion of other cranial lesions or fractures having occurred in the period suggested by a witness, and/or if serial neuroimaging is obtained (9, 63, 64). The recommended work-up of AHT includes a full skeletal survey, which can support both diagnosis and chronicity of abuse with systemic fractures in varying stages of healing.

Spinal imaging of soft tissues with MRI is more recently recognized to support the diagnosis of AHT, and should be strongly considered for inclusion when a brain MRI is obtained in suspected AHT, or when spinal injury is suspected (9). Compared to adults, children have disproportionately large heads, supported on relatively weak necks. Given this physiology and the prevalence of shaking injury, cervical injuries are much more common than previously thought, but until recently clinicians lacked the imaging modalities necessary to make an early diagnosis. Studies in the 1980s and 1990s found a significant incidence of cervical injury in confirmed cases of AHT, however, these findings were made on autopsy (65, 66). In the last decade, the advent of advanced imaging with MRI has been used to estimate the incidence of cervical spine injury with AHT at anywhere from 15 to 46%, with over 80% incidence in those patients with AHT involving bilateral HII (9, 67–69). Interestingly, this type of high cervical injury may torque, stretch, or otherwise injure the brainstem, inducing apnea in an injury pattern that may not only be peculiar to AHT, but may explain differences in clinical presentation and outcomes given the strong association of cervical spine injury and HII (69, 70).

Clinical Prediction Rules

Clinical prediction rules (CPRs) for AHT are intended to facilitate early recognition of abuse as the proximate cause of intracranial injury so that additional confirmatory workup can be pursued and other injuries identified. Ideally, CPRs should also help avoid unnecessary testing and prevent unwarranted accusation of a caregiver. The currently published CPRs for AHT "aids or prompts" the clinician to "seek further information, investigation and assessment" order for them to diagnose AHT (71). CPRs do not diagnose AHT by themselves and should supplant rather than replace clinical acumen. Importantly, each of the CPRs that have been validated are for specific populations

in specific stages of their workup, none of which are in a primary care/outpatient setting. Concern has been raised regarding the potential of a false sense of security, especially in clinicians who are not as familiar/have less experience with AHT, if a CPR gives a low probability of AHT (72). These tools are designed to be used in conjunction with a complete history and physical exam as well as clinician expertise and judgement in order to more robustly approach decision making in AHT evaluations.

Important attempts in recent years to develop CPRs have seen the addition of historical elements, clinical, and imaging findings in order to more accurately identify AHT (**Table 1**). In 2013, the Pediatric Brain Injury Network (PediBIRN) derived a CPR for patients admitted to Pediatric Intensive Care Unit (PICU) based on acute respiratory compromise before admission; the presence of ear, torso, or neck bruising; bilateral, or interhemispheric SDH; and any skull fractures other than an isolated, unilateral, non-diastatic, linear, parietal fracture (73). With just these four criteria, a validation study found that the PediBIRN score identified 98% of PICU patients ultimately diagnosed with AHT (74). Recently, PediBIRN was externally validated in the intended PICU setting as well as in all children <3 years old admitted with imaging-confirmed intracranial injury in Australia and New Zealand. Similar to the original validation study, PediBIRN CPR was highly sensitive with 96% sensitivity among all admitted patients, and 100% sensitive for patients admitted to the PICU (75). Although not yet externally validated, an update to the PediBIRN in 2019 saw the creation of the PediBIRN-7, which includes results of the AHT workup (imaging- skeletal survey and neuroimaging; retinal exam) to predict probability of AHT in order to further inform a clinician's diagnosis (76). The Predicting Abusive Head Trauma (PredAHT) CPR used 6 clinical indicators and found that when ≥3 of these are present, the estimated probability for AHT is >81.5% (77, 78). The sensitivity of the tool based on a 50% probability cut-off is 72.3% and specificity of 85.7% (77, 78). PredAHT-2 was updated to account for missing data, as well as externally validated in an Australian/New Zealand population (79). The Pittsburgh Infant Brain Injury Score (PIBIS) was developed by Berger et al. to guide the decision-making process for neuroimaging in otherwise healthy infants presenting to the ED at risk for AHT given symptoms that could be attributed to intracranial pathology in the absence of a trauma history. The score is based on the presence of abnormal skin exam (bruising), age > 3 months, head circumference > 85th percentile, and serum hemoglobin <11.2 g/dL. Using these data, validation studies identified a sensitivity of 93.3%, a specificity of 53%, and a positive predictive value of 39% for abnormal neuroimaging (80). Research is also ongoing to develop CPRs that will detect AHT even in the case of equivocal history or exam findings; in 2017, Berger et al. introduced the Biomarker of Infant Brain Injury Score (BIBIS), a panel composed of three serum biomarkers and serum hemoglobin, which identified 89.3% of patients with acute intracranial hemorrhage, with a 95.6% negative prediction value (81). By necessity, screening CPRs have high sensitivity with the trade-off of lower specificity. PediBIRN is excellent for prompting the consideration of abuse in young brain-injured children admitted to the PICU, and PIBIS captured a very high rate of acute intracranial pathology on neuroimaging in patients in the ED that otherwise might not be obtained. PredAHT was much more specific than either PediBIRN or PIBIS in patients admitted to the hospital, and may be useful not only as an independent CPR, but in conjunction with PediBIRN and/or PIBIS may guide investigative work-up (71).

Management of AHT

AHT is a heterogeneous insult, and as such, management occupies a broad spectrum of tools and therapies. Initial care in the pediatric patient with AHT is directed toward stabilization of the airway, support of oxygenation, ventilation, hemodynamics, and mitigation of intracranial pathology. Children with AHT should be evaluated at a level 1 Pediatric Trauma center with access to *pediatric* specialists such as neurosurgery, trauma surgery, neurology/epileptologist, child abuse pediatrician, and intensivists. Mild injuries may simply require supportive care; keeping hemodynamics and physicochemical milieu in a normal range, coupled with simple maneuvers such as keeping patients partially upright in bed with the head positioned midline. For more severe injury, the Pediatric Severe TBI Guidelines (severe TBI defined by a GCS<9) suggest the use of invasive intracranial pressure (ICP) monitoring with subsequent ICP-driven management for improved outcomes (82), although there remain differing practices and debate regarding the utility of ICP monitoring in infants with open fontanelles. While the Guidelines do not specifically address the AHT population separately, the authors do state "the presence of open fontanelles and/or sutures in an infant with severe TBI does not preclude the development of intracranial hypertension or negate the utility of ICP monitoring" (83).

Acute Management

Intracranial hemorrhage and edema being commonly seen in AHT, management of the resultant increased ICP has become one of the primary goals of acute treatment, following the *Guidelines for the Management of Pediatric TBI, third edition* (82). However, the exact goals of management remain unclear. In the specific context of AHT, persistent increased ICP > 20 mmHg and cerebral perfusion pressure (CPP) <45 mmHg appear to correlate with worsened outcome (21). What remains to be seen is whether or not more aggressive (lower ICP, higher CPP) goals will add additional therapeutic benefit. Findings by Jha et al. using longitudinally monitored ICP trajectories in adults may provide new insights into AHT interventions and outcomes; when continuously plotted out, patients with persistently low ICP trajectories had unfavorable outcomes that were only slightly better than the patients with severe, persistent intracranial hypertension. Strangely enough, the patients with higher ICP (∼14 mmHg) and frequent spikes had the best outcomes, a finding that may indicate that the practice of driving ICP under 20 mmHg for all patients may be too simplistic (84). Given the highly heterogeneous nature of AHT, it is entirely possible that the optimal intervention is one in which the clinician allows for some of the natural evolution of AHT to take place in order to better phenotype the injury and appropriately treat.

TABLE 1 | Externally validated CPRs for prompting the recognition and/or consideration of AHT as the proximate cause of acute intracranial injury in infants and toddlers.

	Predicting Abusive Head Trauma (PredAHT)	**Pittsburgh Infant Brain Injury Score (PIBIS)**	**Biomarkers for Infant Brain Injury Score (BIBIS)**	**Pediatric Brain Injury Network (PediBIRN-4)**	**7-Variable Clinical Prediction Rule (PediBIRN-7)**
Use	Estimating AHT probability in a brain injured infant or toddler	Screening high risk infants and toddlers for neuroimaging in the absence of a trauma history	Screening high risk infants for neuroimaging in the absence of a trauma history	Estimating AHT probability in a brain injured infant or toddler	Estimating AHT probability in a brain injured infant or toddler
Variables	1) Apnea 2) Head or neck bruising 3) Seizure 4) Rib fracture 5) Long bone fracture 6) Retinal hemorrhages	1) Age > 3 months (1 point) 2) Bruising on skin exam (2 points) 3) Head circumference >85th percentile (1 point) 4) Serum hemoglobin <11.3 g/dL (1 point)	Serum biomarkers: 1) Matrix metallopeptidase-9 2) Neuron-specific enolase 3) Vascular cellular adhesion molecule-1 4) Hemoglobin	1) Respiratory compromise 2) Bruising of ear, neck, or torso 3) Bilateral or interhemispheric subdural(s) hemorrhage or fluid collection(s) 4) Skull fracture other than simple, linear parietal skull fracture	1) Respiratory compromise 2) Bruising of ear, neck, or torso 3) Bilateral or interhemispheric subdural(s) hemorrhage or fluid collection(s) 4) Skull fracture other than simple, linear parietal skull fracture 5) Positive skeletal survey* 6) Positive ophthalmological exam** 7) Brain hypoxia, ischemia, or swelling
Clinical Scenario	< 3 years of age admitted with intracranial injury found on neuroimaging	Well-appearing, afebrile infants without a history of head trauma presenting with: 1) Apnea/apparent life-threatening event 2) Vomiting without diarrhea 3) Seizures or seizure-like activity 4) Soft tissue swelling of scalp 5) Bruising 6) Other nonspecific neurologic symptom such as lethargy, fussiness, poor feeding	Well-appearing, afebrile infants without a history of head trauma presenting with: 1) Apnea/apparent life-threatening event 2) Vomiting without diarrhea 3) Seizures or seizure-like activity 4) Soft tissue swelling of scalp 5) Bruising 6) Other nonspecific neurologic symptom such as lethargy, fussiness, poor feeding	< 3 years of age admitted to pediatric intensive care unit with intracranial injury found on neuroimaging	< 3 years of age admitted to pediatric intensive care unit with intracranial injury found on neuroimaging
Sensitivity/ Specificity during Validation	With a 50% probability cutoff, 72% sensitivity and 86% specificity	At a score of ≥ 2, 93% sensitivity, 53% specificity for abnormal neuroimaging (traumatic or otherwise)	With a cutoff of 0.182 when AUC 0.91, 89.3% sensitivity and 48% specificity for acute intracranial hemorrhage	96% sensitivity and 46% specificity in intensive care patients	With a 50% probability cutoff, 73% sensitivity and 87% specificity in intensive care patients (derivation, not validation study)

**Positive skeletal survey: classic metaphyseal fractures, epiphyseal separation(s), fracture(s) involving the rib(s), digit(s), scapula, sternum, or spinous process(es), or vertebral body fracture or dislocation.*

***Positive ophthalmologic exam: retinoschisis or retinal hemorrhages described as dense, extensive, and/or extending to the periphery (oro serrata).*

HII is prevalent in AHT, and may be related to apnea-associated hypoxemia and hypotension, relative ischemia from early posttraumatic seizures, cerebral edema and vascular compromise, or anemia and hypotension after significant intracranial or systemic hemorrhage (4, 85). Seizure severity seems tied to the degree of HII, and evidence of HII on MRI may evolve over time (86). In a recent study of the first 200 patients of the ADAPT trial, there was significantly more reported or observed apnea in the AHT cohort compared to accidental TBI, despite no differences in rates of documented hypoxemia or hypotension during prehospital care (29). Interestingly, the criteria for hypoxia/hypotension in this study were quite conservative and may have missed clinically relevant episodes of both. Furthermore, AHT patients were more likely to arrive via private vehicle without trained prehospital care providers and consequently, hypoxemia and hypotension were likely unrecognized or undocumented. As with all TBI, hypoxemia and hypotension are key factors linked to poor outcome, and prompt

recognition and correction of these perturbations is essential. Unfortunately, the typical presentation of AHT often delays proper resuscitation.

In addition to HII, age (<2 year) and severity of injury (SDH or GCS<8) are strong predictors of seizures after AHT (87, 88). Primary brain injury is exacerbated by seizure-related excitotoxicity and metabolic stress, and early and effective treatment is necessary. There is a risk of under-recognition, as seizures may be subclinical; Hasbani et al. demonstrated in a study of 32 children with AHT that over half of the children monitored on EEG were found to have seizures. Of these children, 67% had subclinical seizures that would have otherwise gone undetected without EEG (89). As such, there is a role for continuous EEG monitoring in AHT to detect subclinical seizures, particularly in the case of coma after resuscitation, or if the child has received sedation or neuromuscular blockade (90).

Given the potentially devastating effects of seizures after TBI, much effort has been expended in developing therapeutic strategies to mitigate epileptiform activity. The current body of literature indicates that early posttraumatic seizures (EPTS; defined as seizures occurring within 7d of injury) are more common in children vs. their adult counterparts who tend to develop late posttraumatic seizures (LPTS) (91). Retrospective studies demonstrate that upwards of 50% of children with severe AHT experience EPTS without antiepileptic drug (AED) prophylaxis, compared with only 15% who developed EPTS when prophylaxed with phenytoin (92, 93). As such, current guidelines suggest prophylactic treatment for early seizure, but have removed phenytoin from the previous Level III recommendation stating "insufficient evidence to recommend levetiracetam over phenytoin." (82, 94). Alternative AEDs have been investigated in recent years, with levetiracetam being the most common, citing a better side effect profile. However, a recent study failed to show any benefit over phenytoin, in fact showing that levetiracetam may be less efficacious as prophylaxis in pediatric TBI (92).

While the control of post-AHT seizures is a mainstay of therapy, it is unclear whether or not long term functional outcomes are changed by rigorous seizure control. In adults, posttraumatic seizures are associated with a worse long-term functional outcome, and early prophylaxis and aggressive seizure treatment is standard for both adults and children (91). While data indicates that prophylactic AED therapy may prevent EPTS, it also demonstrates no benefit in the reduction of late posttraumatic seizures (LPTS) or posttraumatic epilepsy (95). Indeed, currently, no pharmacologic therapy is as of yet established to prevent the development of LPTS, or to reduce mortality (96, 97).

Post-Acute Management

Care after discharge is equally nebulous. It has been shown that AHT patients make significant functional gain and do benefit from being discharged to an inpatient rehabilitation center (98). Unfortunately, there is a dearth of pediatric rehabilitation facilities in the US requiring patients at times to go far from their home, even out of state for some, or to be discharged home with the hope of receiving adequate outpatient rehabilitation. There also remains the issue of an AHT victim returning home to an unstable or unsafe living environment. The role of stress in the developing pediatric brain is ill-defined, but studies point to the detrimental effects of stress on the immune and inflammatory response (99, 100). Even something as seemingly simple as separation from a caregiver has been demonstrated to upregulate inflammatory factors in animal models, and in human children, domestic stress and violence has been linked to asthma (100–106). More worryingly, current understanding of neuroinflammatory pathways would seem to point toward a discrete role for social stress in potentiating future neurocognitive disabilities in the pediatric patient. Already implicated in anxiety and depression in adults, in the pediatric patient, there may be an increased risk for behavioral dysfunction, if not outright cognitive delay, as rodent models are beginning to suggest that the stress response may be implicated in neural pruning in the hippocampus and amygdala (107, 108). As of now, no studies have clearly defined a relationship to stress and long term neurocognitive outcomes, particularly in the context of head trauma.

PREVENTION

Given the insidious nature of the disease process, and the difficulties inherent to treatment and recovery, the prevention of AHT is the current best strategy available to clinicians. As AHT is by definition an injury perpetrated out of social dysfunction, these preventative measures have been based almost entirely around caregiver education and social support. The current body of literature has identified two primary areas to reducing AHT: parental education about infant crying and risks of shaking a baby (109). Understanding of caregiver personal and social resources is key in developing targeted strategies to ensure safe and effective care. Current psychological therapy geared toward generating this mindset focuses on fostering emotional regulation; articulation of caregivers' particular strengths, empathy, power-sharing in the child-raising unit, and impulse control are core components of therapy and education (110). Such programs have met with mixed success, with some showing up to 35% reduction in AHT admissions, while others showing no reduction in AHT rates (111–113).

The role of the pediatrician is 2-fold, both as a primary clinician responsible for the detection of early symptoms concerning for abuse and as an educator to caregivers. It is important for clinicians to be educated in recognizing the sometimes subtle signs of non-accidental injuries such as bruising or fractures in non-cruising infants, vomiting without diarrhea, lethargy, poor oral intake, or injuries without adequate trauma history (114, 115). Studies have demonstrated frequently missed opportunities to diagnose sentinel abusive injuries in children who were later diagnosed with AHT (116–118). Unfortunately, as shown in a recent study by Letson et al. there has not been a significant improvement in the rate of missed sentinel abuse events over the last two decades (117). Setting expectations with young and first-time parents regarding what constitutes normal crying patterns by primary providers, and what constitutes normal infant interactions has a significant

impact on caregiver satisfaction. Shaking as a behavioral control technique has a particularly insidious element; for a parent that doesn't know better, shaking quiets a crying infant and results in a positive reinforcement loop (119). This is evidenced by the fact that in situations where parents have admitted to shaking their infants, shaking was repeated in 55% of the cases (on average 10 times), occurring daily for several weeks in 20% of the cases, and was repeated because it stopped crying in all cases (7). Methods to mitigate crying in a healthy way range from soothing techniques, to simply educating parents regarding the normal crying patterns of infants, and the dangers of shaking an infant.

There is an association between intimate partner violence (IPV) and child abuse in families (120–124). In one study, 59% of children who were evaluated by child abuse providers after IPV exposure were found to have an injury. Of those, 24.6% had internal injuries including fractures, intracranial, or intra-abdominal injury, with almost all of these children being <1 year. Of those found to have injuries upon evaluation, 44.4% had either no report of direct injury or a mechanism that did not explain the injury. Even more concerning, several of these patients did not have any physical exam findings to suggest their internal injuries (122). This and other studies highlight the need for greater recognition of children in an IPV environment. As pediatricians specialized in child abuse are limited resources, there needs to be a wider net in the medical community who are educated on the risk factors, signs, and symptoms of AHT. This includes adult providers who may be seeing a patient with IPV concerns which should prompt the question "Where are your children? Are they at home with this partner?" IPV has been associated with AHT and a recent meta-analysis determined that the odds of child abuse in a family with reported IPV was 3.64 (98). Police, EMS, CPS, and other such first responders should be educated regarding this association and trained to ask about any children in the home when responding to IPV incidents. If there are children, especially those <1 year of age, they should be seen by a medical provider trained to evaluate for child abuse.

FUTURE DIRECTIONS

Prevention and detection of AHT remains the first line in future management. Studies examining local and statewide educational programs have shown variable results in attempts to reduce AHT incidence, and have so far failed to identify which key components are most effective (111, 112). With the continuation of widespread education, it will be crucial to determine which strategies are most effective. Continued refinement and testing of CPRs will similarly be vital in the future management of AHT, as earlier detection of injury will be key to minimizing morbidity and mortality. Future refinements of CPRs would ideally provide clinicians with powerful tools to increase their confidence in diagnosis and standardize the process (125).

Disproportionately poor outcomes in the moderate to severe spectrum of AHT when compared to age-matched accidental TBI are multifactorial. Delay in medical care, repeated injury, prolonged seizures on presentation, and apnea with its consequences certainly play critical roles, and highlight the need for education, prevention, and intervention before significant injury occurs. A pre-injury factor which warrants investigation is exposure to abusive or neglectful environments. Repeated, unpredictable stress in the developing mammalian brain has been observed to potentiate immunomodulation in animal models, and may produce a unique pro-inflammatory phenotype with a lowered seizure threshold in response to brain injury (100). This is of particular interest in AHT, where victims may spend a great deal of time in abusive households before being identified, or may return to high-stress households during convalescence following treatment.

There remains a great deal of variation in the acute care of TBI, let alone AHT. Lack of clear consensus regarding goals of treatment and outcome metrics contribute to a lack of standardized intervention after AHT is diagnosed. The typical example of this heterogeneity is that ICP monitoring is not standardly employed for these infants, despite evidence that centers with standardized ICP monitoring for pediatric TBI have improved patient outcomes (126). This may reflect improved ICP-guided management, or may indicate that centers with greater expertise are more likely to invasively monitor these patients. While there is a growing body of literature on AHT as a distinct form of TBI, there remains a dearth of evidence for AHT-targeted therapies. These patients have often been excluded from pediatric TBI studies, making it difficult to extrapolate lessons learned from accidental TBI to the AHT population. Inclusion of these patients in larger, multi-center studies of pediatric TBI, with subanalyses of the AHT cohort against age-matched controls, will move the care of these patients forward and identify important differences for focused study.

AUTHOR CONTRIBUTIONS

AMI and NM contributed to conception of the manuscript and wrote sections of the manuscript and revised it critically. JS wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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REFERENCES

1. Chiesa A, Duhaime AC. Abusive head trauma. *Pediatr Clin North Am*. (2009) 56:317–31. doi: 10.1016/j.pcl.2009.02.001
2. Christian CW, Block R, the Committee on child abuse and neglect. Abusive head trauma in infants and children. *Pediatrics*. (2009) 123:1409–11. doi: 10.1542/peds.2009-0408
3. Greeley CS. Abusive head trauma: a review of the evidence base. *Am J Roentgenol*. (2015) 204:967–73. doi: 10.2214/AJR.14.14191
4. Paul AR, Adamo MA. Non-accidental trauma in pediatric patients: a review of epidemiology, pathophysiology, diagnosis and treatment. *Transl Pediatr*. (2014) 3:195–207. doi: 10.3978/j.issn.2224-4336.2014.06.01

5. Cory CZ, Jones MD. Can shaking alone cause fatal brain injury?: a biomechanical assessment of the duhaime shaken baby syndrome model. *Med Sci Law*. (2003) 43:317–33. doi: 10.1258/rsmmsl.43.4.317
6. Bell E, Shouldice M, Levin AV. Abusive head trauma: a perpetrator confesses. *Child Abuse Negl*. (2011) 35:74–7. doi: 10.1016/j.chiabu.2010.11.001
7. Adamsbaum C, Grabar S, Mejean N, Rey-Salmon C. Abusive head trauma: judicial admissions highlight violent and repetitive shaking. *Pediatrics*. (2010) 126:546–55. doi: 10.1542/peds.2009-3647
8. Starling SP, Patel S, Burke BL, Sirotnak AP, Stronks S, Rosquist P. Analysis of perpetrator admissions to inflicted traumatic brain injury in children. *Arch Pediatr Adolesc Med*. (2004) 158:454–8. doi: 10.1001/archpedi.158.5.454
9. Choudhary AK, Servaes S, Slovis TL, Palusci VJ, Hedlund GL, Narang SK, et al. Consensus statement on abusive head trauma in infants and young children. *Pediatr Radiol*. (2018) 48:1048–65. doi: 10.1007/s00247-018-4149-1
10. Wang G, Zhang YP, Gao Z, Shields LBE, Li F, Chu T, et al. Pathophysiological and behavioral deficits in developing mice following rotational acceleration-deceleration traumatic brain injury. *Dis Model Mech*. (2018) 11:dmm030387. doi: 10.1242/dmm.030387
11. Deans KJ, Minneci PC, Lowell W, Groner JI. Increased morbidity and mortality of traumatic brain injury in victims of nonaccidental trauma. *J Trauma Acute Care Surg*. (2013) 75:157–60. doi: 10.1097/TA.0b013e3182984acb
12. Adamo MA, Drazin D, Smith C, Waldman JB. Comparison of accidental and nonaccidental traumatic brain injuries in infants and toddlers: demographics, neurosurgical interventions, and outcomes: clinical article. *J Neurosurg Pediatr*. (2009) 4:414–9. doi: 10.3171/2009.6.PEDS0939
13. Keenan HT, Runyan DK, Marshall SW, Nocera MA, Merten DF. A population-based comparison of clinical and outcome characteristics of young children with serious inflicted and noninflicted traumatic brain injury. *Pediatrics*. (2004) 114:633–9. doi: 10.1542/peds.2003-1020-L
14. Ewing-Cobbs L, Kramer L, Prasad M, Canales DN, Louis PT, Fletcher JM, et al. Neuroimaging, physical, and developmental findings after inflicted and noninflicted traumatic brain injury in young children. *Pediatrics*. (1998) 102:300–7. doi: 10.1542/peds.102.2.300
15. Strouse PJ. Shaken baby syndrome is real. *Pediatr Radiol*. (2018) 48:1043–7. doi: 10.1007/s00247-018-4158-0
16. Saunders D, Raissaki M, Servaes S, Adamsbaum C, Choudhary AK, Moreno JA, et al. Throwing the baby out with the bath water — response to the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) report on traumatic shaking. *Pediatr Radiol*. (2017) 47:1386–9. doi: 10.1007/s00247-017-3932-8
17. Debelle GD, Maguire S, Watts P, Hernandez RN, Kemp AM. Abusive head trauma and the triad: a critique on behalf of RCPCH of 'Traumatic shaking: the role of the triad in medical investigations of suspected traumatic shaking.' *Arch Dis Child*. (2018) 103:606–10. doi: 10.1136/archdischild-2017-313855
18. Moreno JA, Holmgren B. *Dissent into Confusion: The Supreme Court, Denialism, and the False "Scientific" Controversy Over Shaken Baby Syndrome*. Rochester, NY: Social Science Research Network (2013). Available online at: https://papers.ssrn.com/abstract=2369562 (accessed January 14, 2020).
19. Narang SK, Estrada C, Greenberg S, Lindberg D. Acceptance of shaken baby syndrome and abusive head trauma as medical diagnoses. *J Pediatr*. (2016) 177:273–8. doi: 10.1016/j.jpeds.2016.06.036
20. Leventhal JM, Edwards GA. Flawed theories to explain child physical abuse: what are the medical-legal consequences? *JAMA*. (2017) 318:1317–8. doi: 10.1001/jama.2017.11703
21. Kempe CH, Silverman FN, Steele BF, Droegemueller W, Silver HK. The battered-child syndrome. *JAMA*. (1962) 181:17–24. doi: 10.1001/jama.1962.03050270019004
22. Guthkelch AN. Infantile subdural haematoma and its relationship to whiplash injuries. *Br Med J*. (1971) 2:430–1. doi: 10.1136/bmj.2.5759.430
23. Caffey J. On the theory and practice of shaking infants: its potential residual effects of permanent brain damage and mental retardation. *Am J Dis Child*. (1972) 124:161–9. doi: 10.1001/archpedi.1972.02110140011001
24. Nadarasa J, Deck C, Meyer F, Willinger R, Raul JS. Update on injury mechanisms in abusive head trauma–shaken baby syndrome. *Pediatr Radiol*. (2014) 44(Suppl 4):S565–70. doi: 10.1007/s00247-014-3168-9
25. Roth S, Raul JS, Ludes B, Willinger R. Finite element analysis of impact and shaking inflicted to a child. *Int J Legal Med*. (2007) 121:223–8. doi: 10.1007/s00414-006-0129-3
26. Narang S, Clarke J. Abusive head trauma: past, present, and future. *J Child Neurol*. (2014) 29:1747–56. doi: 10.1177/0883073814549995
27. Keenan HT, Runyan DK, Marshall SW, Nocera MA, Merten DF, Sinal SH. A population-based study of inflicted traumatic brain injury in young children. *JAMA*. (2003) 290:621–6. doi: 10.1001/jama.290.5.621
28. Barlow KM, Minns RA. Annual incidence of shaken impact syndrome in young children. *Lancet Lond Engl*. (2000) 356:1571–2. doi: 10.1016/S0140-6736(00)03130-5
29. Miller Ferguson N, Sarnaik A, Miles D, Shafi N, Peters MJ, Truemper E, et al. Abusive head trauma and mortality-an analysis from an international comparative effectiveness study of children with severe traumatic brain injury. *Crit Care Med*. (2017) 45:1398–407. doi: 10.1097/CCM.0000000000002378
30. Díaz-Olavarrieta C, García-Piña CA, Loredo-Abdala A, Paz F, Garcia SG, Schilmann A. Abusive head trauma at a tertiary care children's hospital in Mexico City. a preliminary study. *Child Abuse Negl*. (2011) 35:915–23. doi: 10.1016/j.chiabu.2011.05.017
31. Nuño M, Pelissier L, Varshneya K, Adamo MA, Drazin D. Outcomes and factors associated with infant abusive head trauma in the US. *J Neurosurg Pediatr*. (2015) 16:515–22. doi: 10.3171/2015.3.PEDS14544
32. Wade SL, Taylor HG, Drotar D, Stancin T, Yeates KO. Family burden and adaptation during the initial year after traumatic brain injury in children. *Pediatrics*. (1998) 102:110–6. doi: 10.1542/peds.102.1.110
33. Miller TR, Steinbeigle R, Lawrence BA, Peterson C, Florence C, Barr M, et al. Lifetime cost of abusive head trauma at ages 0–4, USA. *Prev Sci*. (2018) 19:695–704. doi: 10.1007/s11121-017-0815-z
34. Miller TR, Steinbeigle R, Wicks A, Lawrence BA, Barr M, Barr RG. Disability-adjusted life-year burden of abusive head trauma at ages 0–4. *Pediatrics*. (2014) 134:e1545–50. doi: 10.1542/peds.2014-1385
35. Miller T, Bhattacharya S, Zamula W, Lezotte D, Kowalske K, Herndon D, et al. Quality-of-life loss of people admitted to burn centers, United States. *Qual Life Res*. (2013) 22:2293–305. doi: 10.1007/s11136-012-0321-5
36. Vinchon M, Defoort-Dhellemmes S, Desurmont M, Dhellemmes P. Accidental and nonaccidental head injuries in infants: a prospective study. *J Neurosurg Pediatr*. (2005) 102:380–4. doi: 10.3171/ped.2005.102.4.0380
37. Chevignard MP, Lind K. Long-term outcome of abusive head trauma. *Pediatr Radiol*. (2014) 44:548–58. doi: 10.1007/s00247-014-3169-8
38. Lind K, Toure H, Brugel D, Meyer P, Laurent-Vannier A, Chevignard M. Extended follow-up of neurological, cognitive, behavioral and academic outcomes after severe abusive head trauma. *Child Abuse Negl*. (2016) 51:358–67. doi: 10.1016/j.chiabu.2015.08.001
39. Miller Ferguson N, Shein SL, Kochanek PM, Luther J, Wisniewski SR, Clark RS, et al. Intracranial hypertension and cerebral hypoperfusion in children with severe traumatic brain injury: thresholds and burden in accidental and abusive insults. *Pediatr Crit Care Med*. (2016) 17:444–50. doi: 10.1097/PCC.0000000000000709
40. Keenan HT, Runyan DK, Nocera M. Child outcomes and family characteristics 1 year after severe inflicted or noninflicted traumatic brain injury. *Pediatrics*. (2006) 117:317–24. doi: 10.1542/peds.2005-0979
41. Shein SL, Bell MJ, Kochanek PM, Tyler-Kabara EC, Wisniewski SR, Feldman K, et al. Risk factors for mortality in children with abusive head trauma. *J Pediatr*. (2012) 161:716–22.e1. doi: 10.1016/j.jpeds.2012.03.046
42. Barlow K, Thompson E, Johnson D, Minns RA. The neurological outcome of non-accidental head injury. *Pediatr Rehabil*. (2004) 7:195–203. doi: 10.1080/13638490410001715331
43. Vadivelu S, Esernio-Jenssen D, Rekate HL, Narayan RK, Mittler MA, Schneider SJ. Delay in arrival to care in perpetrator-identified nonaccidental head trauma: observations and outcomes. *World Neurosurg*. (2015) 84:1340–6. doi: 10.1016/j.wneu.2015.06.023
44. Maguire S, Pickerd N, Farewell D, Mann M, Tempest V, Kemp AM. Which clinical features distinguish inflicted from non-inflicted brain injury? A systematic review. *Arch Dis Child*. (2009) 94:860–7. doi: 10.1136/adc.2008.150110
45. Piteau SJ, Ward MGK, Barrowman NJ, Plint AC. Clinical and radiographic characteristics associated with abusive and nonabusive

head trauma: a systematic review. *Pediatrics*. (2012) 130:315–23. doi: 10.1542/peds.2011-1545
46. Jünger EC, Newell DW, Grant GA, Avellino AM, Ghatan S, Douville CM, et al. Cerebral autoregulation following minor head injury. *J Neurosurg*. (1997) 86:425–32. doi: 10.3171/jns.1997.86.3.0425
47. Lam JM, Hsiang JN, Poon WS. Monitoring of autoregulation using laser Doppler flowmetry in patients with head injury. *J Neurosurg*. (1997) 86:438–45. doi: 10.3171/jns.1997.86.3.0438
48. Vavilala MS, Muangman S, Waitayawinyu P, Roscigno C, Jaffe K, Mitchell P, et al. Impaired cerebral autoregulation in infants and young children early after inflicted traumatic brain injury: a preliminary report. *J Neurotr*. (2007) 24:87–96. doi: 10.1089/neu.2006.0058
49. Clifton GL, Ziegler MG, Grossman RG. Circulating catecholamines and sympathetic activity after head injury. *Neurosurgery*. (1981) 8:10–4. doi: 10.1227/00006123-198101000-00003
50. Mori T, Katayama Y, Kawamata T. Acute hemispheric swelling associated with thin subdural hematomas: pathophysiology of repetitive head injury in sports. *Acta Neurochir Suppl*. (2006) 96:40–3. doi: 10.1007/3-211-30714-1_10
51. O'Brien NF, Reuter-Rice KE, Khanna S, Peterson BM, Quinto KB. Vasospasm in children with traumatic brain injury. *Intensive Care Med*. (2010) 36:680–7. doi: 10.1007/s00134-009-1747-2
52. Semple BD, Blomgren K, Gimlin K, Ferriero DM, Noble-Haeusslein LJ. Brain development in rodents and humans: identifying benchmarks of maturation and vulnerability to injury across species. *Prog Neurobiol*. (2013) 106–107:1–16. doi: 10.1016/j.pneurobio.2013.04.001
53. Pohl D, Bittigau P, Ishimaru MJ, Stadthaus D, Hübner C, Olney JW, et al. N-Methyl-d-aspartate antagonists and apoptotic cell death triggered by head trauma in developing rat brain. *Proc Natl Acad Sci USA*. (1999) 96:2508–13. doi: 10.1073/pnas.96.5.2508
54. Bittigau P, Sifringer M, Pohl D, Stadthaus D, Ishimaru M, Shimizu H, et al. Apoptotic neurodegeneration following trauma is markedly enhanced in the immature brain. *Ann Neurol*. (1999) 45:724–35. doi: 10.1002/1531-8249(199906)45:6<724::aid-ana6>3.0.co;2-p
55. Kaindl AM, Zabel C, Stefovska V, Lehnert R, Sifringer M, Klose J, et al. Subacute proteome changes following traumatic injury of the developing brain: implications for a dysregulation of neuronal migration and neurite arborization. *Proteomics Clin Appl*. (2007) 1:640–9. doi: 10.1002/prca.200600696
56. Maguire SA, Watts PO, Shaw AD, Holden S, Taylor RH, Watkins WJ, et al. Retinal haemorrhages and related findings in abusive and non-abusive head trauma: a systematic review. *Eye*. (2013) 27:28–36. doi: 10.1038/eye.2012.213
57. Westrick AC, Moore M, Monk S, Greeno A, Shannon C. Identifying characteristics in abusive head trauma: a single-institution experience. *Pediatr Neurosurg*. (2015) 50:179–86. doi: 10.1159/000430846
58. Roach JP, Acker SN, Bensard DD, Sirotnak AP, Karrer FM, Partrick DA. Head injury pattern in children can help differentiate accidental from non-accidental trauma. *Pediatr Surg Int*. (2014) 30:1103–6. doi: 10.1007/s00383-014-3598-3
59. Kemp AM, Jaspan T, Griffiths J, Stoodley N, Mann MK, Tempest V, et al. Neuroimaging: what neuroradiological features distinguish abusive from non-abusive head trauma? A systematic review. *Arch Dis Child*. (2011) 96:1103–12. doi: 10.1136/archdischild-2011-300630
60. Karibe H, Kameyama M, Hayashi T, Narisawa A, Tominaga T. Acute subdural hematoma in infants with abusive head trauma: a literature review. *Neurol Med Chir*. (2016) 56:264–73. doi: 10.2176/nmc.ra.2015-0308
61. Parisi M, Wiester R, Done S, Sugar N, Feldman K. Three-dimensional computed tomography skull reconstructions as an aid to child abuse evaluations. *Pediatr Emerg Care*. (2015) 31:779–86. doi: 10.1097/PEC.0000000000000199
62. Sieswerda-Hoogendoorn T, Postema FAM, Verbaan D, Majoie CB, van Rijn RR. Age determination of subdural hematomas with CT and MRI: a systematic review. *Eur J Radiol*. (2014) 83:1257–68. doi: 10.1016/j.ejrad.2014.03.015
63. Bradford R, Choudhary AK, Dias MS. Serial neuroimaging in infants with abusive head trauma: timing abusive injuries. *J Neurosurg Pediatr*. (2013) 12:110–9. doi: 10.3171/2013.4.PEDS12596
64. Wittschieber D, Karger B, Pfeiffer H, Hahnemann ML. Understanding subdural collections in pediatric abusive head trauma. *Am J Neuroradiol*. (2019) 40:388–95. doi: 10.3174/ajnr.A5855
65. Hadley MN, Sonntag VK, Rekate HL, Murphy A. The infant whiplash-shake injury syndrome: a clinical and pathological study. *Neurosurgery*. (1989) 24:536–40. doi: 10.1227/00006123-198904000-00008
66. Shannon P, Smith CR, Deck J, Ang LC, Ho M, Becker L. Axonal injury and the neuropathology of shaken baby syndrome. *Acta Neuropathol*. (1998) 95:625–31. doi: 10.1007/s004010050849
67. Henry MK, Wood JN. Advanced cervical spine imaging in abusive head trauma: an update on recent literature and future directions. *Acad Pediatr*. (2018) 18:733–5. doi: 10.1016/j.acap.2018.05.008
68. Kadom N, Khademian Z, Vezina G, Shalaby-Rana E, Rice A, Hinds T. Usefulness of MRI detection of cervical spine and brain injuries in the evaluation of abusive head trauma. *Pediatr Radiol*. (2014) 44:839–48. doi: 10.1007/s00247-014-2874-7
69. Choudhary AK, Ishak R, Zacharia TT, Dias MS. Imaging of spinal injury in abusive head trauma: a retrospective study. *Pediatr Radiol*. (2014) 44:1130–40. doi: 10.1007/s00247-014-2959-3
70. Ghatan S, Ellenbogen RG. Pediatric spine and spinal cord injury after inflicted trauma. *Neurosurg Clin N Am*. (2002) 13:227–33. doi: 10.1016/S1042-3680(01)00002-X
71. Pfeiffer H, Crowe L, Kemp AM, Cowley LE, Smith AS, Babl FE, et al. Clinical prediction rules for abusive head trauma: a systematic review. *Arch Dis Child*. (2018) 103:776–83. doi: 10.1136/archdischild-2017-313748
72. Cowley LE, Maguire S, Farewell DM, Quinn-Scoggins HD, Flynn MO, Kemp AM. Acceptability of the predicting abusive head trauma (PredAHT) clinical prediction tool: a qualitative study with child protection professionals. *Child Abuse Negl*. (2018) 81:192–205. doi: 10.1016/j.chiabu.2018.04.022
73. Hymel KP, Willson DF, Boos SC, Pullin DA, Homa K, Lorenz DJ, et al. Derivation of a clinical prediction rule for pediatric abusive head trauma. *Pediatr Crit Care Med*. (2013) 14:210–20. doi: 10.1097/PCC.0b013e3182712b09
74. Hymel KP, Armijo-Garcia V, Foster R, Frazier TN, Stoiko M, Christie LM, et al. Validation of a clinical prediction rule for pediatric abusive head trauma. *Pediatrics*. (2014) 134:e1537–44. doi: 10.1542/peds.2014-1329
75. Pfeiffer H, Smith A, Kemp AM, Cowley LE, Cheek JA, Dalziel SR, et al. External validation of the PediBIRN clinical prediction rule for abusive head trauma. *Pediatrics*. (2018) 141:e20173674. doi: 10.1542/peds.2017-3674
76. Hymel KP, Wang M, Chinchilli VM, Karst WA, Willson DF, Dias MS, et al. Estimating the probability of abusive head trauma after abuse evaluation. *Child Abuse Negl*. (2019) 88:266–74. doi: 10.1016/j.chiabu.2018.11.015
77. Maguire SA, Kemp AM, Lumb RC, Farewell DM. Estimating the probability of abusive head trauma: a pooled analysis. *Pediatrics*. (2011) 128:e550–64. doi: 10.1542/peds.2010-2949
78. Cowley LE, Morris CB, Maguire SA, Farewell DM, Kemp AM. Validation of a prediction tool for abusive head trauma. *Pediatrics*. (2015) 136:290–8. doi: 10.1542/peds.2014-3993
79. Pfeiffer H, Cowley LE, Kemp AM, Dalziel SR, Smith A, Cheek JA, et al. Validation of the PredAHT-2 prediction tool for abusive head trauma. *Emerg Med J*. (2020) 1–8. doi: 10.1136/emermed-2019-208893
80. Berger RP, Fromkin J, Herman B, Pierce MC, Saladino RA, Flom L, et al. Validation of the pittsburgh infant brain injury score for abusive head trauma. *Pediatrics*. (2016) 138:e20153756. doi: 10.1542/peds.2015-3756
81. Berger RP, Pak BJ, Kolesnikova MD, Fromkin J, Saladino R, Herman BE, et al. Derivation and validation of a serum biomarker panel to identify infants with acute intracranial hemorrhage. *JAMA Pediatr*. (2017) 171:e170429. doi: 10.1001/jamapediatrics.2017.0429
82. Kochanek PM, Tasker RC, Carney N, Totten AM, Adelson PD, Selden NR, et al. Guidelines for the management of pediatric severe traumatic brain injury, third edition: update of the brain trauma foundation guidelines. *Pediatr Crit Care Med*. (2019) 20:280–9. doi: 10.1097/PCC.0000000000001735
83. Carney NA, Chesnut R, Kochanek PM. Indications for intracranial pressure monitoring in pediatric patients with severe traumatic brain injury. *Pediatr Crit Care Med*. (2003) 4:S19–24. doi: 10.1097/00130478-200307001-00006

84. Jha RM, Elmer J, Zusman BE, Desai S, Puccio AM, Okonkwo DO, et al. Intracranial pressure trajectories: a novel approach to informing severe traumatic brain injury phenotypes. *Crit Care Med*. (2018) 46:1792–802. doi: 10.1097/CCM.0000000000003361
85. Orru' E, Huisman TAGM, Izbudak I. Prevalence, patterns, and clinical relevance of hypoxic-ischemic injuries in children exposed to abusive head trauma. *J Neuroimaging*. (2018) 28:608–14. doi: 10.1111/jon.12555
86. Dingman AL, Stence NV, O'Neill BR, Sillau SH, Chapman KE. Seizure severity is correlated with severity of hypoxic-ischemic injury in abusive head trauma. *Pediatr Neurol*. (2018) 82:29–35. doi: 10.1016/j.pediatrneurol.2017.12.003
87. Ratan SK, Kulshreshtha R, Pandey RM. Predictors of posttraumatic convulsions in head-injured children. *Pediatr Neurosurg*. (1999) 30:127–31. doi: 10.1159/000028779
88. Hahn YS, Fuchs S, Flannery AM, Barthel MJ, McLone DG. Factors influencing posttraumatic seizures in children. *Neurosurgery*. (1988) 22:864–7. doi: 10.1227/00006123-198805000-00008
89. Hasbani DM, Topjian AA, Friess SH, Kilbaugh TJ, Berg RA, Christian CW, et al. Nonconvulsive electrographic seizures are common in children with abusive head trauma*. *Pediatr Crit Care Med*. (2013) 14:709–15. doi: 10.1097/PCC.0b013e3182917b83
90. Greiner MV, Greiner HM, Caré MM, Owens D, Shapiro R, Holland K. Adding insult to injury: nonconvulsive seizures in abusive head trauma. *J Child Neurol*. (2015) 30:1778–84. doi: 10.1177/0883073815580285
91. Asikainen I, Kaste M, Sarna S. Early and late posttraumatic seizures in traumatic brain injury rehabilitation patients: brain injury factors causing late seizures and influence of seizures on long-term outcome. *Epilepsia*. (1999) 40:584–9. doi: 10.1111/j.1528-1157.1999.tb05560.x
92. Chung MG, O'Brien NF. Prevalence of early posttraumatic seizures in children with moderate to severe traumatic brain injury despite levetiracetam prophylaxis. *Pediatr Crit Care Med*. (2016) 17:150–6. doi: 10.1097/PCC.0000000000000588
93. Lewis RJ, Yee L, Inkelis SH, Gilmore D. Clinical predictors of post-traumatic seizures in children with head trauma. *Ann Emerg Med*. (1993) 22:1114–8. doi: 10.1016/S0196-0644(05)80974-6
94. Kochanek PM, Carney N, Adelson PD, Ashwal S, Bell MJ, Bratton S, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents–second edition. *Pediatr Crit Care Med J Soc Crit Care Med World Fed Pediatr Intensive Crit Care Soc*. (2012) 13(Suppl 1):S1–82. doi: 10.1097/PCC.0b013e31823f435c
95. Temkin NR, Dikmen SS, Wilensky AJ, Keihm J, Chabal S, Winn HR. A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. *N Engl J Med*. (1990) 323:497–502. doi: 10.1056/NEJM199008233230801
96. Iudice A, Murri L. Pharmacological prophylaxis of post-traumatic epilepsy. *Drugs*. (2000) 59:1091–9. doi: 10.2165/00003495-200059050-00005
97. Thompson K, Pohlmann-Eden B, Campbell LA, Abel H. Pharmacological treatments for preventing epilepsy following traumatic head injury. *Cochrane Database Syst Rev*. (2015) CD009900. doi: 10.1002/14651858.CD009900.pub2
98. Risen SR, Suskauer SJ, DeMatt EJ, Slomine BS, Salorio CF. Functional outcomes in children with abusive head trauma receiving inpatient rehabilitation compared with children with nonabusive head trauma. *J Pediatr*. (2014) 164:613–9.e2. doi: 10.1016/j.jpeds.2013.10.075
99. Johnson SB, Riley AW, Granger DA, Riis J. The science of early life toxic stress for pediatric practice and advocacy. *Pediatrics*. (2013) 131:319–27. doi: 10.1542/peds.2012-0469
100. Johnson FK, Kaffman A. Early life stress perturbs the function of microglia in the developing rodent brain: new insights and future challenges. *Brain Behav Immun*. (2018) 69:18–27. doi: 10.1016/j.bbi.2017.06.008
101. Hennessy MB, Deak T, Schiml-Webb PA. Early attachment-figure separation and increased risk for later depression: potential mediation by proinflammatory processes. *Neurosci Biobehav Rev*. (2010) 34:782–90. doi: 10.1016/j.neubiorev.2009.03.012
102. Danese A, Moffitt TE, Pariante CM, Ambler A, Poulton R, Caspi A. Elevated inflammation levels in depressed adults with a history of childhood maltreatment. *Arch Gen Psychiatry*. (2008) 65:409–15. doi: 10.1001/archpsyc.65.4.409
103. Suglia SF, Enlow MB, Kullowatz A, Wright RJ. Maternal intimate partner violence and increased asthma incidence in children: buffering effects of supportive caregiving. *Arch Pediatr Adolesc Med*. (2009) 163:244–50. doi: 10.1001/archpediatrics.2008.555
104. Suglia SF, Duarte CS, Sandel MT, Wright RJ. Social and environmental stressors in the home and childhood asthma. *J Epidemiol Community Health*. (2010) 64:636–42. doi: 10.1136/jech.2008.082842
105. Chen E, Fisher EB, Bacharier LB, Strunk RC. Socioeconomic status, stress, and immune markers in adolescents with asthma. *Psychosom Med*. (2003) 65:984–92. doi: 10.1097/01.PSY.0000097340.54195.3C
106. Chen E, Chim LS, Strunk RC, Miller GE. The role of the social environment in children and adolescents with asthma. *Am J Respir Crit Care Med*. (2007) 176:644–9. doi: 10.1164/rccm.200610-1473OC
107. Charmandari E, Kino T, Souvatzoglou E, Chrousos GP. Pediatric stress: hormonal mediators and human development. *Horm Res*. (2003) 59:161–79. doi: 10.1159/000069325
108. Swaab DF, Bao AM, Lucassen PJ. The stress system in the human brain in depression and neurodegeneration. *Ageing Res Rev*. (2005) 4:141–94. doi: 10.1016/j.arr.2005.03.003
109. Lopes NRL, Williams LC de A. Pediatric abusive head trauma prevention initiatives: a literature review. *Trauma Violence Abuse*. (2018) 19:555–66. doi: 10.1177/1524838016675479
110. Russell B, Alpert L, Trudeau J. Child abuse prevention during infancy: intervention implications for caregivers' attitudes toward emotion regulation. *J Hum Behav Soc Environ*. (2009) 19:540–53. doi: 10.1080/10911350902992789
111. Barr RG, Barr M, Rajabali F, Humphreys C, Pike I, Brant R, et al. Eight-year outcome of implementation of abusive head trauma prevention. *Child Abuse Negl*. (2018) 84:106–14. doi: 10.1016/j.chiabu.2018.07.004
112. Dias MS, Rottmund CM, Cappos KM, Reed ME, Wang M, Stetter C, et al. Association of a postnatal parent education program for abusive head trauma with subsequent pediatric abusive head trauma hospitalization rates. *JAMA Pediatr*. (2017) 171:223–9. doi: 10.1001/jamapediatrics.2016.4218
113. Zolotor AJ, Runyan DK, Shanahan M, Durrance CP, Nocera M, Sullivan K, et al. Effectiveness of a statewide abusive head trauma prevention program in North Carolina. *JAMA Pediatr*. (2015) 169:1126–31. doi: 10.1001/jamapediatrics.2015.2690
114. Petska HW, Sheets LK, Knox BL. Facial bruising as a precursor to abusive head trauma. *Clin Pediatr*. (2013) 52:86–8. doi: 10.1177/0009922812441675
115. Petska HW, Sheets LK. Sentinel injuries: subtle findings of physical abuse. *Pediatr Clin North Am*. (2014) 61:923–35. doi: 10.1016/j.pcl.2014.06.007
116. Jenny C, Hymel KP, Ritzen A, Reinert SE, Hay TC. Analysis of missed cases of abusive head trauma. *JAMA*. (1999) 281:621–6. doi: 10.1001/jama.281.7.621
117. Letson MM, Cooper JN, Deans KJ, et al. Prior opportunities to identify abuse in children with abusive head trauma. *Child Abuse Negl*. (2016) 60:36–45. doi: 10.1016/j.chiabu.2016.09.001
118. Feldman K, Tayama T, Strickler L, Johnson LA, Kolhatkar G, DeRidder CA et al. A prospective study of the causes of bruises in premobile infants. *Pediatr Emerg Care*. (2020) 36:e43–e49. doi: 10.1097/PEC.0000000000001311
119. Barr RG. Crying as a trigger for abusive head trauma: a key to prevention. *Pediatr Radiol*. (2014) 44 (Suppl 4):S559–64. doi: 10.1007/s00247-014-3100-3
120. Jouriles EN, McDonald R, Slep AMS, Heyman RE, Garrido E. Child abuse in the context of domestic violence: prevalence, explanations, and practice implications. *Violence Vict*. (2008) 23:221–35. doi: 10.1891/0886-6708.23.2.221
121. Li S, Zhao F, Yu G. Childhood maltreatment and intimate partner violence victimization: a meta-analysis. *Child Abuse Negl*. (2019) 88:212–24. doi: 10.1016/j.chiabu.2018.11.012
122. Tiyyagura G, Christian C, Berger R, Lindberg D. Occult abusive injuries in children brought for care after intimate partner violence: an exploratory study. *Child Abuse Negl*. (2018) 79:136–43. doi: 10.1016/j.chiabu.2018.02.003
123. Chan KL, Chen Q, Chen M. Prevalence and correlates of the co-occurrence of family violence: a meta-analysis on family polyvictimization. *Trauma Violence Abuse*. (2019) 8:1524838019841601. doi: 10.1177/1524838019841601
124. Chang JJ, Theodore AD, Martin SL, Runyan DK. Psychological abuse between parents: associations with child maltreatment from

a population-based sample. *Child Abuse Negl.* (2008) 32:819–29. doi: 10.1016/j.chiabu.2007.11.003

125. Cowley LE, Farewell DM, Kemp AM. Potential impact of the validated predicting abusive head trauma (PredAHT) clinical prediction tool: a clinical vignette study. *Child Abuse Negl.* (2018) 86:184–96. doi: 10.1016/j.chiabu.2018.09.017
126. Bennett TD, Riva-Cambrin J, Keenan HT, Korgenski EK, Bratton SL. Variation in intracranial pressure monitoring and outcomes in pediatric traumatic brain injury. *Arch Pediatr Adolesc Med.* (2012) 166:641–7. doi: 10.1001/archpediatrics.2012.322

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REVIEW
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Management of Spasticity After Traumatic Brain Injury in Children

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Traumatic brain injury is a common cause of disability worldwide. In fact, trauma is the second most common cause of death and disability, still today. Traumatic brain injury affects nearly 475 000 children in the United States alone. Globally it is estimated that nearly 2 million people are affected by traumatic brain injuries every year. The mechanism of injury differs between countries in the developing world, where low velocity injuries and interpersonal violence dominates, and high-income countries where high velocity injuries are more common. Traumatic brain injury is not only associated with acute problems, but patients can suffer from longstanding consequences such as seizures, spasticity, cognitive and social issues, often long after the acute injury has resolved. Spasticity is common after traumatic brain injury in children and up to 38% of patients may develop spasticity in the first 12 months after cerebral injury from stroke or trauma. Management of spasticity in children after traumatic brain injury is often overlooked as there are more pressing issues to attend to in the early phase after injury. By the time the spasticity becomes a priority, often it is too late to make meaningful improvements without reverting to major corrective surgical techniques. There is also very little written on the topic of spasticity management after traumatic brain injury, especially in children. Most of the information we have is derived from stroke research. The focus of management strategies are largely medication use, physical therapy, and other physical rehabilitative strategies, with surgical management techniques used for long-term refractory cases only. With this manuscript, the authors aim to review our current understanding of the pathophysiology and management options, as well as prevention, of spasticity after traumatic brain injury in children.

Keywords: traumatic brain injury, spasticity, management, rehabilitation, children

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INTRODUCTION

Traumatic brain injury (TBI) is a common cause of disability in children worldwide (1). In the United Kingdom alone, from 2001 to 2003, 5.6 per 100 000 population of children between 0–14 years were admitted to pediatric intensive care units (ICU) for TBI (2). In the United States an estimated 475 000 children in the same 0–14 yr age group suffer TBI each year (3). These injuries are associated with significant sensory and motor deficits, including spasticity, which leads to further problems such as contractures, muscle weakness and pain (4, 5).

The TBI-associated cognitive, behavioral, and memory impairments can make evaluating and managing spasticity more difficult compared to other causes of spasticity (6). The degree of spasticity may vary with some patients experiencing mild spasticity that causes muscle stiffness and

slow movements, while others may have severe uncontrollable spasms with contractures and fixed joint positions that make any movement impossible (7). If left unchecked, spasticity can also lead to deformities of the limbs and spine, decubitus ulcers, and severe pain. Further, this condition affects not only the child's movement, but also activities of daily living such as eating, sitting, writing, changing clothes, brushing hair, playing, sleeping and washing (8). It is not uncommon for these secondary consequences of TBI to be the main hindrance to re-entry into mainstream society for patients after the acute rehabilitation is complete.

It is challenging to predict which TBI patients will develop spasticity. From older literature, such as the noble prize winning work of Sherrington, it was assumed that spasticity is caused by injury to the corticospinal tract that leads to a loss of "higher center control" of the monosynaptic reflex arc (9). We know today that this is not the complete pathogenesis of spasticity. Only about 38% of patients with cerebral injury due to stroke, will develop spasticity at 12 months post ictus (5). Most of what we know about cerebral injury patterns and how it causes spasticity is gathered from stroke data, so TBI patterns that may lead to spasticity are mostly surmised from these stroke studies. Spasticity is managed by physical rehabilitation that is commonly aided by medications that lowers abnormal muscle tone and by treating comorbidities. There are very few studies that guides the management of spasticity in TBI children, therefore in this article we will review the current management of spasticity after TBI and make some recommendations based on this evidence and our own experience in children with TBI.

DEFINITION OF SPASTICITY

Clinicians and families of patients use various terms to indicate spasticity. The words "spasms" and "stiffness" as well as "spasticity" are often used interchangeably, and it is, therefore, necessary to accurately define the term. The Support Program for Assembly of a Database for Spasticity Management (SPASM) definition refers to a disorder of "sensory-motor control" that is caused by disruption to the upper motor neuron system (10). Lance defined spasticity as a velocity dependent increase in muscle tone, with exaggerated muscle tendon jerks that is caused by an exaggeration of the muscle stretch reflex (11). Lance's definition still forms the mainstay of our definition and understanding of spasticity today, but, as can be seen from the definition that is used by the SPASM group, it neglects the role that the sensory system (or the "feedback system") plays in spasticity and control of muscle tone in general (8). Burke added the "clasp knife"-like reference to the definition of Lance and this is very useful in underlining the clinical differentiating factor of spasticity from other conditions of increased tone, like rigidity (12). Mayer divides the clinical signs of upper motor neuron lesions into two groups: Positive signs (spasticity, release of flexor reflexes) and Negative signs (loss of finger dexterity, weakness and loss of selective control of muscles and limb segments) (13). This article will focus on this "positive phenomena" of spasticity in children after TBI.

WHEN SHOULD SPASTICITY BE TREATED?

Spasticity is also not always all bad. In some cases the spasticity may even aid in movement and add the much needed increased tone that a child requires to stand up, even if it is with the help of an abnormal supportive reflex (14). Indiscriminate reduction of spasticity may lead to reduced functional ability in some cases, and warrants careful evaluation by a multidisciplinary team, keeping the individual child and their unique circumstances in consideration.

However, in its severe form spasticity is detrimental to the child and should be treated. If spasticity impairs function, hinders personal and hygienic care, causes deformities, pressure sores or pain, it should always be treated. Spasticity can even impact growth in children as it may lead to imbalanced muscles, abnormal deposition of bone and injury to growth plates (14).

PATHOPHYSIOLOGY OF SPASTICITY

Sherrington's studies on cats were the ground breaking work that started our understanding of the physiological principles of muscle tone and spasticity (9). Before Sherrington, there were clinicians performing posterior cordotomies and rhizotomies, but mainly for pain. These pioneers in functional neurosurgery noted a reduction in muscle tone as well as reduction in pain (15, 16). The early theory on muscle tone still rested on the concept of a receptor inside the muscle spindle as well as its afferent fiber (Ia), which is inside the posterior nerve root (17). This reflex arc excites the alfa-motor neuron in the spinal cord to induce a contraction, with the brain being the higher center that controls the response. Spasticity was then thought to result from a loss of inhibition of this reflex mechanism due to an injury to the corticospinal system (17). In other words: the muscle spindle would continue to contract if the higher centers (brain and spinal cord) do not fulfill their "dampening" effect on the monosynaptic reflex arc.

We know today that the original argument that spasticity is caused by hyper excitability of the gamma-loop, due to interruption of the pyramidal tract, is not the complete story (17, 18). Sherrington probably sectioned through the reticulospinal tracts as well as the corticospinal tracts in his cat experiments. It is this reticulospinal tract injury, and likely vestibulospinal tract (the so called para-pyramidal tracts) injury, that leads to spasticity in mammals (19–22). Bucy et al. (21). and Travis (20), in their experiments on mammals, have shown that injury to the corticospinal tract or primary motor area's of the brain, is not enough to cause spasticity (22). From studies done in monkeys it is noted that destruction of the primary motor cortex, sectioning of the pyramidal tracts in the medulla as well as lesioning of the lateral corticospinal tract, leads to weakness and hypotonia that persists for several months, but no spasticity develops (22). Similarly, direct destruction of the pyramidal tract (corticospinal tract) at the level of the brainstem in humans, does not lead to spasticity (23–25).

Other than these central processes, there are also some more peripheral explanations for spasticity. Abnormal intraspinal processing whereby the alpha-motor neuron becomes hyperactive after cerebral injury, such as stroke or TBI, can also lead to spasticity (26). Further, Myklebust showed that if there is impaired reciprocal inhibition, abnormal activation of opposing muscle groups will lead to co-contraction or reciprocal activation of muscle (18). He described different types of inhibition (18) reciprocal Ia inhibition; presynaptic inhibition; recurrent inhibition; group II afferent inhibition and Golgi tendon organ inhibition (17). The interneuron, that acts on the Ia afferent, is also influenced by corticospinal tracts (27). Therefore, reduced presynaptic inhibition of Ia fibers can lead to spasticity. This inhibition is mediated by Gamma Amino Butyric Acid (GABA) (17). This inhibitory effect of GABA, and the contribution it has on spasticity, is also a target for on-going research. Key to our understanding of spasticity today is the injury to these para-pyramidal tracts (like the reticulospinal tract) and their role in dampening muscle activity (19).

At the level of the spinal cord there are also some changes in patients with spasticity that adds to the pathophysiology. Histochemical changes occur in the spinal cord due to this loss of inhibition from the descending parapyramidal tracts. Researchers have also shown that the muscle sarcomere and tendon itself undergo physiological changes in patients with spasticity (28). These changes are likely secondary adaptive changes due to the increased muscle tone, however. There are, unfortunately, still a great deal of unknowns in terms of the exact pathophysiology of spasticity in humans.

PREDICTORS OF SPASTICITY AFTER TBI

TBI includes a heterogeneous group of injury mechanisms and patterns. The distribution of contusions, tissue tears, hemorrhagic damage and ischemic injury varies greatly, making each patient's injury unique. Therefore, predicting the spread, or even presence, of spasticity after TBI is very difficult, if not impossible. We do know, however, that there are some useful broad generalizations.

Most of what we know about spasticity comes from research in children with cerebral palsy and adults after stroke. From stroke research it is known that few patients who initially develop increased tone, often within the first week after ictus, will have long-lasting spasticity (29). The initial upper motor neuron weakness syndrome that includes spasticity, is usually transient after stroke. We see the same in children after TBI. More children have increased tone within the first week after severe TBI, than 3 months later.

Around 42% of patients with initial central paresis after stroke, will develop spasticity that is still present at 3 months after ictus (29). although this percentage varies between studies. Similarly, long term spasticity rates range between 19 and 42% due to variability across study follow up rates and sample sizes (5, 30, 31). In all of these studies, the percentage of significant spasticity (significantly impacting activities of daily living, Modified Ashworth Score more than or equal to 3) ranged between 15 and 22% only (29). On the other hand, data from the TBI Model Systems National Database (a United States of America database) show that of the 75,000–100,000 severe TBIs that occur each year, up to 85% of patients develop contractures due to spasticity (7).

Patients with a more severe initial paresis post stroke developed more disabling persistent spasticity (29). Associated sensory deficits seem to be an important predictor of the risk of spasticity (29). In stroke, a higher Modified Ashworth Scale scores early after ictus, increases the risk of later spasticity (29). In stroke patients the distribution of spasticity is higher in the antigravity muscles, similar to cerebral palsy children, and the upper limbs seem to be more affected than the legs (29). A similar pattern is noted in TBI patients. This may be because the middle cerebral artery supplies the lateral and frontal convexity of the brain, which is more responsible for the upper limb motor function (32, 33). Most patients will still suffer more from paresis after stroke, rather than spasticity (29).

LOCALIZATION OF INJURIES THAT LEAD TO SPASTICITY

Understanding the pathophysiology of spasticity helps predict which cerebral injuries may lead to spasticity. Spasticity in humans is less likely from an isolated injury to the primary motor area or the corticospinal tract, but more likely from an associated injury to the supplementary motor area and area's of associated motor planning and function (22). Some researchers have reported that in human brain injury, whether traumatic or ischemic, flaccid paralysis may be present for as long as 6 weeks, before any spasticity ensues (22) **Table 1** lists the common area's involved with spasticity after cerebral injury.

Widespread cortical injury involving the premotor area and the supplementary motor area causes weakness as well as spasticity in monkeys, while injury to the motor area alone, causes weakness only (22). Woolsey showed in his experiments on monkeys that bilateral injury to the motor cortex lead to spasticity more commonly than unilateral injury (22). This also underscores the bilateral supply and involvement in muscle tone control and motor planning. Large middle cerebral artery area infarcts will also damage most of the descending fibers of the corticospinal tract origin (corona radiata). In time these lesions will also cause spasticity added to the weakness, most likely

TABLE 1 | Summary of Central Nervous system area's involved in spasticity after TBI (22, 34, 35).

Corticospinal tract injury alone is not enough to lead to spasticity; but injury to the following structures does:

- Associated injury to the supplementary motor area
- Pre-motor area
- More common if bilateral motor cortex injury
- Cortico-reticular fiber tracts injury
- Frontal cortex and anterior limb of the internal capsule
- Anterior funiculus of the spinal cord and dorsal half of the lateral funiculus of the spinal cord (vestibulospinal and reticulospinal tracts)

because of injury to both the corticospinal tracts and the cortico-reticular projections (22).

Lesions in the frontal cortex and internal capsule may also lead to spasticity due to loss of cortical input to the inhibition center in the brainstem. However, brainstem lesions in humans rarely cause spasticity. Lesions in the inhibitory center in the brainstem will often involve the respiratory and vasomotor center, so these are mostly fatal (22) Deep-seated injuries to the internal capsule may also lead to spasticity. Injuries of the anterior limb of the internal capsule cause spasticity quite readily, while posterior limb injuries (where the corticospinal tract is situated) does not lead to spasticity in patients after small focal strokes (34). This once again illustrates that it is the associated motor control tracts that are injured in patients who develop spasticity (22).

Injury to the anterior funiculus of the spinal cord can lead to spasticity due to damage to the vestibulospinal and reticulospinal tracts. It therefore seems, that to cause spasticity, the lesion must involve the dorsal half of the lateral funiculus. This is where the reticulospinal tract runs (22, 35). Injury to the corticospinal tract alone causes weakness. Loss of inhibitory control by the dorsal reticulospinal tract is necessary to cause spasticity. This causes unopposed medial reticulospinal tract and vestibulospinal tract functioning with consequent severe spasticity, mostly in the antigravity muscles (leg extensors and upper limb flexors) (22).

MANAGEMENT OPTIONS

Non-drug Therapy

Recovery after TBI, similar to cerebral stroke, follows a reasonably predictable sequential pattern. Brunnstrom outlined the stages of motor recovery after stroke as follows: flaccidity; synergies, some spasticity; marked spasticity; out of synergy, less spasticity; selective control of movement; isolated/coordinated movement (36). Although each step follows the other, the process may be interrupted at any point and this halts all on-going progress (36, 37). Spasticity usually starts relatively soon after the cerebral injury, in general, but in many cases resolves, following the aforementioned stepwise process, likely due to plasticity (38). If plasticity does not aid in the recovery of motor function, spasticity will persist (28).

Due to the concern of potential negative interactions between drug therapies for spasticity and the process of neural recovery, therapeutic interventions to treat spasticity early after TBI are delayed, often for the first year after injury (7), but this may be too late. In an animal TBI model, Bose et al. (39). found that early initiation of treatment (at 1 week post TBI) with intrathecal Baclofen prevented the onset of spasticity and reduced spinal cord histochemical changes that lead to excitability of neural pathways and lower limb spasticity. The beneficial effect was reduced if Intrathecal Baclofen therapy was started after 4 weeks (39). Further research is still needed to show the long term safety in humans in the acute phase after TBI as well as to determine the cognitive effect of chronic Intrathecal Baclofen therapy after TBI in children (7).

Patients may benefit from physical therapy and mobilization in the acute phase, even while patients are still in the Intensive Care Unit. A delicate balance, however, needs to be maintained between stimulatory activities and allowing adequate rest for the brain so as not to compromise neural recovery (6). Stretching forms the corner stone of management—passive stretching and limb positioning aids in preventing contractures and modulates muscle tone (40). Comforting therapies, such as hydrotherapy, warm water baths (avoid extreme temperatures so as to prevent burns) and horse riding therapy are all valuable tools for later use (8). The use of splinting and casting of limbs can greatly benefit maintaining passive stretch as well as normal range of motion in the patient while in the acute phase, as well as maintain and increase the range of motion and muscle stretch during the active rehabilitation phase (40). Care should be taken to avoid additional pressure points and adequate padding is important. The therapist must also ensure that the splint or cast does not enhance the positive supportive reflexes—such as the plantar reflex—as this will add to the increase in abnormal muscle tone if left unchecked. These passive positioning aids need not be worn all the time. A period of rest is allowed and a different night splint can be used to keep the limb or joint in a passive position of rest, thereby limiting patient discomfort while still maintaining the range of motion in a specific joint (40). Cryotherapy—application of a cold pack for up to 20 min—to a troublesome spastic limb may also help muscle relaxation. Combinations of electrotherapy, cryotherapy, heat therapy, stretching and positioning are all valuable non-invasive therapeutic strategies (40). All of these can be used in the ICU setting.

Considering the patients and their experience of spasticity when deciding on a treatment strategy is important. Patients experience spasticity differently from what the clinician observes and their definition of spasticity is often also different (41). Spasticity affects the whole body of the child, therefore, patients often do not perceive themselves as having improved mobility when in a wheelchair (8, 41). Comorbidities and associated conditions like pain, urinary tract infections, extremes of temperatures and pressure ulcers, all increase spasticity and should be actively investigated as part of management (8, 28).

It is important to differentiate spasticity from other conditions of increased muscle tone such as dystonia and rigidity, which can be precipitated by trauma to the basal ganglia and thalamus. The management of these conditions, that affect the basal ganglia and thalamus, is different.

Psychological and social supportive strategies such as play therapy, formal psychology management and support are all valuable, as the loss of function, together with the brain injury itself, often lead to psychosocial challenges in these patients (8). Reintegration into the school environment is important for brain plasticity and reanimation of activities of daily living. However, this requires attention to movement impairment, psychosocial disability and cognitive challenges to avoid the child becoming despondent and resistant to rehabilitation efforts (42).

Drug Therapy

Systemic medication aid in the management of spasticity after TBI, especially in the acute phase, where surgical techniques should be avoided. However, some of the associated side effects may be detrimental such as the use of oral

Baclofen and benzodiazepines to reduce muscle tone and aid in mobilization and positioning. These agents may reduce the level of consciousness at higher doses and impact all striated muscle, including the oropharyngeal and laryngeal musculature. However, oral Baclofen does not negatively impact breathing and apnoea frequency during sleep (43, 44). Animal studies have also shown that Baclofen does not negatively affect laryngeal control and vocal cord movement (44). Any intervention that negatively affects intracranial pressure or cerebral oxygenation should be avoided. Close surveillance is advised and the treating team should not be solely focused on muscle tone, at the cost of the internal cerebral milieu or good cerebral protective mechanisms, including optimal cerebral perfusion pressure, adequate cerebral metabolic rate control, proper cerebral oxygenation and nutrition. Any treatment that does not adhere to these principles, or threatens them, should be avoided, even if it leads to poor spasticity control or treatment.

Infection, metabolic crises, undiagnosed fractures and pain (noticeable or not) are all factors that will lead to increased muscle tone in the severely injured child.

Baclofen forms the mainstay of all oral regimens to treat spasticity in children and in adults, including post TBI. Baclofen is a GABA-B receptor agonist and has similar pharmacodynamics to the benzodiazepines (45). The use of Baclofen in the treatment of patients with chronic spasticity such as spinal cord injury, cerebral palsy, multiple sclerosis and after stroke, has been better studied than in the acute setting (40). Baclofen may also impair neural recovery in the setting of cerebral injury (46) and its use may be limited in the acute setting of a ventilated TBI patient due to its suppressant effect on the cough reflex and increased likelihood of bronchoconstriction (40). It lowers the seizure threshold and has been shown to impair cognition and memory in children (40). In about 17% of children it causes excessive somnolence. Furthermore, oral baclofen seems more effective in reducing lower than upper limb spasticity after pediatric TBI (possibly due to GABA-B receptors being less involved with upper limb tone) (47).

Intrathecal Baclofen is promising as it causes fewer systemic side effects. Much lower dosages are required (On average 100-−200 mg per day compared with more than 15 mg per day in children) and the drug is delivered directly where it is needed. Most centers will only trial Intrathecal Baclofen if spasticity is still present after 6 months (40) but there are teams that will use it early on, even as a preventative strategy, and in very young children as well (48, 49). Becker et al. evaluated long term results for 110 patients (79 children) with Intrathecal baclofen for TBI induced spasticity (50). They found it to be safe and very effective and recommended early use to prevent long term complications of spasticity such as contractures and pressure sores (50). A consensus panel has stated that intrathecal Baclofen is safe for children with TBI induced spasticity (51). The same consensus panel has shown benefit of intrathecal baclofen in treating the autonomic dysfunction often be associated with TBI—which is generally very resistant to treatment (52). No specific recommendation as to the timing of an intrathecal Baclofen implant after TBI has been made. Toxic doses of Baclofen causes loss of consciousness and respiratory suppression, while rapid withdrawal from Baclofen can lead to seizures, hallucinations and hyperthermia with eventual multi organ failure due to rhabdomyolysis (53). Patients and their families should be cautioned that cessation of Baclofen can lead to serious complications, so they should never run out of the medicine.

Dantrolene sodium is best known for its treatment of malignant hyperthermia in anesthesia. Due to its high cost it is not readily available in the developing world and is only used in our setting in its intravenous formulation during anesthesia. Dantrolene acts directly on the sarcoplasmic reticulum in the muscle cell and impairs calcium release (45). Side effects may make Dantrolene less appealing as it can impair diaphragmatic contractility, hepatic function and platelet activation. Its use in TBI may, therefore, be risky, but it has been successfully used as a first line therapy in the acute phase after TBI for patients with severe spasticity with no noticeable complications (40).

Longer acting benzodiazepines, such as Diazepam, has antispasmodic effect due to agonistic activity on the GABA-A receptors where it opens chloride channels and causes hyperpolarisation of the nerve cells (45). Its main effect is sedation and it may lead to hypotension and low levels of consciousness in patients. This sedating effect is useful in the agitated patient or during the acute phase where intracranial pressure is high and sedation is required, but its use may be limited in the emerging patient that needs to participate in the rehabilitation process. The antispasmodic effect of Diazepam is only prominent at very high doses (45), close to anesthetic doses, but it acts as a useful adjunct to other antispasmodic drugs such as Baclofen. At low dosages, titrated to prevent hypotension and excessive sedation, it is very valuable in treating spasticity.

α^2-agonists, such as Clonidine, inhibits excitatory nor-Adrenalin release at the presynaptic receptor, while facilitating the action of Glycine, which is an inhibitory neurotransmitter (40). There is some concern that α^2-agonists may dampen neural recovery after cerebral injury, especially in animal studies (46). It may also induce hypotension. However, with careful use it is a good adjunct in treating the child emerging from coma, especially in a restless phase, as it has calming properties without excessive sedation. Clonidine is a good adjunct to analgesics and it has been shown to lessen spasticity after severe TBI, without significant side effects (40).

Gabapentin is one of the older antiepileptic drugs. Its use in epilepsy has declined dramatically, as there are better drugs available, but it is used commonly as an adjunct to analgesia regimens for neuropathic pain. It is used commonly in neurosurgical practice, even in children, for its additive effect to neuropathic pain management regimens. The mechanism of action is largely unclear but its down- regulation of irritable nerve cells is clear in its role in pain management (40). Gabapentin also has an antispasmodic effect that is not hampered by its interaction with other medications. It can safely be co-administered with Baclofen and other medication like Clonidine and benzodiazepines. Slow introduction is important, and the dosage should be increased in a stepwise fashion over a few days as children often feel drowsy on initiating the drug.

In a 2017 Cochrane review of post TBI spasticity treatment, there was insufficient evidence to report on the efficacy of the non-pharmacologic strategies (splinting, casting, physiotherapy, tilt table use and electrical stimulation) as well as the pharmacological strategies used (Baclofen and Tizanidine) in treating or preventing spasticity in patients after TBI (54). The review specifically mentioned that the studies looking at Baclofen in TBI-related spasticity, did not report their results adequately, so the role of Baclofen in TBI could not be evaluated (54).

There are also on-going studies looking at new drugs, these include Cannabinoid receptor agonists, Serotonin receptor agonists, Glycine agonists and Kynurenic acid, which is a derivative of Tryptophane (53).

It is important to note that there are concerns about all the above-mentioned drugs and their potential to impair neural recovery after cerebral injury such as stroke and TBI. It is therefore wise to limit their use and duration to where absolutely necessary (40, 46). These drugs should only aid as adjuncts to the proven and very effective non-invasive treatment strategies discussed in the preceding section of this article.

Due to the lack of definite evidence showing improved spasticity outcomes after TBI from any one modality in isolation (54), combination therapeutic strategies are recommended. Combining different medications (while keeping interactions and side effect profiles in consideration) and physical therapy as well as Botulinum toxin injection strategies are encouraged (7).

The best-studied intervention in spasticity after TBI is Botulinum toxin A (54). Its efficacy and safety have been well examined (55). Combinations of the weakness caused by the upper motor neuron injury in TBI and the spasticity caused by the same injury leads to the typical muscle imbalances that form the clinical picture in patients with spasticity (56). A classical example is the flexed elbow, wrist and clenched hand that are seen in children with a spastic upper limb after cerebral injury. "Therapeutic weakness" of the overactive (spastic) muscle can be induced by Botulinum toxin, phenol chemical denervation and even by orthopedic procedures such as tendon lengthening. This procedure aids in "rebalancing" the muscular imbalances around a joint and may aid greatly in the rehabilitation process (28). Botox injection of the biceps and brachialis muscle in a child with spastic flexed upper limbcan aid active strengthening of the antagonist muscle (triceps brachi in this example) is more effective (13). This allows better positioning of the limb, less pain during stretching, better weight bearing through a straight arm and active movement—this greatly aids in the rehabilitation of movement and reducing spasticity, while stimulating cerebral plasticity to take place (57). The spasticity and shortening of muscles and associated functional impairment, sometimes, do not return after the Botulinum toxin has worn off (58). This improves rehabilitation and function and is a good reason not to skip Botulinum toxin treatment and head straight to permanent and more invasive lesioning surgeries.

Early after severe TBI a global hypertonia may also be part of severe brain and brainstem injury, manifest as gross flexor- or extension-posturing. These posturing episodes localize the injury to deep nuclei and the brainstem. It must be managed as such and a prognostic decision should be made. In children, we generally find that some can recover remarkably after severe TBI, even patients with initially very low levels of consciousness. When these aggressive posturing episodes is on-going, it is detrimental for intracranial pressure, so active sedation with benzodiazepines is recommended in this phase. These are reflex activities and not merely diffuse spasticity. The fact that it comes and goes and that certain head and body positions elicit or relieve it, is the differentiating clue (59). **Table 2** summarizes management options and **Table 3** summarizes evidence for these.

Other Management Considerations

It is common for severe TBI patients who are immobile for prolonged periods to have comorbid joint pathology around spastic limbs, such as: joint capsule contractions, myositis ossificans, muscle fibrosis, and muscle contractions (56). These all contribute to the loss of function, pain and immobility. In these cases, mere reduction of spasticity in a muscle will not lead to improved range of motion and function. Orthopedic procedures and aggressive physiotherapy (except in the case of the frozen elbow where aggressive mobilization leads to myositis ossificans) (60). are required in addition to procedures to improve spasticity. It is important to predict this before surgery and is relatively easy to do. The author uses peripheral nerve blocks to determine if muscle contracture or joint pathology limits mobility around a joint before performing any neurosurgical procedure to reduce spasticity such as selective peripheral neurotomy (SPN). If there is good passive range of motion possible after the peripheral nerve block (e.g., N Musculocutaneous if testing elbow extension range of motion in a patient with elbow flexion spasticity) the chance of the SPN on N Musculocutaneous leading to improved range of motion and function in the elbow is greater than if there is no improvement in range of elbow flexion.

TABLE 2 | Summary of management options in children with spasticity after TBI.

Management options	
Physical management options	
	• Physiotherapy
	• Occupational therapy
	• Splinting
	• Hydrotherapy
	• Tilting table
Medications	
	• Dantrolene
	• Baclofen (oral or intrathecal)
	• Benzodiazepines
	• Gabapentin
	• Clonidine
	• Botulinum Toxin
Surgical options	
	• Intrathecal Baclofen pump placement
	• Selective peripheral neurotomy
	• Selective dorsal rhizotomy
	• Orthopedic surgery (tendon lengthening, etc.)

TABLE 3 | Evidence for various management strategies.

Pre-clinical evidence	Clinical evidence
	Physical therapy, stretching and splinting (6, 40)
	Hydrotherapy, Cryotherapy, horse riding (8, 40)
	Manage comorbidities (8, 28)
	Psychological support
	Oral Baclofen (43, 44) Performs better at reducing lower limb spasticity than upper limb (47)
Intrathecal Baclofen Animal studies shows great benefit if early use (1st week), compared to at week 4 (39)	Intrathecal Baclofen Early use safe, safe in children (48–51)
	Dantrolene Poor evidence, high risk (40, 45)
	Benzodiazepines High dose needed, good adjunct (45)
Clonidine May dampen neural recovery (46)	Clonidine Good adjunct treatment, low side effect profile (40)
	Gabapentin Good adjunct (40)
Cannabinoids, SSRI's, Glycine agonists, Kynurenic acid All experimental (53)	
	In a Cochrane review (54) All above has no strong evidence for or against in TBI
	Botox Very good clinical studies and effect (54, 55)
	None of the lesioning techniques have been well studied in clinical TBI-related spasticity studies

If there is no improvement in range of elbow extension after the nerve block, the patient will require concomitant orthopedic surgery to release the tendons or free up the joint or its capsule.

Neuromuscular electrical stimulation, as well as constraint induced therapy, are also popular in the rehabilitation of many injuries and ailments. There is some evidence to suggest that this may also aid in recovery after TBI. Biofeedback techniques may have potential to help in recovery of function and prevent some complications later in the recovery process after TBI. There are encouraging data from randomized trials on neuromuscular electrical stimulation but there is still insufficient evidence for routine therapy after TBI. Neuromuscular electrical stimulation therapy does not have any direct effect on spasticity, but it is proven to relieve pain, and this has a beneficial effect on muscle tone (61).

Some preliminary work on the use of transcranial magnetic stimulation (TMS) also shows promise aiding the process of locomotor retraining (7). The effect of TMS is, however, transient and multiple long-term therapy sessions, as well as treatment in the acute setting, are still not feasible.

A large basic science fraternity is investigating the role of inflammation in the injury causation as well as the recovery of patients after TBI. There may be a place for down regulating the inflammatory response to prevent or treat spasticity after TBI as well (7). This is still preliminary research.

Surgical Management

When choosing lesioning techniques to manage spasticity after pediatric TBI, it is important to evaluate therapies for spasticity against the loss of function that may follow the treatment. Patients with severe spasticity are sometimes able to "walk" in their own way. The deformities and abnormal wear that is placed on their limbs and joints cause severe pain and further long term complications such as spinal deformities and hip dislocations (14). Effective treatment of a patient's abnormal spasticity may prevent these serious long term complications, but the parents or caregivers may see this as unacceptable because it may make it impossible for them to "walk" as before. It is essential to educate the caregivers about the advantages and disadvantages of each approach. Often it is the long term benefits that outweigh short term losses (14). In making this, often challenging, decision the multidisciplinary team may use the IDAHO criteria. The IDAHO Criteria offers a simple alternative schematic to assist in evaluating an individual's potential to recover function. This model guides goal setting and recognizes the importance of many factors integral to attaining functional improvement; treatment options are evaluated holistically for optimal outcomes. This aids in enhanced patient and caregiver satisfaction, while allowing the team to consider each child individually and make decisions based on their unique needs and circumstances. IDAHO criteria considers: infrastructure, desire, ability, hospital access and opportunity in planning interventions in patients (14).

The evaluation of each child for spasticity surgery is a meticulous process wherein the patient should be evaluated over time, in various scenarios, and in their daily milieu to which they must return after rehabilitation. The physiotherapists and occupational therapists play a very important role herein and video recording is a valuable aid. It is paramount that the child and caregivers are involved in the decision making process (14). Functional activities should be the focus of the evaluation process. Test the child by doing the activities to which they must return: writing, drawing, playing, walking, running, sitting at a desk, brushing their hair, eating, etc. Documenting and evaluating tone, power, reflexes and range of motion is important and adds to the decision-making process, but the goal is restoration of function, not merely reducing tone or improving degrees in range of motion in a joint.

Involving the family in the daily rehabilitation process post-surgery is invaluable. Children do better if their day is filled with regular activities that are guided by caring parents and families, interspersed with formal physiotherapy and occupational therapy sessions (58). Continuous cognitive, social and schooling support should be offered in a context-specific way to the child after TBI (58). All efforts should be aimed at reintegration that is appropriate for the child and their family.

Surgical Options

In deciding which surgical technique is best suited for each child, the spasticity should be classified according to its spread: focal spasticity vs. global spasticity. Certain techniques are best suited to treat focal spasticity, while others are better suited to global spasticity—see **Figure 1**. Some techniques are reversible, while other treatments are permanent, and this

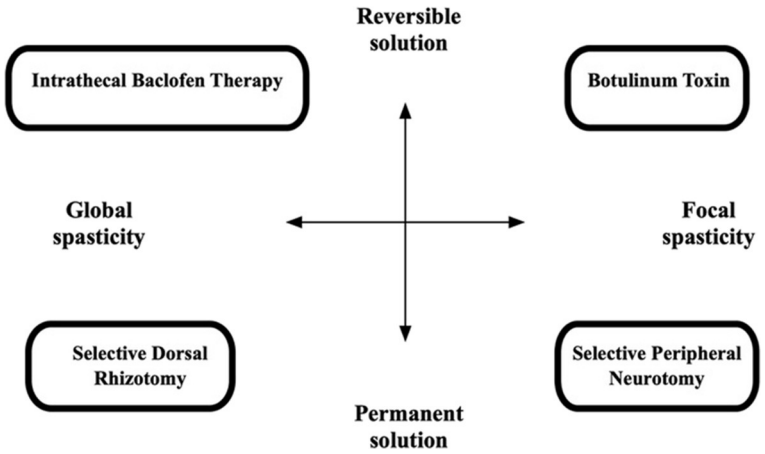

FIGURE 1 | Diagram to illustrate choice of management technique in spasticity (62).

has significant implications on treatment choice and careful counseling and discussion with caregivers and other members of the treating team is needed. Surgical management options for spasticity include: Intrathecal Baclofen pump placement, Microsurgical DREZotomy (dorsal root entry zone lesioning) and Selective peripheral neurotomy. Deep brain lesioning or deep brain stimulation can offer treatment options for the other movement disorders consequent to TBI, such as Holmes tremor and dystonia (63, 64). Surgery as a treatment for spasticity after TBI should only be considered once permanence of the spasticity has been confirmed. As stated above: many patients who show spasticity in the early phase after severe TBI do not go on to have permanent spasticity when evaluated after 3–6 months. There is, however, a small group of patients described (40) that suffer severe early onset spasticity. This group are challenging to manage, and more aggressive strategies are needed to prevent contractures and impaired mobilization. In general, a certain amount of time should, therefore, lapse before surgery is considered. This is especially relevant to the lesioning options, as they cannot be undone, and no surgical procedure is without risks. It is our practice not to do lesioning procedures within the first 2 years after stroke or TBI. This does not mean that the patient should be untreated for this period, Botulinum toxin administration and oral, or intrathecal Baclofen therapy are great options for this interim period while the rehabilitation process and temporal evolution of spasticity are being evaluated. It is mostly clear after the first 12 months which way the patient is heading with regards to his mobility, cognitive recovery and muscle power and tone.

Botulinum toxin can be used safely in patients with TBI related spasticity (56). The author uses it extensively in pre-operative workup of patients prior to selective peripheral neurotomies (SPN) and even as part of selective dorsal rhizotomy (SDR) workup. The selective injection of Botulinum toxin, using ultrasound guidance, into specific muscles to test individual muscles' role in the dysfunction or impairment that a patient experiences due to spasticity is invaluable. In doing this, the author can test a "mechanical hypothesis" on what the role of each muscle is in the abnormal biomechanics of a patient's functional impairment. The injection results in temporary loss of function, which returns once the Botox has worn off (anything from 3 to 6 months). Valuable knowledge is gained by using this strategy as the clinician can pinpoint each muscle's role in the individual patient's functional impairment. Ultrasound guidance of Botulinum toxin injection is the author's preferred method as it simultaneously allows selective muscle injection and confirmation of the target injected. Dynamic EMG-guided Botulinum toxin injection is also used, but this is less selective and less specific (65).

Selective peripheral neurotomy (SPN) offers an effective long-term therapeutic strategy for focal spasticity in patients after TBI. Its use in pediatrics has been demonstrated in children with spasticity due to cerebral palsy (66). The procedure is based on the microsurgical dissection of the motor branch that supplies a specific muscle in which spasticity is limiting function. The motor branch to the offending muscle is then sectioned partially (about 80% of the fibers are cut) (62). With the use of intraoperative neurophysiological tests good specificity and selectivity of the procedure can be achieved and the risk of erroneous sensory nerve sectioning and "wrong-nerve" sectioning is eliminated. The procedure causes selective partial denervation to the agonistic spastic muscle, allowing the weak antagonist to be strengthened, thereby allowing a more balanced muscular force-relationship around a joint (similar to the biceps vs. triceps example described previously in this article). The multidisciplinary team carefully agrees upon the muscles targeted, after multiple patient evaluations. Before a lesioning technique like this is performed, the author tests the functional effect that reduction in spasticity in these selected muscles will have by using Botulinum toxin injected selectively into the same muscles via ultrasound guidance. In effect this acts as a 4–6 month trial in the functional benefit of the potential selective peripheral neurotomy. This helps greatly in selecting which muscles to target and prevents treating spasticity that has

a beneficial role in the specific patient, as discussed before. If reduction in spasticity in a specific muscle leads to functional loss, that muscle is not targeted. SPN, like all surgical techniques, should only be considered once spasticity has been shown to be permanent and non-responsive to conservative strategies, and if there is function-impairing spasticity that returns after Botulinum toxin treatment.

Children recover well from SPN and aggressive mobilization can start immediately postoperative. No casting or immobilization is needed. Active strengthening of the antagonist muscles must be prioritized, as weakness is only appreciable once the spasticity is reduced. Parents should be prepared for this to avoid unnecessary panic. The technique aids rehabilitation and is a good adjunct to the more traditional therapies such as physiotherapy and occupational therapy as it does not require immobilization post operatively and effectively in reduces troubling spasticity.

Performance of a peripheral nerve block, or the preoperative Botulinum test, can indicate if any concomitant orthopedic surgery to lengthen tendons, etc. will be required. These procedures are often done in the same sitting in our unit if range of motion will be significantly impaired due to short muscles and tendons. Mild muscle shortening will mostly improve with reduced spasticity and aggressive stretching, therefore routine orthopedic surgery may not be required.

Some units also discuss selective dorsal rhizotomy (SDR) to treat spasticity related to TBI, but working in the unit that has been performing modern SDR for the longest period (Warwick Peacock started performing his variation of an old technique here in 1979) (67), we feel it is a procedure best kept for more widespread spasticity in both lower limbs. This is rare in spasticity related to TBI, unless it is a consequence of associated spinal cord injury. We prefer not to use it in TBI patients in general given the risks of opening the thecal sac to perform SDR and reduced precision and ease of targeting individual muscles.

Prevention

Early mobilization and active positioning is important from the outset. In the acute phase the goal is to maintain full range of movement in all limbs (40). This may be difficult in a polytrauma patient, but is critically important. A detailed history of the child's functional abilities and any neurological or orthopedic deficits prior to the TBI should be obtained, as this pre-existing impairment may limit the outcome as well. Constant vigilance is required for associated injuries, such as spinal cord injuries, long bone fractures, heterotopic ossification and muscle/tendon injuries, as these may all impact muscle tone and impair the mobilization of individual limbs as well as the child as a whole (68). Commonly used medication in the severe TBI child, such as Thiopentone, Propofol, benzodiazepines, and muscle relaxants all impact the evaluation of muscle tone and may often mask the underlying problem in the acute phase. As these medications are weaned the level of spasticity becomes more apparent. The daily advised sedation breaks should be optimally used to evaluate and document tone using a scoring system such as the Ashworth score (40) This early objective documentation of muscle tone helps as a guide to determine progression or resolution of the spasticity as the child awakens from the acute phase and during rehabilitation. Passive range of motion exercises and positioning are important in this acute phase. Once the acute phase of auto-regulatory disturbances after severe TBI has stabilized, passive stretching, positioning, and most importantly mobilization in and out of bed must begin. Weight bearing through joints is the most beneficial method of active rehabilitation of movement, balance, muscle tone, and proprioception, all vital for ambulation. Regrettably children who have suffered a severe TBI are too frequently left in a supine position in a bed with cot sides due to fear of them falling out of bed or because they are not yet able to walk. In the early phase after TBI an inability to walk does not suggest poor progress or prognosis and other activities can be considered as valuable milestones. Sitting, whether in a chair next to the bed, or inside a fully supportive buggy is a major step in the rehabilitation and recovery process and should not be underestimated. Even a child with a low level of consciousness (GCS 9-14/15) can be made to sit in a well-supported chair or buggy. The consequent vestibulo-cerebellar and postural stimulation is worthwhile in the rehabilitation and recovery process.

A Suggested Approach to Spasticity After TBI in Children

There is no clear evidence-based guideline or stepwise approach to treating spasticity in children, or adults, after TBI. It is, however, possible to recommend an approach based on the author's experience and the scientific knowledge available in the literature. **Figure 2** summarizes our approach:

- Immediately after the injury: cerebral protection and treating the brain injury is the main priority. Sedation and hemodynamic stabilization are key. Perform passive range of motion bed exercises only, and this only if it does not cause an increase in ICP or hemodynamic instability. Limited stimulation is important, as cerebral autoregulation is often impaired. Usually the child will have weakness or hypotonia in this phase. If spasticity is detected it is important to differentiate this from brainstem reflex patterns that require sedation treatment, or that may be indicative of serious brain injury and poor prognosis, such as decerebrate posturing. If localized limb spasticity is present, slow and maintained stretching and positioning exercises can start in the bed and splints can be employed to keep the limbs in a neutral position in between the stretching sessions. Pressure care and pain management is important. Manage associate injuries and fractures.
- When the child is stable regular, even 2–3 times a day, physical therapy should begin. Passive full range of motion exercises should be done. In the child who is awake, even if still confused, activities that allow the shoulder girdle, pelvic girdle, and trunk to rotate and stretch through their full range are advised. Weight bearing through a spastic limb and joint forms a major part of the neuro-rehabilitation process and the earlier it can start the better. If limbs show early spasticity, splinting to keep the joint and muscle in a neutral position can be used in bed.

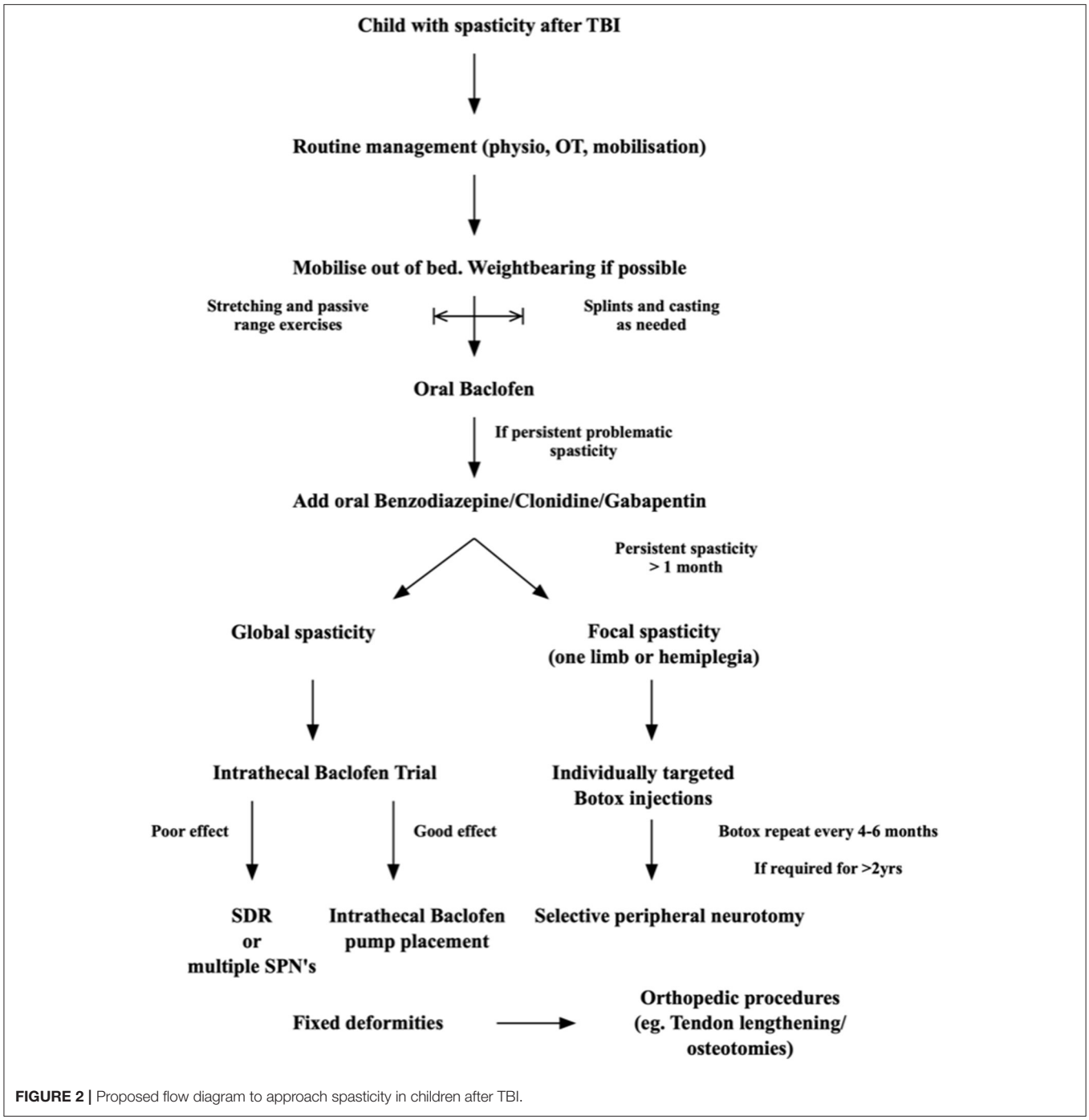

FIGURE 2 | Proposed flow diagram to approach spasticity in children after TBI.

- As soon as the comorbid injuries (fractures, chest and abdominal injuries) and the brain injury allows, even if still on a ventilator for airway or with impaired consciousness, mobilization in and out of the bed should start. Placing a child in a well-supported buggy is excellent for lung function, renal function, cognitive rehabilitation and family morale. The benefit of enrolling the postural- and vestibular- control systems early in the neural rehabilitation process is immense.
- If muscle tone is significantly increased, and impairs the movement therapy, oral Baclofen can be initiated. Start with low doses and slowly increase as needed in 5 mg increments and as regularly as four times a day if needed. Slow increases are important, as children become drowsy easily. If this is still not enough then a low dose of long acting benzodiazepine can be added daily. Keep in mind that all these drugs may reduce wakefulness and impair cognitive function as well as neural recovery, so only use if really needed to make mobility therapy possible.
- Once the child is out of ICU and mobility is easier, standing and walking activities should start. Weight bearing is again

very important, and together with daily activity simulation and retraining, this forms the cornerstone of all neuro-rehabilitation strategies. Standing frame or tilt-table is useful.
- Use splints and casting as needed to keep limbs in a neutral position, or to maintain stretch on spastic muscles, as needed. Pressure care is important throughout.
- If after 1 month the spasticity is chronic, we recommend starting Botulinum injections under ultrasound guidance in a selective way from the onset. This will aid in surgical decision making later, if needed. Clear documentation of the muscles targeted, and the functional effect of their injection must be maintained. Use the reduced tone in the rehabilitation process. Reintegration into school and society/home life is the goal.
- After 6 months (Botox® effect 3–6 months), once the Botulinum Toxin has worn off, and the treating multidisciplinary team notices that function-impairing spasticity returns, a selective peripheral neurotomy can be done to allow continuous mobility and activities as was possible during the Botox period. In our unit I prefer to allow up to 2 years before lesioning techniques are used, as neural recovery can still take place 2–3 years post-injury (from my own experience) and I do not want to limit the natural neural recovery process by any unnecessary surgical intervention. There are some exceptions, however, where we notice after 1 year that the spasticity is progressing, and no rehabilitation is possible outside of the Botox®-effect period.
- Children with global spasticity are not ideal candidates for SPN, so in them I would prefer to do a trial of Intrathecal Baclofen therapy and implant a pump if there is a good function-improving effect. This is also considered only after 1 year, for the above stated reasons, although there is literature supporting early, even 1 week post injury, intrathecal Baclofen therapy. In settings with resource constraints the use of any implants may be restricted.
- Throughout the process, adjuncts to treatment are used: adequate analgesia and adjuncts to analgesics that do not cause excessive sedation, such as Gabapentin as it also lessens spasticity. Clonidine can be used as an adjunct to pain therapy as it reduces the need for opiates and has a sedating effect in the restless and confused post TBI child. However, as already stated, Clonidine should only be used for short defined periods, as it may have deleterious effects on neural recovery.
- As a last resort, for patients with fixed deformities and contractures, orthopedic procedures such as tendon release, tendon transfers and/or derotation osteotomies are employed. In all these patients the main problem of muscle spasticity should be addressed concomitantly or prior to these interventions. Otherwise deformities and pain recur in our experience.

CONCLUSION

There are no evidence-based guidelines available for the management of spasticity after TBI in children or adults. A rational approach is therefore based on a clear understanding of the pathophysiology of spasticity and the localization of injuries that cause it. A multi-disciplinary team is valuable to form an individualized treatment protocol for each child. Vigilance is needed to look for and treat concomitant injuries, such as fractures, infections and pain, as these increase muscle tone. From the acute phase, the basic principle of neuro-rehabilitation should be employed to prevent and treat spasticity in children after TBI. Mobilization as far as the cerebral injury allows is key and drugs should be used with caution in the recovering brain in children but may be very helpful. Botulinum toxin plays a key role in managing focal spasticity and surgical options such as selective peripheral neurotomy and intrathecal Baclofen pump therapy should be considered in the long-term management of refractory spasticity. No one recipe will fit each case and the challenge is to make an individual plan for each child after TBI, based on their unique environment, activity level and injury pattern.

Future directions for researchers should be to do a multicentre review of clinical outcomes in children after TBI that was treated with a simple algorithmic approach such as the one suggested. The scarcity of data in spasticity after TBI can only be rectified if more researchers focus on this. We cannot keep forming therapeutic assumptions based on stroke data. Most of the lesioning techniques and other surgical therapies discussed, teats the end-organ (muscle and peripheral nerves), newer developments in the field of neuromodulation, where spasticity is targeted (such as DBS) may hold promise in future to treat this very difficult condition. Newer targets are constantly found in the brain and as the movement control network is further explored, new therapies are, hopefully, on the horizon.

AUTHOR CONTRIBUTIONS

JE: writing of the article and research for the article. UR: editing and flow check of the manuscript. AF: supervisor, editing, and scientific writing help.

REFERENCES

1. Segui-Gomez M, MacKenzie EJ. Measuring the public health impact of injuries. *Epidemiol Rev*. (2003) 25:3–19. doi: 10.1093/epirev/mxg007
2. Parslow RC, Morris KP, Tasker RC, Forsyth RJ, Hawley CA. Epidemiology of traumatic brain injury in children receiving intensive care in the UK. *Arch Dis Child*. (2005) 90:1182–7. doi: 10.1136/adc.2005.072405
3. Langlois JA, Rutland-Brown W, Thomas KE. The incidence of traumatic brain injury among children in the united states: differences by race. *J Head Trauma Rehabil*. (2005) 20:229–38. doi: 10.1097/00001199-200505000-00006
4. Bose P, Hou J, Thompson FJ. Traumatic brain injury (TBI)-induced spasticity: neurobiology, treatment, and rehabilitation. In: Kobeissy FH, editor. *Brain Neurotrauma*. Boca Raton, FL: CRC Press (2015). p. 182–93. doi: 10.1201/b18126-17
5. Barnes MP, Johnson GR. *Upper Motor Neurone Syndrome and Spasticity: Clinical Management and Neurophysiology*. Cambridge: Cambridge University Press (2008). doi: 10.1017/CBO9780511544866

6. Watkins C, Leathley M, Gregson J, Moore A, Smith T, Sharma A. Prevalence of spasticity post stroke. *Clin Rehabil*. (2002) 16:515–22. doi: 10.1191/0269215502cr512oa
7. Pattuwage L, Olver J, Martin C, Lai F, Piccenna L, Gruen R, et al. Management of spasticity in moderate and severe traumatic brain injury: evaluation of clinical practice guidelines. *J Head Trauma Rehabil.* 32:E1–12. doi: 10.1097/HTR.0000000000000234
8. Sherrington C. Decerebrate rigidity, and reflex coordination of movements. *J Physiol*. (1898) 22:319–32. doi: 10.1113/jphysiol.1898.sp000697
9. Bhimani R, Anderson L. Clinical understanding of spasticity: implications for practice, rehabilitation research and practice. *Rehabil Res Pract*. (2014) 2014:279175. doi: 10.1155/2014/279175
10. Burridge J, Wood D, Hermens HJ, Voerman G, Johnson G, Wijck FV, et al. Theoretical and methodological considerations in the measurement of spasticity. *Disabil Rehabil*. (2005) 27:69–80. doi: 10.1080/09638280400014592
11. Lance JW. The control of muscle tone, reflexes, and movement: Robert Wartenbeg lecture. *Neurology*. (1980) 30:1303. doi: 10.1212/WNL.30.12.1303
12. Burke D, Knowles L, Andrews C, Ashby P. Spasticity, decerebrate rigidity and the clasp-knife phenomenon: an experimental study in the cat. *Brain*. (1972) 95:31–48. doi: 10.1093/brain/95.1.31
13. Mayer NH. Clinicophysiologic concepts of spasticity and motor dysfunction in adults with an upper motoneuron lesion. *Muscle Nerve Suppl*. (1997) 20:1–14.
14. Shilt JS, Seibert PS, Kadyan V. Optimal management for people with severe spasticity. *Degener Neurol Neuromuscul Dis.* (2012) 2:133–40. doi: 10.2147/DNND.S16630
15. Abbe R. Resection of the posterior roots of spinal nerves to relieve pain, pain reflex, athetosis, and spastic paralysis: Dana's operation. *Med Rec*. (1911) 79:377–81.
16. Bennett WH. A case in which acute spasmodic pain in the left lower extremity was completely relieved by sub-dural division of the posterior roots of certain spinal nerves, all other treatment having proved useless. Death from sudden collapse and cerebral hæmorrhage on the twelfth day after the operation, at the commencement of apparent convalescence. *Med Chir Trans*. (1889) 72:329–48. doi: 10.1177/095952878907200119
17. Smyth MD, Peacock WJ. The surgical treatment of spasticity. *Muscle Nerve*. (2000) 23:153–63. doi: 10.1007/s11832-013-0512-9
18. Myklebust BM, Gottlieb GL, Penn RD, Agarwal GC. Reciprocal excitation of antagonistic muscles as a differentiating feature in spasticity. *Ann Neurol*. (1982) 12:367–4. doi: 10.1002/ana.410120409
19. Sheean G. The pathophysiology of spasticity. *Eur J Neurol*. (2002) 9:3–9. doi: 10.1046/j.1468-1331.2002.0090s1003.x
20. Travis AM. Neurological deficiencies following supplementary motor area lesions in Macaca mulatta. *Brain*. (1955) 78:174–5. doi: 10.1093/brain/78.2.174
21. Bucy PC, Ladpli R, Ehrlich A. Destruction of the pyramidal tract in the monkey: the effects of bilateral section of the cerebral peduncles. *J Neurosurg*. (1966) 25:1–23. doi: 10.3171/jns.1966.25.1.0001
22. Brown P. Pathophysiology of spasticity. *J Neurol Neurosurg Psychiatry*. (1994) 57:773–7. doi: 10.1136/jnnp.57.7.773
23. Bucy PC, Keplinger JE, Siqueira EB. Destruction of the "pyramidal tract" in man. *J Neurosurg*. (1964) 21:385–98. doi: 10.3171/jns.1964.21.5.0385
24. Bucy PC. Is there a pyramidal tract?. *Brain*. (1957) 80:376–92. doi: 10.1093/brain/80.3.376
25. Hyndman OR. Physiology of the spinal cord: I. role of the anterior column in hyperreflexia. *Arch Neurol Psychiatry*. (1941) 46:695–703. doi: 10.1001/archneurpsyc.1941.02280220128009
26. Katz RT, Rymer WZ. Spastic hypertonia: mechanisms and measurement. *Arch Phys Med Rehabil*. (1989) 70:144–55.
27. Burke D, Spasticity as an adaptation to pyramidal tract injury. *Adv Neurol*. (1988) 47:401–23.
28. Li S, Francisco GE. New insights into the pathophysiology of post-stroke spasticity. *Front Human Neurosci.* (2015) 9:192. doi: 10.3389/fnhum.2015.00192
29. Urban PP, Wolf T, Uebele M, Jr, Marx J, Vogt T, Stoeter P, et al. Occurence and clinical predictors of spasticity after ischemic stroke. *Stroke*. (2010) 41:2016–20. doi: 10.1161/STROKEAHA.110.581991
30. Wissel J, Schelosky LD, Scott J, Christe W, Faiss JH, Mueller J. Early development of spasticity following stroke: a prospective, observational trial. *J Neurol*. (2010) 257:1067–72. doi: 10.1007/s00415-010-5463-1
31. Lundström E, Terént A, Borg J. Prevalence of disabling spasticity 1 year after first-ever stroke. *Eur J Neurol*. (2008) 15:533–39. doi: 10.1111/j.1468-1331.2008.02114.x
32. Paciaroni M, Silvestrelli G, Caso V, Corea F, Venti M, Milia P, et al. Neurovascular territory involved in different etiological subtypes of ischemic stroke in the Perugia stroke registry. *Eur J Neurol*. (2003) 10:361–5. doi: 10.1046/j.1468-1331.2003.00646.x
33. Bogousslavsky J, Van Melle G, Regli F. The lausanne stroke registry: analysis of 1,000 consecutive patients with first stroke. *Stroke*. (1988) 19:1083–92. doi: 10.1161/01.STR.19.9.1083
34. Fries W, Danek A, Scheidtmann K, Hamburger C. Motor recovery following capsular stroke: role of descending pathways from multiple motor areas. *Brain*. (1993) 116:369–82. doi: 10.1093/brain/116.2.369
35. Liddell E, Matthes K, Oldberg E, Ruch T. Reflex release of flexor muscles by spinal section. *Brain*. (1932) 55:239–46. doi: 10.1093/brain/55.2.239
36. Brunnstrom S. Motor testing procedures in hemiplegia: based on sequential recovery stages. *Phys Ther*. (1966) 46:357–75. doi: 10.1093/ptj/46.4.357
37. Twitchell TE. The restoration of motor function following hemiplegia in man. *Brain*. (1951) 74:443–80. doi: 10.1093/brain/74.4.443
38. Ward AB. A literature review of the pathophysiology and onset of post-stroke spasticity. *Eur J Neurol*. (2012) 19:21–7. doi: 10.1111/j.1468-1331.2011.03448.x
39. Bose P, Hou J, Nelson R, Nissim N, Parmer R, Keener J, et al. Effects of acute intrathecal baclofen in an animal model of TBI-induced spasticity, cognitive, and balance disabilities. *J Neurotrauma*. (2013) 30:1177–91. doi: 10.1089/neu.2012.2740
40. Zafonte R, Elovic EP, Lombard L. Acute care management of post-TBI spasticity. *J Head Trauma Rehabil*. (2004) 19:89–100. doi: 10.1097/00001199-200403000-00002
41. Bhimani RH, McAlpine CP, Henly SJ. Understanding spasticity from patients' perspectives over time. *J Adv Nursing*. (2012) 68:2504–14. doi: 10.1111/j.1365-2648.2012.05949.x
42. McNamee S, Walker W, Cifu DX. Minimizing the effect of TBI-related physical sequelae on vocational return. *J Rehabil Res Dev*. (2009) 46:893. doi: 10.1682/JRRD.2008.08.0106
43. Finnimore A, Roebuck M, Sajkov D, McEvoy R. The effects of the GABA agonist, baclofen, on sleep and breathing. *Eur Respir J*. (1995) 8:230–4. doi: 10.1183/09031936.95.08020230
44. Castillo D, Pitts T. Influence of baclofen on laryngeal and spinal motor drive during cough in the anesthetized cat. *Laryngoscope*. (2013) 123:3088–92. doi: 10.1002/lary.24143
45. Goodman LS. *Goodman and Gilman's the Pharmacological Basis of Therapeutics*. New York, NY: McGraw-Hill (1996).
46. Goldstein LB. Common drugs may influence motor recovery after stroke. *Neurology*. (1995) 45:865–71. doi: 10.1212/WNL.45.5.865
47. Meythaler JM, Clayton W, Davis LK, Guin-Renfroe S, Brunner RC. Orally delivered baclofen to control spastic hypertonia in acquired brain injury. *Journal Head Trauma Rehabil.* (2004) 19:101–8. doi: 10.1097/00001199-200403000-00003
48. François B, Vacher P, Roustan J, Salle JY, Vidal J, Moreau JJ, Vignon P. Intrathecal baclofen after traumatic brain injury: early treatment using a new technique to prevent spasticity. *J Trauma*. (2001) 50:158–61. doi: 10.1097/00005373-200101000-00035
49. Posteraro F, Calandriello B, Galli R, Logi F, Iardella L, Bordi L. Timing of intrathecal baclofen therapy in persons with acquired brain injury: influence on outcome. *Brain Injury*. (2013) 27:1671–5. doi: 10.3109/02699052.2013.828852
50. Becker R, Alberti O, Bauer B. Continuous intrathecal baclofen infusion in severe spasticity after traumatic or hypoxic brain injury. *J Neurol*. (1997) 244:160–6. doi: 10.1007/s004150050067
51. Berweck S, Lütjen S, Voss W, Diebold U, Mücke KH, Aisch A, et al. Use of intrathecal baclofen in children and adolescents: interdisciplinary consensus table 2013. *Neuropediatrics*. (2014) 45:294–308. doi: 10.1055/s-0034-1387818
52. Becker R, Sure U, Petermeyer M, Bertalanffy H. Continuous intrathecal baclofen infusion alleviates autonomic dysfunction in patients with severe

supraspinal spasticity. *J Neurol Neurosurg Psychiatry*. (1999) 66:114. doi: 10.1136/jnnp.66.1.114
53. Pérez-Arredondo A, Cázares-Ramírez E, Carrillo-Mora P, Martínez-Vargas M, Cárdenas-Rodríguez N, Coballase-Urrutia E, et al. Baclofen in the therapeutic of sequele of traumatic brain injury: spasticity. *Clin Neuropharmacol*. (2016) 39:311–19. doi: 10.1097/WNF.0000000000000179
54. Synnot A, Chau M, Pitt V, O'Connor D, Gruen RL, Wasiak J, et al. Interventions for managing skeletal muscle spasticity following traumatic brain injury. *Cochrane Database Syst Rev*. (2017) 11:CD008929. doi: 10.1002/14651858.CD008929.pub2
55. Gracies JM, Brashear A, Jech R, McAllister P, Banach M, Valkovic P, et al. Safety and efficacy of abobotulinumtoxinA for hemiparesis in adults with upper limb spasticity after stroke or traumatic brain injury: a double-blind randomised controlled trial. *Lancet Neurol*. (2015) 14:992–1001. doi: 10.1016/S1474-4422(15)00216-1
56. Mayer NH. Choosing upper limb muscles for focal intervention after traumatic brain injury. *Journal Head Trauma Rehabil*. (2004) 19:119–42. doi: 10.1097/00001199-200403000-00005
57. Fock J, Galea MP, Stillman BC, Rawicki B, Clark M. Functional outcome following botulinum toxin A injection to reduce spastic equinus in adults with traumatic brain injury. *Brain Injury*. (2004) 18:57–63. doi: 10.1080/0269905031000149498
58. Ylvisaker M, Adelson PD, Braga LW, Burnett SM, Glang A, Feeney T, et al. Rehabilitation and ongoing support after pediatric TBI: twenty years of progress. *Journal Head Trauma Rehabil*. (2005) 20:95–109. doi: 10.1097/00001199-200501000-00009
59. Walshe MRF. The decerebrate rigidity of sherington in man: its recognition and differentiation from other forms of tonic muscular contraction. *Arch Neurol Psychiatry*. (1923) 10:1–28. doi: 10.1001/archneurpsyc.1923.02190250004001
60. de Palma L, Rapali S, Paladini P, Ventura A. Elbow heterotopic ossification in head-trauma patients: diagnosis and treatment. *Orthopedics*. (2002) 25:665–8.
61. Malhotra S, Pandyan A, Day C, Jones P, Hermens H. Spasticity, an impairment that is poorly defined and poorly measured. *Clin Rehabil*. (2009) 23:651–8. doi: 10.1177/0269215508101747
62. Mertens P, Sindou M. Selective peripheral neurotomies for the treatment of spasticity. In: Mertens P, Georgoulis G, Sindou M, editors. *Neurosurgery for Spasticity*. Vienna: Springer (1991). p. 119–32. doi: 10.1007/978-3-7091-6708-3_18
63. Foote KD, Okun MS. Ventralis intermedius plus ventralis oralis anterior and posterior deep brain stimulation for posttraumatic Holmes tremor: two leads may be better than one. *Neurosurgery*. (2005) 56(Suppl. 2):E445. doi: 10.1227/01.NEU.0000157104.87448.78
64. Krauss JK, Jankovic J. Head injury and posttraumatic movement disorders. *Neurosurgery*. (2002) 50:927–40. doi: 10.1227/00006123-200205000-00003
65. Yun JS, Chung MJ, Kim HR, So JI, Park JE, Oh HM, et al. Accuracy of needle placement in cadavers: non-guided versus ultrasound-guided. *Ann Rehabil Med*. (2015) 39:163. doi: 10.5535/arm.2015.39.2.163
66. Sindou MP, Simon F, Mertens P, Decq P. Selective peripheral neurotomy (SPN) for spasticity in childhood. *Child's Nervous Syst*. (2007) 23:957–70. doi: 10.1007/s00381-007-0399-1
67. Enslin JMN, Langerak NG, Fieggen AG. The evolution of selective dorsal rhizotomy for the management of spasticity. *Neurotherapeutics*. (2019) 16:3–8. doi: 10.1007/s13311-018-00690-4
68. Keren O, Reznik J, Groswasser Z. Combined motor disturbances following severe traumatic brain injury: an integrative long-term treatment approach. *Brain Injury*. (2001) 15:633–8. doi: 10.1080/02699050010009568

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REVIEW
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Cerebral Blood Flow Measurement in Healthy Children and Children Suffering Severe Traumatic Brain Injury—What Do We Know?

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Traumatic brain injury is the leading cause of death in children. Children with severe TBI are in need of neurointensive care where the goal is to prevent secondary brain injury by avoiding secondary insults. Monitoring of cerebral blood flow (CBF) and autoregulation in the injured brain is crucial. However, there are limited studies performed in children to investigate this. Current studies report on age dependent increase in CBF with narrow age range. Low initial CBF following TBI has been correlated to poor outcome and may be more prevalent than hyperemia as previously suggested. Impaired cerebral pressure autoregulation is also detected and correlated with poor outcome but it remains to be elucidated if there is a causal relationship. Current studies are few and mainly based on small number of patients between the age of 0–18 years. Considering the changes of CBF and cerebral pressure autoregulation with increasing age, larger studies with more narrow age ranges and multimodality monitoring are required in order to generate data that can optimize the therapy and clinical management of children suffering TBI.

Keywords: pediatric brain injury, cerebral blood flow, cerebral autoregulation, traumatic brain injury, Xenon-CT, TCD, head injury children

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INTRODUCTION

Traumatic brain injury is a leading cause of death among children and affects children all over the world. The worldwide annual incidence of pediatric TBI ranges between 47 and 280 per 100,000 children depending on the country (1). The U.S. Centers for Disease Prevention and Control estimated that in 2014, 837,000 TBI-related emergency department (ED) visits, hospitalizations, and deaths occurred among children (2).

Although the majority of TBIs are mild, a large number of children with severe TBI require neurointensive care with neuromonitoring. Despite the size of this patient population there is still a lack of evidence-based guidelines for how to manage TBI in children (3).

Acute TBI is characterized by primary and secondary injuries. Primary brain injury is the direct injury to the brain parenchyma at the time of the initial impact. The primary injury in children is even more heterogeneous and complex than in adults considering the impact of inflicted TBI. A common consequence of different primary injuries is triggering of secondary processes leading to secondary injury such as breakdown of the blood–brain barrier, neurons damage, disturbed cerebral pressure autoregulation, ischemia, and brain herniation (4, 5).

The goal of TBI management in the acute setting is to prevent secondary insults and brain injuries by achieving adequate CBF (6). This is mainly achieved by monitoring of ICP and CPP to optimize CBF, which is crucial in order to deliver substrates to the injured brain. The normal brain represents 2% of body weight but receives 15% of cardiac output. It has a high energy demand utilizing 20% of available oxygen and 60% of glucose by the whole body in the resting state. The brain glucose consumption peaks at age of 5 and is 2 times more the daily glucose use of the adult brain (7). Boys have higher brain glucose consumption compared to girls that becomes equal in adulthood (8).

The CBF to match the high demand of brain is on average 50 ml/100 g/min, higher in gray matter compared to white, 80 and 20 ml/100 g/min, respectively.

A tight regulation of blood flow and oxygen delivery is critical for neuronal survival which becomes even more important in the injured brain.

This regulation is controlled by several homeostatic mechanisms. The most important ones are cerebral metabolism, cerebral pressure autoregulation, $PaCO_2$ and PaO_2.

CBF is tightly coupled to cerebral metabolism and during normal conditions CBF is well-correlated with cerebral metabolic rate of oxygen ($CMRO_2$). The $CMRO_2$ is 3.5 ml/100 g/min and is four times higher in gray matter compared to white.

Cerebral pressure autoregulation is the mechanism that regulates this constant cerebral blood supply in spite of fluctuations in blood pressure by adjusting the diameter of cerebral vessels. An increase in MAP/CPP will lead to vasoconstriction and a decrease will lead to vasodilatation. This protects the brain from brain ischemia and edema/hemorrhage (9).

In the seminal work by Lassen it was shown that the CBF is maintained constant at changes in mean arterial pressure (MAP) between 60 and 160 mm Hg in healthy adults and the classic triphasic curve of CBF was presented (10). However, this range has shown to be narrower in infants. The upper limit of MAP was shown to be as low as 45 mmHg at birth and increased to 100 during first weeks after birth (11). In another paper, the lower limit was reported to be within the same range as in adults (46–70 mmHg) and no correlation with age could be seen (12).

$PaCO_2$ is the most potent vasodilatory agent that increases the CBF by 2–4%/mmHg. The CBF response to PaO_2 changes occur in seconds and is used clinically by hyperventilation in order to decrease ICP.

The influence of PaO_2 on cerebral circulation is much less compared to $PaCO_2$ and with less clinical significance. The changes are minimal in PaO_2 above 50 mmHg and when PaO_2 is below 50 mmHg the CBF increases but the changes are slow and take more than 6 min.

Although the relationships between ICP, MAP, CPP, and CBF can be straightforward in the healthy brain it is more complex in the injured brain in particular in the developing brain. Many physiological parameters such as CO_2 reactivity, O_2 reactivity, and cerebral pressure autoregulation can be disturbed and compromise the need of adequate substrate delivery. Disturbed cerebral pressure autoregulation and hypoperfusion have been observed in children with TBI and has been correlated to worse outcome (13–16). Younger children <4 years are at a higher risk of impaired cerebral pressure autoregulation and have worse outcome than older children.

Although a lot of work has been done in order to monitor and understand the cerebral hemodynamic changes following TBI there is little known about children with TBI. In order to optimize therapeutic and management protocols of children with severe TBI an extensive understanding of the normal physiology and cerebral hemodynamic changes following TBI is necessary. In this review we have made an effort to summarize current studies on monitoring of CBF in healthy and severely brain injured children.

CBF in Healthy Pediatric Population

One of the earliest studies on healthy children was performed by Settergren et al. who measured CBF in 70 healthy, anesthetized children between 11 days and 15 years of age. The children had slightly higher CBF compared to adults and 77% had mean CBF below 65 ml/100 g/min (17).

The gradual changes of CBF by age have been reported in smaller studies. Using PET in 24 healthy children it was shown that regional CBF and $CMRO_2$ were low in neonates but increased in children >1 year and peaked at 3–8 years to reach adult values at >8 years (18). The values in this study are given as ratio compared to adults thus comparison of absolute CBF values with other studies is difficult. Although, this study reported on normal values, the included children had underlying diagnoses such as Moyamoya disease, skull deformity and craniosynostosis, but they had normal development and no signs of intracranial hypertension. Several of these diagnoses may be associated with disturbed CBF such as Moyamoya disease. In a previous study using133Xe intravenous injection method it was shown that children with non-symptomatic Moyamoya disease have lower CBF than normal children so it has been questioned if reported CBF levels should be interpreted as normal (19). There is also a difference in the CBF alteration between white and gray matter where CBF decreases in gray matter with age but not in white matter (20). The peak of CBF in gray matter was detected at the age of 3–4 years (20).

The gradual changes in CBF by age have also been demonstrated indirectly by transcranial doppler. Verlhac who used transcranial Doppler (TCD) found that the CBF velocity in MCA increased with age starting in newborns at around 24 cm/s and peaking in 6–10 years of age to 97 cm/s. This was followed by a decrease in older children (age 10–16.9 years) to 81 cm/s (21). In healthy adults it has been shown that CBF velocity is decreased to 50 cm/s (21, 22). It should be noted that TCD measures changes in flow velocity in one large vessel usually MCA and is not a direct measurement of global or regional CBF.

The dynamic changes in CBF through childhood was also shown by Chiron et al. (23) using SPECT and 133Xe in 42 children. The mean CBF at birth was found to be 50 ml/100 g/min and peaked by the age of 5–71 ml/100 g/min.

Using perfusion CT in 77 children aged 7 months to 18 years, Wintermark et al. found values of 40 ml/100 g/min at 6 months with a peak of 130 ml/100 g/min at 2–4 years of age that stabilized

TABLE 1 | Summary of papers reporting on CBF measurements in healthy children.

References	Method	*n*	Age	CBF (ml/100 g/min)	Age of peak CBF	Subjects
Settergren et al. (17)	10% NO	70	11 days−15 y	Mean 65	–	Before elective surgery
Ogawa et al. (19)	Xenon injection	16	5–15 year	92.1 ± 21.5	–	
Chiron et al. (23)	Xe-133 and SPECT	42	2 day−19 year	50–71	5 year	Neurological problems
Takahashi et al. (18)	PET	24	10 day−16 year	–	7 year	Moyamoya, craniosynostosis
Vivalala (22)	TCD	9	12–17	75.2 ± 15.2		Healthy volunteers
Wintermark (24)	CT-perfusion	53	7 day−18 year	40-130-50	2–4 year	TBI, headache, seizure, meningitis, those with normal CT were included
Satterthwaite et al. (29)	MRI-ASL	922	8–22 year	–	<10 year	Healthy
Carsin-Vu et al. (26)	MRI-ASL	84	6 month−15 year	50–69	2–3 year	Headache, seizures
Paniukov et al. (27)	MRI-ASL	96	2–7 year	–	7 year	Healthy

at 50 ml/100 g/min at 7–8 years of age (24). The study included healthy children based on normal CT-scans but the children were admitted for headache and mild TBI which could affect the CBF measurements in children as shown in other studies (25).

Recent advancement in imaging techniques provides the opportunity to use non-invasive and radiation free CBF measurements. Carsin-Vu et al. used MRI—arterial spin label (ASL) technique in 84 children with headache, seizure and autism. The children were aged 6 months up to 15 years and the mean CBF measured was 64 ml/100 g/min in gray matter and 29.3 ml/100 g/min in white matter (26).

Most of the studies reporting on normal CBF values have been performed on children with an underlying diagnosis and in a small number of subjects in different age ranges. Paniukov et al. have recently performed a study on healthy children using MRI-ASL in 96 volunteers and they also found an age-dependent increase in CBF. The CBF increased by 3.2 ml/100 g/min per year from 2 to 7 years with no difference in males and females (27). Most of the studies mentioned above could not show any differences in CBF between boys and girls. Both boys and girls show linear correlation between CBF and age with a shifting point around puberty (28). However, in the largest CBF study, including 922 youths aged 8–22, Satterthwaite et al. reported that CBF continue to decline after puberty in males but increased thereafter in females (29). This indicates that the age when TBI occurs may have different effects in females compared to males.

Several of the studies above also reported on regional variation in CBF that corresponds well with brain maturation and development that may have different impact in the functional outcome depending on the age of children.

One can conclude that there is a great variation in CBF in children related to age and that the values are very different compared to adults. Thus, when evaluating CBF measurements in children it is important to take into account the large difference observed between children and adults and also the large differences between age groups within the pediatric population. Accordingly, narrow age ranges should be used when normal CBF reference values are presented. However, one should keep in mind some limitations of these studies such as that different methods for CBF measurements were used and not all of them report on absolute CBF values which limits a comparison between the studies (**Table 1**). There is also a large variation in age span studied and most of the studies have few cases. Furthermore, most of the included subjects considered as healthy were actually either admitted for different symptoms or had an underlying diagnosis. Thus, further studies are needed in particular in younger healthy children to obtain absolute CBF values.

CBF in Children With Severe TBI

One of the first studies investigating CBF in children with TBI was the study by Kasoff et al. (30) using Xe133 injections in the internal carotid artery. They studied 10 children aged 9 months to 12 years with severe TBI and found hyperemic episodes and poor control of vasomotor tone. Hyperemic episodes were also reported by Bruce et al. who observed cerebral swelling as a common first sign in severe head injured children (31). The study included 85 children and 6 of these underwent CBF measurement showing hyperemia. The authors concluded that the observed cerebral swelling could be explained by acute "vasomotor paralysis" and hyperemia and not by regular brain edema. Therefore, it was suggested that the treatment of high ICP should be focused on the vascular compartment which could be reduced by hyperventilation (4). Also Muizelaar et al. reported hyperemic events in 88% of the TBI children they studied. They concluded that luxury perfusion is common in the pediatric population, although a small group of 6 children was studied (32). These findings were challenged by Skippen et al. who showed that CBF was reduced following TBI in children and that hyperventilation (<4.7 kPa) increased the proportion of children with ischemia (defined as CBF <18 ml/100 g/min) from 28.9 to 73.1%, warranting caution in use of hyperventilation (15).

Several following studies in children with TBI could not find that hyperemia was common, e.g., the study by Sharples et al. (33) who could only detect this in 7% of the children. It should be noted that they used a higher CBF level as normal value, 65 ml/100 g/min.

Using Xenon-CT, Adelson et al. investigated CBF in children <8 years of age with severe TBI (14). The CBF at admission was 25 ml/100 g/min in mean and after 24 h it peaked to 59 ml/100 g/min. The mean CBF during days 2–6 was 55 ml/100

g/min. Children with poor outcome had significantly lower CBF on admission (9.9 ml/100 g/min) compared to those with good outcome (43.9 ml/100 g/min) and several children with admission CBF of <20 ml/100 g/min died.

A subsequent study by Adelson et al. with a larger cohort of 95 children were consistent with these findings (34). The mean admission CBF was 32 ml/100 g/min and there was a significant difference between children who had favorable outcome (46 ml/100 g/min) compared to those that had an unfavorable outcome (18 ml/100 g/min). This important work by Adelson et al. shifted the emphasis away from hyperemia in children with TBI toward the importance of early hypoperfusion and its relation to outcome. The association of initial low CBF following TBI and poor outcome had also been reported earlier by Sharples et al. (33).

In order to maintain adequate CBF cerebral pressure autoregulation is vital and it has been shown that this is disturbed in children suffering TBI (13, 34–37).

Several studies have used different methods and endpoints to assess the cerebral pressure autoregulation in pediatric TBI. Sharples et al. calculated cerebrovascular resistance through CBF measurements (calculated from CVR = CPP/CBF) and preserved cerebral pressure autoregulation was defined as a significant correlation between CPP and CVR (33). Children with worse outcome had impaired cerebral autoregulation defined as above.

Using TCD in 36 severe TBI children, Chaiwat et al. assessed cerebral pressure autoregulation in 36 children with severe TBI by continuous measurements of CPP and flow velocity in MCA during infusion of phenylephrine (37). They report impaired cerebral autoregulation as an independent risk factor for poor 6-month outcome.

Freeman et al. also used TCD and infusion of phenylephrine to assess cerebral pressure autoregulation and reported that children <4 years had a higher incidence of impaired cerebral autoregulation and worse 12-month outcome (38). Adelson et al. used CO_2 vascular reactivity as a measure of cerebral autoregulation and showed that impaired cerebral autoregulation within 48 h of injury was associated with an unfavorable outcome (34).

In l996 continuous measurement of pressure reactivity index was developed and have been applied to assess cerebral autoregulation (39). Brady et al. evaluate PRx in 21 children with severe TBI and found that non-survivors had impaired cerebral autoregulation (40). This was later also seen by Young et al. in 12 children where PRx showed significant outcome separation between survivors and non-survivors (41). Lewis et al. analyzed the association of PRx and 6 months outcome in 36 children with severe TBI and found worse PRx in patients with unfavorable outcome (42). However, further studies are needed to elucidate if correlation of impaired cerebral autoregulation and outcome in children is causal or just a marker of severity of TBI.

Although the studies above provide valuable information on the injured brain of the pediatric population with TBI there is still a large gap of knowledge (**Table 2**). As presented above the number of studies assessing CBF in children with severe TBI are limited. The studies cover different age spans ranging 0–18 years and include very few cases they also assess the CBF at different time points post-injury, all of which could hamper a

TABLE 2 | Summary of papers reporting on CBF measurements and autoregulation in children with severe TBI.

References	Method	*n*	Age	CBF (ml/100 g/min)/autoregulation	CBF measurement time after TBI	TBI Severity
Kasoff et al. (30)	Xe injection	10	9 month−12 year		Hours-2 months	GCS <8
Muizelaar et al. (32)	Xe133 inhalation/inj	32	3–18 year	Good outcome 48.8 ± 24.8	Within 72 h	GCS <7
				Poor outcome 34.7 ± 9.9		
Sharples et al. (33)	10% NO	17	2–16 year	Low CBF in patients with worse outcome	Within 24 h	GCS <8
Skippen et al. (15)	Xe-CT	23	3 month−16 year	Mean 49.6 ± 14.6		GCS <8
Adelson et al. (14)	Xe-CT	30	0–8	Mean 55	Admission−day 9	GCS <8
				Poor outcome 9.9		
				Good outcome 43.9		
Adelson et al. (34)	Xe-CT	95		Mean 32	Admission−day 9	GCS <8
				Good outcome 46		
				Poor outcome 18		
Sharples et al. (13)	10% NO	21	2–16 year	Day 1 40–60 ml/100 g/ml	6–57 h	GCS <8
Muizelaar et al. (35)	Xe133-phenylephrine	26	8–18 year	No correlation between autoregulation and outcome	Before and after 36 h	GCS <7
Vivalala (36)	TCD	28	5–15 year	Impaired autoregulation-worse 6 m outcome	Within 72 h	GCS <9
Freeman et al. (38)	TCD-phenylephrine	37	8 month−16	Impaired autoregulation in <4 year	Within 72 h	GCS <13
Chaiwat et al. (37)	TCD	36	8 month−16 year	Impaired autoregulation-worse outcome	Within 72 h	GCS <9
Brady et al. (40)	PRx	21	3 month−15 year	PRx associated with survival		GCS <8
Young et al. (41)	PRx	12	3 month−13 year	PRx correlates with 6 months outcome		GCS <8
Lewis et al. (42)	PRx	36	6 month−16 year	PRx correlates with outcome		GCS <8

comparison between the studies. In addition, they use different methods to measure CBF and most of them used TCD. Although TCD have advantages such as being non-invasive it is not a direct measurements of CBF and the correlation of flow velocities with actual CBF in the injured brain is weak (43). This calls for further well-designed larger studies in children with severe TBI in order to understand the alterations of CBF post-injury and its correlation to cerebral autoregulation and metabolism and its impact on outcome.

CONCLUSION

It is apparent that the pathophysiology of brain injury changes from birth to 18 years of age. Children's physiology and anatomy changes tremendously during growth and during the development of the brain regarding e.g., skull dimensions, suture elasticity, vascular maturation, tortuosity, gray, and white matter ratio (44). This makes it very likely that not only the biomechanics of injury to the brain is different but also the response of the brain to the injury. The differences in CBF found in healthy children of different ages, as presented in this review, suggest that the tolerability/vulnerability of the brain is very different depending on the age and that the differences may be very large even with very small differences in age.

Accordingly, the outcome following TBI has shown to be age depended with children under the age of 4–5 years having worse outcome. More studies of specific cerebral hemodynamic changes following TBI in different age groups of children are needed in order to improve the management of children with severe TBI. The importance of this is underlined by estimates from the U.S. Centers for Disease Prevention and Control that show rates of TBI-related emergency department visits for children 0–4 years increased by more than 50%.

AUTHOR CONTRIBUTIONS

ER conceptualized the idea and wrote the paper. PN provided critical feedback. PE provided with critical feedback and helped to shape the manuscript.

REFERENCES

1. Dewan MC, Mummareddy N, Wellons JC III, Bonfield CM. Epidemiology of global pediatric traumatic brain injury: qualitative review. *World Neurosurg.* (2016) 91, 497–509.e1. doi: 10.1016/j.wneu.2016.03.045
2. Centers for Disease Control and Prevention. *Surveillance Report of Traumatic Brain Injury-Related Emergency Department Visits, Hospitalizations, and Deaths*. Department of Health and Human Services (2019).
3. Kochanek PM, Tasker RC, Bell MJ, Adelson PD, Carney N, Vavilala MS, et al. Management of pediatric severe traumatic brain injury: 2019 consensus and guidelines-based algorithm for first and second tier therapies. *Pediatr Crit Care Med*. (2019) 20:269–79. doi: 10.1097/PCC.0000000000001737
4. Bruce DA, Alavi A, Bilaniuk L, Dolinskas C, Obrist W, Uzzell B. Diffuse cerebral swelling following head injuries in children: the syndrome of "malignant brain edema". *J Neurosurg.* (1981) 54:170–8. doi: 10.3171/jns.1981.54.2.0170
5. Siesjo BK, Siesjo P. Mechanisms of secondary brain injury. *Eur J Anaesthesiol.* (1996) 13:247–68. doi: 10.1097/00003643-199605000-00004
6. Figaji AA. Practical aspects of bedside cerebral hemodynamics monitoring in pediatric TBI. *Childs Nerv Syst.* (2010) 26:431–9. doi: 10.1007/s00381-009-1036-y
7. Kuzawa CW, Chugani HT, Grossman LI, Lipovich L, Muzik O, Hof PR, et al. Metabolic costs and evolutionary implications of human brain development. *Proc Natl Acad Sci USA*. (2014) 111:13010–5. doi: 10.1073/pnas.1323099111
8. Vandekar SN, Shou H, Satterthwaite TD, Shinohara RT, Merikangas AK, Roalf DR, et al. Sex differences in estimated brain metabolism in relation to body growth through adolescence. *J Cereb Blood Flow Metab.* (2019) 39:524–35. doi: 10.1177/0271678X17737692
9. Udomphorn Y, Armstead WM, Vavilala MS. Cerebral blood flow and autoregulation after pediatric traumatic brain injury. *Pediatr Neurol.* (2008) 38:225–34. doi: 10.1016/j.pediatrneurol.2007.09.012
10. Lassen NA. Cerebral blood flow and oxygen consumption in man. *Physiol Rev.* (1959) 39:183–238. doi: 10.1152/physrev.1959.39.2.183
11. Ramaekers VT, Casaer P, Daniels H, Marchal G. Upper limits of brain blood flow autoregulation in stable infants of various conceptional age. *Early Hum Dev*. (1990) 24:249–58. doi: 10.1016/0378-3782(90)90032-E
12. Vavilala MS, Lee LA, Lam AM. The lower limit of cerebral autoregulation in children during sevoflurane anesthesia. *J Neurosurg Anesthesiol.* (2003) 15:307–12. doi: 10.1097/00008506-200310000-00003
13. Sharples PM, Matthews DS, Eyre JA. Cerebral blood flow and metabolism in children with severe head injuries. Part 2: cerebrovascular resistance and its determinants. *J Neurol Neurosurg Psychiatry.* (1995) 58:153–9. doi: 10.1136/jnnp.58.2.153
14. Adelson PD, Clyde B, Kochanek PM, Wisniewski SR, Marion DW, Yonas H. Cerebrovascular response in infants and young children following severe traumatic brain injury: a preliminary report. *Pediatr Neurosurg.* (1997) 26:200–7. doi: 10.1159/000121192
15. Skippen P, Seear M, Poskitt K, Kestle J, Cochrane D, Annich G, et al. Effect of hyperventilation on regional cerebral blood flow in head-injured children. *Crit Care Med.* (1997) 25:1402–9. doi: 10.1097/00003246-199708000-00031
16. Wintermark M, Chiolero R, Van Melle G, Revelly JP, Porchet F, Regli L, et al. Relationship between brain perfusion computed tomography variables and cerebral perfusion pressure in severe head trauma patients. *Crit Care Med.* (2004) 32:1579–87. doi: 10.1097/01.CCM.0000130171.08842.72
17. Settergren G, Lindblad BS, Persson B. Cerebral blood flow and exchange of oxygen, glucose ketone bodies, lactate, pyruvate and amino acids in anesthetized children. *Acta Paediatr Scand.* (1980) 69:457–65. doi: 10.1111/j.1651-2227.1980.tb07114.x
18. Takahashi T, Shirane R, Sato S, Yoshimoto T. Developmental changes of cerebral blood flow and oxygen metabolism in children. *AJNR Am J Neuroradiol.* (1999) 20:917–22.
19. Ogawa A, Yoshimoto T, Suzuki J, Sakurai Y. Cerebral blood flow in moyamoya disease. Part 1: correlation with age and regional distribution. *Acta Neurochir.* (1990) 105:30–4. doi: 10.1007/BF01664854
20. Ogawa A, Sakurai Y, Kayama T, Yoshimoto T. Regional cerebral blood flow with age: changes in rCBF in childhood. *Neurol Res.* (1989) 11:173–6. doi: 10.1080/01616412.1989.11739886
21. Verlhac S. Transcranial doppler in children. *Pediatr Radiol.* (2011) 41(Suppl. 1):S153–65. doi: 10.1007/s00247-011-2038-y
22. Vavilala MS, Newell DW, Junger E, Douville CM, Aaslid R, Rivara FP, et al. Dynamic cerebral autoregulation in healthy adolescents. *Acta Anaesthesiol Scand.* (2002) 46:393–7. doi: 10.1034/j.1399-6576.2002.460411.x
23. Chiron C, Raynaud C, Maziere B, Zilbovicius M, Laflamme L, Masure MC, et al. Changes in regional cerebral blood flow during brain maturation in children and adolescents. *J Nucl Med.* (1992) 33:696–703.
24. Wintermark M, Lepori D, Cotting J, Roulet E, Van Melle G, Meuli R, et al. Brain perfusion in children: evolution with age assessed by quantitative perfusion computed tomography. *Pediatrics.* (2004) 113:1642–52. doi: 10.1542/peds.113.6.1642
25. Barlow KM, Marcil LD, Dewey D, Carlson HL, Macmaster FP, Brooks BL, et al. Cerebral perfusion changes in post-concussion syndrome: a

prospective controlled cohort study. *J Neurotrauma.* (2017) 34:996–1004. doi: 10.1089/neu.2016.4634
26. Carsin-Vu A, Corouge I, Commowick O, Bouzille G, Barillot C, Ferre JC, et al. Measurement of pediatric regional cerebral blood flow from 6 months to 15 years of age in a clinical population. *Eur J Radiol.* (2018) 101:38–44. doi: 10.1016/j.ejrad.2018.02.003
27. Paniukov D, Lebel RM, Giesbrecht G, Lebel C. Cerebral blood flow increases across early childhood. *Neuroimage.* (2019) 204:116224. doi: 10.1101/587139
28. Kobayashi A, Ito M, Shiraishi H, Kishi K, Sejima H, Haneda N, et al. [A quantitative study of regional cerebral blood flow in childhood using 123I-IMP-SPECT: with emphasis on age-related changes]. *No To Hattatsu.* (1996) 28:501–7.
29. Satterthwaite TD, Shinohara RT, Wolf DH, Hopson RD, Elliott MA, Vandekar SN, et al. Impact of puberty on the evolution of cerebral perfusion during adolescence. *Proc Natl Acad Sci USA.* (2014) 111:8643–8. doi: 10.1073/pnas.1400178111
30. Kasoff SS, Zingesser LH, Shulman K. Compartmental abnormalities of regional cerebral blood flow in children with head trauma. *J Neurosurg.* (1972) 36:463–70. doi: 10.3171/jns.1972.36.4.0463
31. Bruce DA, Raphaely RC, Goldberg AI, Zimmerman RA, Bilaniuk LT, Schut L, et al. Pathophysiology, treatment and outcome following severe head injury in children. *Childs Brain.* (1979) 5:174–91. doi: 10.1159/000119817
32. Muizelaar JP, Marmarou A, Desalles AA, Ward JD, Zimmerman RS, Li Z, et al. Cerebral blood flow and metabolism in severely head-injured children. Part 1: relationship with GCS score, outcome, ICP, and PVI. *J Neurosurg.* (1989) 71:63–71. doi: 10.3171/jns.1989.71.1.0063
33. Sharples PM, Stuart AG, Matthews DS, Aynsley-Green A, Eyre JA. Cerebral blood flow and metabolism in children with severe head injury. Part 1: relation to age, glasgow coma score, outcome, intracranial pressure, and time after injury. *J Neurol Neurosurg Psychiatry.* (1995) 58:145–52. doi: 10.1136/jnnp.58.2.145
34. Adelson PD, Srinivas R, Chang Y, Bell M, Kochanek PM. Cerebrovascular response in children following severe traumatic brain injury. *Childs Nerv Syst.* (2011) 27:1465–76. doi: 10.1007/s00381-011-1476-z
35. Muizelaar JP, Ward JD, Marmarou A, Newlon PG, Wachi A. Cerebral blood flow and metabolism in severely head-injured children. Part 2: autoregulation. *J Neurosurg.* (1989) 71:72–6. doi: 10.3171/jns.1989.71.1.0072
36. Vavilala MS, Muangman S, Tontisirin N, Fisk D, Roscigno C, Mitchell P, et al. Impaired cerebral autoregulation and 6-month outcome in children with severe traumatic brain injury: preliminary findings. *Dev Neurosci.* (2006) 28:348–53. doi: 10.1159/000094161
37. Chaiwat O, Sharma D, Udomphorn Y, Armstead WM, Vavilala MS. Cerebral hemodynamic predictors of poor 6-month Glasgow Outcome Score in severe pediatric traumatic brain injury. *J Neurotrauma.* (2009) 26:657–63. doi: 10.1089/neu.2008.0770
38. Freeman SS, Udomphorn Y, Armstead WM, Fisk DM, Vavilala MS. Young age as a risk factor for impaired cerebral autoregulation after moderate to severe pediatric traumatic brain injury. *Anesthesiology.* (2008) 108:588–95. doi: 10.1097/ALN.0b013e31816725d7
39. Czosnyka M, Smielewski P, Kirkpatrick P, Laing RJ, Menon D, Pickard JD. Continuous assessment of the cerebral vasomotor reactivity in head injury. *Neurosurgery.* (1997) 41, 11–17; discussion: 17–19. doi: 10.1097/00006123-199707000-00005
40. Brady KM, Shaffner DH, Lee JK, Easley RB, Smielewski P, Czosnyka M, et al. Continuous monitoring of cerebrovascular pressure reactivity after traumatic brain injury in children. *Pediatrics.* (2009) 124:e1205–1212. doi: 10.1542/peds.2009-0550
41. Young AM, Donnelly J, Czosnyka M, Jalloh I, Liu X, Aries MJ, et al. Continuous multimodality monitoring in children after traumatic brain injury-preliminary experience. *PLoS ONE.* (2016) 11:e0148817. doi: 10.1371/journal.pone.0148817
42. Lewis PM, Czosnyka M, Carter BG, Rosenfeld JV, Paul E, Singhal N, et al. Cerebrovascular pressure reactivity in children with traumatic brain injury. *Pediatr Crit Care Med.* (2015) 16:739–49. doi: 10.1097/PCC.0000000000000471
43. Reinstrup P, Ryding E, Asgeirsson B, Hesselgard K, Unden J, Romner B. Cerebral blood flow and transcranial doppler sonography measurements of CO_2-reactivity in acute traumatic brain injured patients. *Neurocrit Care.* (2014) 20:54–9. doi: 10.1007/s12028-012-9727-8
44. Figaji AA. Anatomical and physiological differences between children and adults relevant to traumatic brain injury and the implications for clinical assessment and care. *Front Neurol.* (2017) 8:685. doi: 10.3389/fneur.2017.00685

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Injury Causes and Severity in Pediatric Traumatic Brain Injury Patients Admitted to the Ward or Intensive Care Unit: A Collaborative European Neurotrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) Study

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Background: Traumatic brain injury (TBI) is the leading cause of death and disability in children. It includes a range of different pathologies that differ considerably from adult TBI. Analyzing and understanding injury patterns of pediatric TBI is essential to establishing new preventive efforts as well as to improve clinical management.

Methods: The multi-center, prospectively collected CENTER-TBI core and registry databases were screened and patients were included when younger than 18 years at enrollment and admitted to the regular ward (admission stratum) or intensive care unit (ICU stratum) following TBI. Patient demographics, injury causes, clinical findings, brain CT imaging details, and outcome (GOSE at 6 months follow-up) were retrieved and analyzed. Injury characteristics were compared between patients admitted to the regular ward and ICU and multivariate analysis of factors predicting an unfavorable outcome (GOSE 1-4) was performed. Results from the core study were compared to the registry dataset which includes larger patient numbers but no follow-up data.

Results: Two hundred and twenty seven patients in the core dataset and 687 patients in the registry dataset were included in this study. In the core dataset, road-traffic incidents were the most common cause of injury overall and in the ICU stratum, while incidental falls were most common in the admission stratum. Brain injury was considered serious to severe in the majority of patients and concurrent injuries in other body parts were very common. Intracranial abnormalities were detected in 60% of initial brain CTs. Intra- and extracranial surgical interventions were performed in one-fifth of patients. The overall mortality rate was 3% and the rate of unfavorable outcome 10%, with those numbers being considerably higher among ICU patients. GCS and the occurrence of secondary insults could be identified as independent predictors for an unfavorable outcome. Injury characteristics from the core study could be confirmed in the registry dataset.

Conclusion: Our study displays the most common injury causes and characteristics of pediatric TBI patients that are treated in the regular ward or ICU in Europe. Road-traffic incidents were especially common in ICU patients, indicating that preventive efforts could be effective in decreasing the incidence of severe TBI in children.

Keywords: pediatric TBI, children, traumatic brain injury, injury characteristics, CT imaging, outcome

INTRODUCTION

Traumatic brain injury (TBI) is considered to be the leading cause of death and disability in children (1, 2). Neurological and psychological deficits resulting from TBI can be a high burden for patients and their relatives, deeply affecting the child's physical, cognitive and behavioral development. Pediatric TBI is a global problem with high incidence numbers reported from both, developed and developing countries including the United States, Europe, Iran, and India (3). In the United States alone, it accounts for more than 1 billion US-Dollars in hospital charges every year (1). While pediatric TBI encompasses a wide range of traumatic brain pathologies, it differs from adult TBI in terms of pathophysiology, injury causes, and management. It is therefore important to recognize pediatric TBI as an own entity and study injury characteristics separately from adult TBI. Analyzing and understanding injury patterns of pediatric TBI is essential to finding and establishing new preventive efforts and public campaigns as well as to improve clinical management. Prevention plays a critical role in pediatric TBI, as the vast majority of brain injuries in children occur unintentionally. The multi-center CENTER-TBI study provides the opportunity to analyze injury patterns, clinical characteristics, and radiological findings in pediatric patients from many countries across Europe. We hope that insights from our study can help to better understand pediatric TBI, reflect on current clinical care, and provide information to shape targeted preventive efforts to reduce the incidence of this very serious condition.

MATERIALS AND METHODS

Study Design and Patient Selection

For the present analysis, data from the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) core study and the CENTER-TBI registry were used. The CENTER-TBI core study is a multi-center prospective longitudinal and observational cohort study conducted in Europe and Israel. Eligibility criteria for this study were a clinical diagnosis of TBI, presentation within 24 h of injury, an indication for brain CT scanning, and informed consent (see below) (4). Participants were recruited from December 2014 through December 2017 from 59 centers and enrolled in three strata, differentiated by care path: Emergency Room (ER) stratum (patients discharged from the ER), admission (ADM) stratum (patients admitted to the hospital ward), or Intensive Care Unit (ICU) stratum (patients admitted primarily to the ICU). Besides the core study, CENTER-TBI however also includes a registry with observational data of an even larger cohort of patients with TBI and an indication for brain CT scanning which is meant to permit validation and generalization of results from the core dataset but includes fewer variables and in particular no follow-up data such as Glasgow Outcome Scale extended (GOSE) ratings. The CENTER-TBI study protocol was approved by the national and local ethics committees for each recruiting site and informed consent by a legal representative/next of kin was obtained, according to local legislations, for all recruited pediatric patients. The sites, ethical committees, approval numbers, and approval dates are listed on the website: https://www.center-tbi.eu/project/ethical-approval. For the present study, all patients within the CENTER-TBI core and registry dataset were screened and included if they met the following inclusion criteria: (a) admission to either the regular ward (admission stratum) or the ICU (ICU stratum) and (b) age at presentation $<$ 18 years (a flow-diagram of patient selection is provided in **Figure 1**).

Data Collection

Our study was primarily conducted with the CENTER-TBI core dataset because it provides more variables and especially outcome-related data such as GOSE ratings in comparison to the CENTER-TBI registry. Where possible, we compared key results from the core dataset with the registry dataset to confirm findings in an even larger patient cohort. The following variables regarding patient demographics and injury causes were collected from the core dataset: age, sex, injury type, place, area, cause, and intention. To assess injury severity and clinical status at admission, the AVPU (Alert, Verbal, Pain, Unresponsive) status, Glasgow Coma Scale (GCS), GCS—motor score, pupillary response, total Injury Severity Score (ISS), and Abbreviated Injury Scale (AIS) for brain injury, head/neck, cervical/thoracic/lumbar spine, thorax, abdomen/pelvis, upper and lower extremities, and skin were retrieved. Radiological injury characteristics (e.g., presence of midline shift, epidural hematoma, acute or subacute subdural hematoma, subarachnoidal hemorrhage, intraventricular hemorrhage, contusion, traumatic axonal injury, cisternal compression, subdural collections/mixed density hematoma, mass lesion, skull fracture) as well as the Marshall and Rotterdam CT scores were obtained from initial brain CT scans. In terms of clinical care, the performance of surgical interventions (intra- and extracranial) was recorded. Secondary injury insults during the pre-hospital and emergency room phase were evaluated and included hypoxia (PaO_2 $<$60 mmHg and/or SaO_2 $<$90% or suspected by clinical signs such as cyanosis), hypotension (systolic blood pressure $<$90 mmHg, patients reported to be in shock and/or absent brachial pulse not related to extremity injury), hypothermia (documented core temperature $<$35°C),

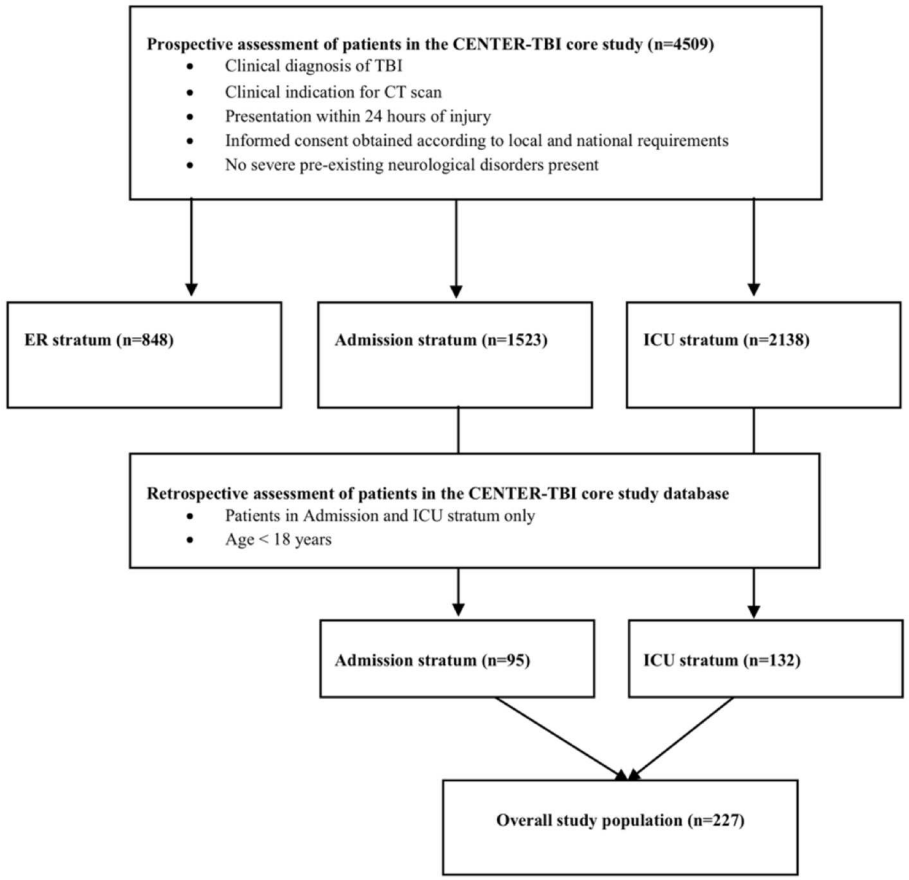

FIGURE 1 | Flow-Diagram of patient selection within the CENTER-TBI core study (separate from the CENTER-TBI registry).

seizures (partial, generalized, status epilepticus), or cardiac arrest. The imputed six month Glasgow Outcome Scale Extended (GOSE) variable provided in the Neurobot database which includes both, observed ratings and imputed values was used to assess outcome. Values were only imputed if at least one GOSE rating from another time point was available per patient. Unfavorable outcome was defined as a GOSE score from 1 to 4 and a favorable outcome as a GOSE score from 5 to 8. From the registry dataset, the variables age, sex, injury type, place, cause, total ISS, AIS Brain Injury, GCS motor/verbal/eyes, and presence of abnormality on brain CT were obtained. All variables were retrieved from the CENTER-TBI Neurobot database (CENTER core version 2.0 and registry version 2.0).

Statistical Analysis

Patient demographics, injury, and imaging characteristics as well as clinical data were summarized using descriptive statistics. Results are given as median + interquartile range (IQR) unless stated otherwise. For group comparisons, the Mann-Whitney *U* test was used for continuous variables while the chi-squared test was used for categorical variables. For outcome analysis, only patients with available GOSE ratings at six months were included. Multivariate logistic regression to an unfavorable outcome (GOSE 1-4) was performed with a model that included the predictors age, gender, road-traffic-incident (yes/no), GCS at admission, total ISS and secondary insults (yes/no). Hereby, missing data were addressed using complete case analysis. A p-value < 0.05 was considered statistically significant. No p value adjustment for multiple testing was performed due to the exploratory design of this study. All analyses were conducted with the statistical software R (5).

RESULTS

Patient Cohort

In total, 227 TBI patients younger than 18 years from the CENTER-TBI core dataset were included in this study. Pediatric patients had been enrolled in 33 of the 59 participating centers. 95 (42%) of them were admitted to the hospital ward (admission stratum) while 132 (58%) patients required critical care and were admitted to the ICU (ICU stratum). The median age of the entire cohort was 14 (IQR 8–16, range 0–17) years and 64% of patients ($n = 146$) were males. Patient demographics were similar in the admission and ICU subgroup (**Table 1**).

TABLE 1 | Injury causes- and details of pediatric TBI patients in the admission and ICU stratum of the CENTER-TBI core study.

Characteristic	Total	Admission stratum	ICU stratum	*p*-value
Number of patients	227	95 (42%)	132 (58%)	-
Age (IQR)	14 (8-16)	13 (9-16)	14 (8-16)	0.583
Sex				0.695
- Female	81 (36%)	32 (34%)	49 (37%)	
- Male	146 (64%)	63 (66%)	83 (63%)	
Injury area				0.072
- Urban	153 (67%)	72 (76%)	81 (61%)	
- Rural	65 (29%)	20 (21%)	45 (34%)	
- Unknown	9 (4%)	3 (3%)	6 (5%)	
Injury intention				0.805
- Intentional	6 (3%)	3 (3%)	3 (2%)	
- Unintentional	212 (93%)	94%)	123 (93%)	
- Undetermined	9 (4%)	3 (3%)	6 (5%)	
Injury cause				**0.010**
- Road traffic incident	110 (48%)	33 (35%)	77 (58%)	
- Incidental fall	78 (34%)	41 (43%)	37 (28%)	
- Other non-intentional injury	22 (10%)	11 (12%)	11 (8%)	
- Violence	5 (2%)	4 (4%)	1 (1%)	
- Other	11 (5%)	5 (5%)	0 (0%)	
- Unknown	1 (0%)	1 (1%)	6 (5%)	
Injury road incidents				0.069
- Motor vehicle occupant	21 (19%)	3 (9%)	18 (23%)	
- Pedestrian	37 (34%)	11 (33%)	26 (34%)	
- Cyclist	27 (25%)	11 (33%)	16 (21%)	
- Scooter	13 (12%)	7 (21%)	6 (8%)	
- Motor Bike	10 (9%)	1 (3%)	9 (12%)	
- Other	2 (2%)	1 (3%)	2 (3%)	
Injury place				**0.015**
- Street/Highway	118 (52%)	38 (40%)	80 (61%)	
- Home	40 (18%)	19 (20%)	21 (16%)	
- School	14 (6%)	7 (7%)	7 (5%)	
- Sport/Recreation	40 (18%)	21 (22%)	19 (14%)	
- Public location	11 (5%)	8 (8%)	3 (2%)	
- Other	2 (1%)	0 (0%)	2 (2%)	
- Unknown	2 (1%)	2 (2%)	0 (0%)	
Total ISS (IQR)	18 (10-32)	10 (9-17)	26 (17-41)	**<0.001**
AIS Brain Injury	4 (3-4)	3 (3-3)	4 (4-5)	**<0.001**
Face injury	68 (30%)	28 (29%)	40 (30%)	1
Head/ Neck injury	104 (46%)	44 (46%)	59 (45%)	1
Cervical spine injury	12 (5%)	5 (5%)	7 (5%)	1
Thoracic spine injury	7 (3%)	3 (3%)	4 (3%)	1
Lumbar spine injury	4 (2%)	1 (1%)	3 (2%)	0.859
Thorax injury	55 (24%)	5 (5%)	50 (38%)	**<0.001**
Abdominal injury	16 (7%)	2 (2%)	14 (11%)	**0.027**
Pelvic injury	15 (7%)	3 (3%)	12 (9%)	0.133
Upper extremity injury	40 (18%)	18 (19%)	22 (17%)	0.788
Lower extremity injury	37 (16%)	10 (11%)	27 (20%)	0.069
Skin injury	31 (14%)	8 (8%)	23 (17%)	0.080

***AIS**, Abbreviated Injury Scale; **ISS**, Injury Severity Score; **IQR**, Interquartile range. Significant differences (p-value of <0.05 in the Mann-Whitney U test for continuous variables and chi-squared test for categorical variables) between the admission and ICU stratum are printed bold.*

Injury Causes

The most common places of injury overall were streets and highways (52%), especially in the ICU stratum where more than 60% of injuries occurred in that setting (**Figure 2A**). Injuries that occurred at home and sport/recreational places came second and accounted together for more than 40% of injuries in the admission stratum. Correspondingly, road traffic incidents were overall the most common cause of pediatric TBIs because of its high prevalence in the ICU stratum (58%), whereas incidental falls were the most common cause of injury in the admission stratum (43%, **Figure 2B**). In road-traffic incidents, the young patients were involved as pedestrians in one-third of cases (**Table 1**). Notably, more than half (52%) of all patients involved in an accident as cyclists, scooter drivers, or motor bikers did not wear a safety helmet.

Injury Severity and Clinical Status at Admission

Twenty two percent of pediatric patients in our cohort presented with mild TBI (GCS 13-15) while moderate (GCS 9-12) and severe TBI (GCS 3-8) occurred in 12 and 61%, respectively. Brain injury was considered serious to severe in the majority of patients (AIS 3 (3–4), **Table 1**). Concurrent injuries in other body regions were very common, especially in the ICU stratum. Overall, 176 patients (77%) presented with at least one concurrent injury. These mostly involved the face (30%) and head (46%), but also e.g., upper (18%) and lower extremities (16%). A simultaneous thorax injury was documented in 38% of all ICU patients as opposed to 5% in the admission stratum ($p < 0.001$). As expected, the total ISS and AIS Brain Injury scores in the ICU stratum were significantly higher than in the admission stratum (26 (17–41) vs. 10 (9–17), $p < 0.001$ and 4 (4–5) vs. 3 (3-3), $p < 0.001$, respectively). GCS as well as GCS—motor at admission were significantly higher in the admission stratum compared to the ICU stratum (15 (15–15) vs. 11 (6–14); $p < 0.00$; and 6 (6–6) vs. 5 (1–6); $p < 0.001$). In the ICU stratum, 28% of patients had no motor response to stimuli at all and one in ten patients had two unresponsive pupils at admission. The most common presenting symptoms are provided in **Figure 3**.

Brain CT Imaging

In pediatric TBI patients within the core dataset, an intracranial abnormality was detected in more than 60% of all patients in the initial brain CT scan (**Table 2**). The most common pathologies were traumatic subarachnoid hemorrhage (29%) followed by contusion (27%), epidural hematoma (25%), and acute subdural hematoma (19%). As expected, the prevalence of those pathologies was higher among ICU patients. A skull fracture was present in almost half of all patients in the admission and ICU strata. The median Marshall and Rotterdam scores for the entire cohort were 2 (IQR: 1–2) and 2 (IQR: 2–3), respectively.

Clinical Care and Outcome

The median length of stay for pediatric TBI patients was 2 (IQR 1-4) days in the admission stratum and 10 (IQR 5-24) days in the ICU stratum. An emergency intracranial

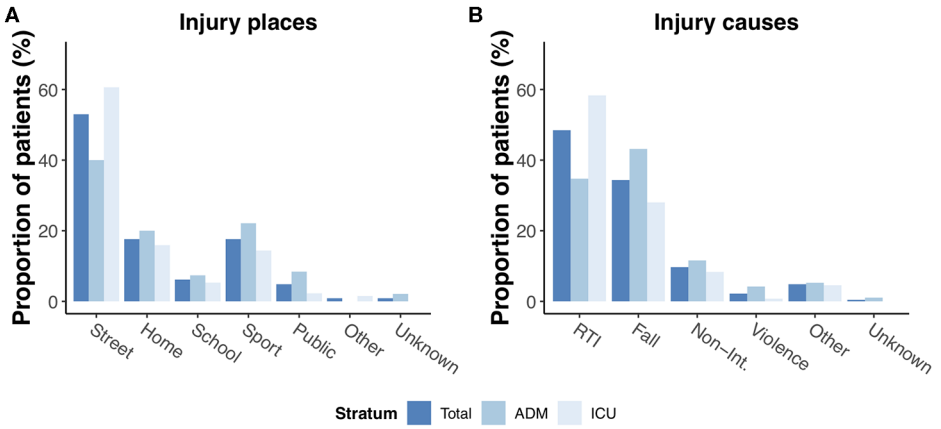

FIGURE 2 | Injury places **(A)** and causes **(B)** of pediatric TBI in the entire core dataset and admission/ICU patients. RTI: Road-traffic incident; Non-Int.: Other non-intentional injury.

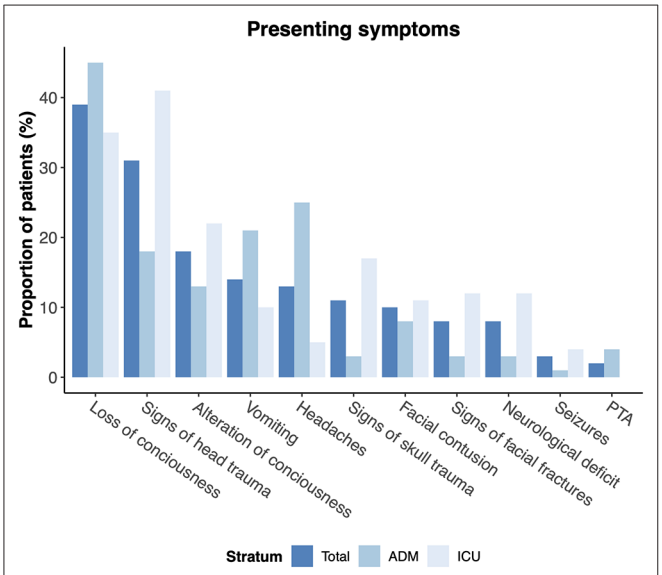

FIGURE 3 | Presenting symptoms of pediatric patients with TBI. PTA: Post-traumatic amnesia.

surgery was performed in 15% of ICU patients while 18% underwent emergency extracranial surgery. One-third of all ICU patients required emergency or non-emergency intracranial surgery during their entire hospital stay (this included placement of intracranial pressure monitoring devices). This differed significantly from patients in the admission stratum where no emergency intracranial surgery ($p < 0.001$) and 2 (2%) emergency extracranial surgeries ($p < 0.001$) were performed. At six months follow-up, the mortality rate and rate of an unfavorable outcome of pediatric TBI patients in the ICU stratum were 5 and 16% respectively (**Table 3**). In the admission stratum, no patient died (mortality rate: 0%) and with 1% (1 patient), the rate of an unfavorable outcome was significantly lower compared to ICU patients ($p = 0.001$). Taken together, this yields a mortality rate of 3% and rate of an unfavorable outcome of 10% for the entire pediatric CENTER-TBI cohort in our study. Of the six patients with a fatal outcome, four died due to their initial head injury. In the remaining two patients, the exact cause of death was not documented. In multivariate analysis, 35 patients were excluded due to missing data. In the remaining pediatric TBI patients admitted to the regular ward or ICU, only total GCS as well as the occurrence of secondary insults were significant predictors for an unfavorable outcome six months after the injury (**Table 4**).

Mild TBI: Admission vs. ICU

Notably, 50 patients with mild TBI (GCS 13–15) were admitted to the ICU. Accidents in those patients were more commonly set in streets/highways when compared to patients with mild TBI in the admission stratum (58 vs. 39%; $p = 0.034$). While 81% of patients with mild TBI in the admission stratum had a GCS of 15 (median GCS: 15 (15–15), this was only the case in 52% of patients with mild TBI that were admitted to the ICU (median GCS: 15 (14–15; $p < 0.001$). Prevalence of concurrent injuries (e.g., abdominal injuries: 11% (ICU) vs. 2% (admission); $p = 0.109$) was higher in the mild TBI patients in the ICU compared to the regular ward and the ISS was significantly higher in those patients as well (21 (16–57) vs. 16 (9–22); $p < 0.001$). At six months follow-up, the median GOSE was 8 (7–8) in the admission stratum vs. 7 (6–8) in the ICU stratum ($p = 0.001$).

Severe TBI: Favorable vs. Unfavorable Outcome

Severe TBI (GCS 3–8) occurred in 46 patients all of whom were subsequently admitted to the ICU. An unfavorable outcome was reported in 13 of 43 patients (30%) with severe TBI and available GOSE at 6 months (**Table 5**). Patients with severe TBI and an unfavorable outcome were considerably more often involved in road traffic incidents compared to patients with favorable outcome (69 vs. 53%; $p = 0.332$). Median GCS at presentation was lower in the unfavorable outcome group (4 (3–6) vs. 6 (3–7); $p = 0.157$) and bilateral unreactive pupillary response was documented in almost one-third of patients. Secondary insults

TABLE 2 | Details of initial brain CT imaging.

Characteristic	Total	Admission stratum	ICU stratum	*p*-value
Contusion	58 (27%)	9 (10%)	49 (39%)	**<0.001**
Traumatic axonal injury	28 (13%)	6 (7%)	22 (18%)	**0.030**
Acute subdural hematoma	40 (19%)	8 (9 %)	32 (26%)	**0.003**
Subacute or chronic subdural hematoma	0 (0%)	0 (0%)	0 (0%)	-
Traumatic subarachnoid hemorrhage	62 (29%)	9 (10%)	53(42%)	**<0.001**
Epidural hematoma	32 (15%)	8 (9%)	24 (19%)	0.053
Intraventricular hemorrhage	21 (10%)	1 (1%)	20 (16%)	**<0.001**
Skull Fracture	103 (48%)	30 (33%)	73 (58%)	**<0.001**
Subdural collection density	0 (0%)	0 (0%)	0 (0%)	-
Mass lesion	9 (4%)	0 (0%)	9 (7%)	**0.023**
Cisternal compression	21 (10%)	1 (1%)	20 (16%)	**<0.001**
Midline shift	7 (3%)	0 (0%)	7 (6%)	0.057
Any intracranial abnormality	133 (62%)	33 (36%)	100 (80%)	**<0.001**
Marshall CT Score (IQR)	2 (1-2)	1 (1-2)	2 (2-2)	**<0.001**
Rotterdam CT Score (IQR)	2 (2-3)	2 (2-2)	2 (2-3)	**<0.001**

***CT**, Computed Tomography; **IQR**, Interquartile range. Significant differences (p-value of <0.05 in the Mann-Whitney U test for continuous variables and chi-squared test for categorical variables) between the admission and ICU stratum are printed bold.*

at presentation, while rather rare in the group with favorable outcomes, were significantly more common in the group with unfavorable outcomes (**Figure 4**, **Table 5**).

Comparison With the CENTER-TBI Registry Dataset

The CENTER-TBI registry was used to compare the 227 pediatric TBI patients in the core dataset with a substantially larger cohort of 687 pediatric TBI patients in the registry dataset and confirm key findings regarding injury causes and severity (**Table 6**). Pediatric patients had been registered in 46 of the 59 CENTER-TBI registry participants. The median age in pediatric TBI patients within the registry dataset was 12 (IQR 4-16, range 0–17) years and 64% of patients were males. The fraction of patients in the admission stratum was considerably higher (62%) compared to the core dataset (42%). Corresponding to the results from the core dataset, streets were the most common injury place (42%), followed by injuries at home (28%). Likewise, road-traffic incidents (41%) and falls (40%) were the most common causes of pediatric TBI in the CENTER-TBI registry. In road-traffic incidents, pediatric patients were most commonly involved as cyclists or pedestrians (together 61%). Total ISS scores were comparable to those obtained in the core dataset and amounted to 10 (5–13) in the admission stratum and 25 (16–38) in the ICU stratum, underlining the close association of pediatric TBI to concurrent injuries especially in the ICU setting. Similar to the results from the core dataset, brain injury was classified as serious to severe in most cases (AIS 3 (2–4)). GCS ratings were also similar to the CENTER-TBI core study with a GCS of 15 (14–15) in the admission stratum and 12 (7–15) in the ICU stratum. On brain CT, an abnormality was detected in 49% of pediatric TBI patients in the registry dataset.

DISCUSSION

Traumatic brain injury in children is a very serious condition that can lead to lifelong disability but still presents as a scientific field with a general lack of research and evidence (6). Furthermore, due to particularities in the pathophysiology of pediatric TBI with e.g., different absorption of traumatic forces and different dynamics of head acceleration, it is precarious to transfer findings from adult TBI patients to the pediatric population (2). In an effort to contribute to a better understanding of injury characteristics and clinical care of pediatric TBI, we, therefore, analyzed the multi-center, prospectively collected CENTER-TBI core and registry datasets for patients younger than 18 years with TBI who were admitted to the hospital ward or ICU. Our key findings in the core study could be confirmed in the larger registry dataset, supporting the external validity of our results.

Road traffic incidents were the most common injury causes overall (admission and ICU stratum) ahead of incidental falls, which is in line with previous reports (7, 8). While road traffic incidents were especially prominent in the ICU stratum and associated with severe injuries, an association that can also be seen in previous studies (9, 10), incidental falls were the most common injury cause in the admission stratum. This differs from the overall, predominately adult CENTER-TBI patient population where incidental falls were the most common cause of TBI. However, similarly to our findings in the pediatric cohort, road-traffic incidents also were the most common cause of TBI in ICU patients (11). Pediatric patients in road traffic incidents were most commonly involved as pedestrians. When children were involved as cyclists, scooter drivers or motor bikers, more than half of them did not wear a safety helmet which is an important and noteworthy finding in regard to possible preventive targets and efforts.

Brain CT imaging in the young patients in our analysis allowed insights into common pathologies behind pediatric TBI.

TABLE 3 | Clinical status, hospital course, and outcome of pediatric TBI patients in the admission and ICU stratum of the CENTER-TBI core study.

Characteristic	Total	Admission stratum	ICU stratum	*p*-value
AVPU				**<0.001**
- Alert	115 (51%)	80 (84%)	35 (27%)	
- Verbal	23 (10%)	12 (13%)	11 (8%)	
- Pain	20 (8%)	1 (1%)	19 (14%)	
- Unresponsive	60 (26%)	1 (1%)	59 (45%)	
- Unknown	9 (4%)	1 (1%)	8 (6%)	
GCS (IQR)	14 (10-15)	15 (15-15)	11 (6-14)	**<0.001**
GCS – motor (IQR)	6 (5-6)	6 (6-6)	5 (1-6)	**<0.001**
Pupillary response				**0.001**
- Both reactive	205 (92%)	92 (100%)	113 (86%)	
- One reactive	5 (2%)	0 (0%)	5 (4%)	
- Both unreactive	13 (6%)	0 (0%)	13 (10%)	
Vomiting	28 (14%)	17 (21%)	11 (10%)	**0.040**
Signs of facial fractures	16 (8%)	2 (3%)	14 (12%)	**0.030**
Facial contusion	19 (10%)	6 (8%)	13 (11%)	0.512
Signs of head/skull trauma	61 (31%)	14 (18%)	47 (41%)	**<0.001**
Signs of skull base trauma	21 (11%)	2 (3%)	19 (17%)	**0.004**
Alteration of Consciousness	35 (18%)	10 (13%)	25 (22%)	0.136
Loss of consciousness	76 (39%)	36 (45%)	40 (35%)	0.214
Seizures	6 (3%)	1 (1%)	5 (4%)	0.412
Post-traumatic amnesia < 4 h	3 (2%)	3 (4%)	0 (0%)	0.136
Headaches	26(13%)	20 (25%)	6 (5%)	**<0.001**
Neurological deficit	16 (8%)	2 (3%)	14 (12%)	**0.030**
Length of stay	5 (2-13)	2 (1-4)	10 (5-24)	**<0.001**
Emergency intracranial surgery	20 (10%)	0 (0%)	20 (15%)	**<0.001**
Emergency extracranial surgery	25 (11%)	2 (2%)	23 (18%)	**<0.001**
Intracranial surgery	47 (21%)	3 (3%)	44 (33%)	**<0.001**
Extracranial surgery	45 (20%)	7 (7%)	38 (28%)	**<0.001**
GOSE at six months (IQR)	7 (6-8)	8 (7-8)	6 (5-8)	**<0.001**
Mortality	6 (3%)	0 (0%)	6 (5%)	0.099
Unfavorable outcome (GOSE 1-4) at 6 months	20 (10%)	1 (1%)	19 (16%)	**0.001**

***AVPU**, Awake, Verbal, Pain, Unresponsive; **GCS**, Glasgow Coma Scale; **GOSE**, Glasgow Outcome Scale Extended; **IQR**, Interquartile range. Significant differences (p-value of <0.05 in the Mann-Whitney U test for continuous variables and chi-squared test for categorical variables) between the admission and ICU stratum are printed bold.*

TABLE 4 | Multivariate logistic regression analysis to unfavorable outcome (GOSE 1-4) in pediatric TBI patients in the admission and ICU stratum of the CENTER-TBI core study.

Predictor	Beta	*p*-value	OR (95% CI)
Age	0.030	0.738	0.543 (0.020-11.529)
Gender	−0.884	0.248	1.030 (0.871-1.241)
RTI	0.472	0.599	0.413 (0.086-1.851)
GCS	−0.378	< 0.001	0.686 (0.535-0.833)
Total ISS	0.014	0.625	1.014 (0.958-1.075)
Secondary insult	3.081	< 0.001	21.782 (4.137-160.287)

***GCS**, Glasgow Coma Scale; **ISS**, Injury Severity Score; **RTI**, Road traffic incident; **OR**, Odds ratio; **CI**, Confidence interval. The p-value tests the hypothesis that the given variable has no association with unfavorable outcome at six months.*

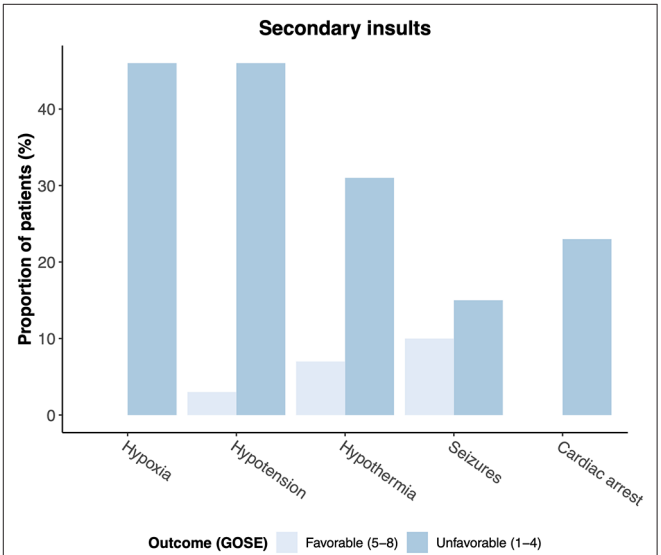

FIGURE 4 | Secondary insults at admission in patients with favorable (GOSE 5–8) and unfavorable (GOSE 1–4) outcome at six months.

The most common finding hereby was traumatic subarachnoid hemorrhage which is a relevant diagnosis in children as its complications include hydrocephalus and cerebral vasospasms (12). Other common findings were epidural and acute subdural hematomas. Skull fractures were remarkably present in nearly half of the pediatric patient cohort. Those findings correspond well to the numbers from previous studies that in summary reported skull fractures and cerebral contusions as the most common CT abnormalities (3). In 40% of patients in our study, no intracranial abnormality could be detected on the initial brain CT.

Because TBI patients within the CENTER-TBI study were stratified into different strata upon enrollment, analysis of the data offers the opportunity to directly compare pediatric TBI patients treated in different hospital settings, in particular patients treated on the regular ward vs. the ICU. We found, as expected, considerable differences in injury cause and severity between the admission and ICU stratum. While patients requiring intensive care were more often involved in road-traffic incidents, incidental falls were the most common cause in patients in the admission stratum. Injury severity was in general significantly higher in ICU patients, as indicated by higher ISS and GCS scores, and prevalence of concurrent injuries in other body regions, especially thorax and abdomen, was greater. Notably, more than three quarters of patients also suffered from other body injuries, emphasizing the importance of a general and extensive clinical examination in pediatric TBI patients. A total of 61% of pediatric patients in our cohort were classified as mild TBI. Interestingly, 36% of them were admitted to the ICU. While this finding corresponds to the number of mild TBI patients admitted to the ICU in the adult CENTER-TBI patient population (36%), discussed reasons such as advanced

TABLE 5 | Comparison of pediatric severe TBI patients with favorable or unfavorable outcome in the CENTER-TBI core study.

Characteristic	Total	Favorable outcome (*n* = 185)	Unfavorable outcome (*n* = 20)	*p*-value
Age (IQR)	15 (9-16)	15 (8-16)	15 (10-17)	0.717
Sex				0.108
- Female	17 (37%)	7 (23%)	7 (54%)	
- Male	29 (63%)	23 (77%)	6 (46%)	
Injury cause				0.056
- Road traffic incident	28 (61%)	16 (53%)	9 (69%)	
- Incidental fall	10 (22%)	10 (33%)	0 (0%)	
- Other non-intentional injury	7 (15%)	4 (13%)	3 (23%)	
- Violence	0 (0%)	0 (0%)	0 (0%)	
- Other/Unknown	1 (2%)	0 (0%)	1 (8%)	
Injury road incident				0.930
- Motor vehicle occupant	7 (25%)	4 (25%)	2 (22%)	
- Pedestrian	7 (25%)	3 (19%)	3 (33%)	
- Cyclist	6 (21%)	3 (19%)	2 (22%)	
- Scooter	3 (11%)	2 (13%)	1 (11%)	
- Motor Bike	4 (14%)	3 (19%)	1 (11%)	
- Other	1 (4%)	1 (6%)	0 (0%)	
Safety helmet (cyclist, scooter, motor bikers)				0.301
- Yes	6 (46%)	4 (50%)	2 (50%)	
- No	6 (46%)	4 (50%)	1 (50%)	
- Unknown	1 (8%)	9 (0%)	1 (25%)	
Total ISS (IQR)	34 (25-48)	29 (21-49)	41 (34-57)	**0.008**
GCS (IQR)	5 (3-7)	6 (3-7)	4 (3-6)	0.157
GCS motor (IQR)	2 (1-4)	3 (1-5)	2 (1-4)	0.694
Pupillary response				0.342
- Both reactive	36 (78%)	25 (83%)	9 (69%)	
- One reactive	2 (4%)	1 (3%)		
- Both unreactive	8 (17%)	4 (13%)	4 (31%)	
Secondary Insult: Hypoxia	7 (15%)	0 (0%)	6 (46%)	**<0.001**
Secondary Insult: Hypotension	7 (15%)	1 (3%)	6 (46%)	**0.001**
Secondary Insult: Cardiac arrest	3 (7%)	0 (0%)	3 (23%)	**0.038**
Secondary Insult: Hypothermia	6 (13%)	2 (7%)	4 (31%)	**0.008**
Secondary Insult: Seizures	5 (11%)	3 (10%)	2 (15%)	0.836
Length-of-stay (IQR)	28 (10-43)	28 (10-42)	29 (6-59)	0.814
GOSE at 6 months (IQR)	6 (4-7)	7 (6-8)	3 (1-3)	**<0.001**

***GCS**, Glasgow Coma Scale; **GOSE**, Glasgow Outcome Scale Extended; **ISS**, Injury Severity Score; **IQR**, Interquartile range. Significant differences (p-value of < 0.05 in the Mann-Whitney U test for continuous variables and chi-squared test for categorical variables) between the favorable and unfavorable outcome group are printed bold.*

age, comorbidities or antithrombotic drugs which might increase the risk for lesion progression are not applicable for the pediatric patients assessed in our study (11). Rather, we found a higher prevalence of road-traffic incidents with more concurrent injuries in other body parts in affected mild TBI patients as well as an increased presence of neurological deficits which could be possible explanations for the physician's decision in those cases. Moreover, the high rate of extra- and intracranial surgeries in general might have warranted observation of pediatric mild TBI patients on the ICU in some cases. Because participating centers within the CENTER-TBI study were not generally specialized in treating pediatric TBI, overtreatment cannot be ruled out and might have additionally affected the high ICU admission rate of pediatric mild TBI patients.

Severe TBI was present in 22% of all patients in our cohort of pediatric TBI. As expected, all of those patients were treated in the ICU with an injury so grave that emergency intracranial surgery had to be performed in 4 of 46 patients (9%). An unfavorable outcome was reported in 30% of pediatric severe TBI patients in our cohort, showing associations with road traffic incidents, lower GCS at presentation as well as the occurrence of secondary injury insults such as hypotension at admission. The high prevalence of road-traffic incidents in children with severe TBI and an unfavorable outcome emphasizes the need and potential for more preventive efforts.

Considering the overall outcome in our cohort of pediatric TBI patients, a GOSE score of 7 or 8 could be observed in 64% of cases. However, an unfavorable outcome (GOSE 1-4) was still present in 10% of pediatric TBI patients which is comparable to numbers from single-center studies reported from India (10%) and the United States (16%) (13, 14). Independent predictors for an unfavorable outcome six months after TBI in pediatric patients who were admitted to the regular ward or ICU were GCS and the occurrence of secondary insults in multivariate analysis. Secondary systemic insults such as hypoxia and hypotension were significantly more common in patients with unfavorable outcome which seems to confirm previous studies from both pediatric and adult patient cohorts (15–22). Importantly, these physiological parameters impose potential treatment targets: Active airway management such as early intubation and early tracheostomy have been shown to be associated with better outcomes in adults (23–26). Similarly, the relationship between low preadmission blood pressures and mortality is well established and recent results from large multi-center trials suggest to consider notably higher blood pressure targets than the >90 mmHg systolic blood pressure threshold stated in current guidelines (27, 28). Future studies examining blood pressure treatment levels in both adult and pediatric patients are needed to find optimal treatment thresholds.

Despite a relatively high injury severity, mortality was still rather low in the overall pediatric CENTER-TBI cohort assessed in our study (3%) as well as in the group of pediatric severe TBI patients (9%) and thus lower than in the overall CENTER-TBI cohort that includes predominately adult patients (14.9% for patients admitted to the regular ward or ICU) (11). Similar results for pediatric TBI have been reported in several comparable studies, indicating the great potential for recovery in children, even when presenting with severe TBI (1, 7, 29, 30). In the literature, differences in outcome between pediatric and adult TBI patients have been explained by reasons such as a greater flexibility of cranial bones in young children, providing a higher capacity of traumatic force absorption (31). Although research on this specific field is still very limited, lower mortality in the pediatric population of the CENTER-TBI study compared

TABLE 6 | Comparison of patient characteristics between the CENTER-TBI core vs. registry datasets.

Characteristic	Total		Admission stratum		ICU stratum	
	Core	Registry	Core	Registry	Core	Registry
Number of patients	227	687	95	423	132	264
Age (IQR)	14 (8-16)	12 (4-16)	13 (9-16)	12 (5-16)	14 (8-16)	12 (4-16)
Sex						
- Female	81 (36%)	246 (36%)	32 (34%)	147 (35%)	49 (37%)	99 (38%)
- Male	146 (64%)	441 (64%)	63 (66%)	276 (65%)	83 (63%)	165 (62%)
Injury Place						
- Street	118 (52%)	298 (42%)	38 (40%)	169 (38%)	80 (61%)	129 (49%)
- Home	40 (18%)	192 (28%)	19 (20%)	126 (30%)	21 (16%)	66 (25%)
- Work/School	14 (6%)	4 (1%)	7 (7%)	3 (1%)	7 (5%)	1 (0%)
- Sport	40 (18%)	72 (10%)	21 (22%)	56 (13%)	19 (14%)	16 (6%)
- Public	11 (5%)	96 (14%)	8 (8%)	69 (4%)	3 (2%)	36 (14%)
- Other	2 (1%)	31 (5%)	0 (0%)	16 (4%)	2 (2%)	15 (6%)
- Unknown	2 (1%)	3 (0%)	2 (2%)	2 (0%)	0 (0%)	1 (0%)
Injury Cause						
- RTI	110 (48%)	282 (41%)	33 (35%)	152 (36%)	77 (58%)	130 (49%)
- Fall	78 (34%)	276 (40%)	41 (43%)	184 (43%)	37 (28%)	92 (35%)
- Other	39 (17%)	129 (19%)	21 (22%)	87 (21%)	18 (14%)	42 (16%)
GCS (IQR)	14 (10-15)	15 (13-15)	15 (15-15)	15 (14-15)	11 (6-14)	12 (7-15)
GCS – motor (IQR)	6 (5-6)	6 (6-6)	6 (6-6)	6 (6-6)	5 (1-6)	6 (4-6)
AIS Brain Injury (IQR)	4 (3-4)	3 (2-4)	3 (3-3)	2 (1-3)	4 (4-5)	4 (3-5)
ISS (IQR)	18 (10-32)	13 (9-22)	10 (9-17)	10 (5-13)	26 (17-41)	25 (16-38)
Pupillary response						
- Both reactive	205 (92%)	619 (94%)	92 (100%)	403 (99%)	113 (86%)	216 (85%)
- One reactive	5 (2%)	20 (3%)	0 (0%)	5 (1%)	5 (4%)	15 (6%)
- Both unreactive	13 (6%)	23 (3%)	0 (0%)	0 (0%)	13 (10%)	23 (9%)
CT Brain: Any intracranial abnormality	133 (59%)	318 (49%)	33 (35%)	115 (30%)	100 (76%)	203 (77%)

***AIS**, Abbreviated Injury Scale; **CT**, Computed Tomography; **GCS**, Glasgow Coma Scale; **ISS**, Injury Severity Scale; **IQR**, Interquartile range; **RTI**, Road-traffic incident.*

to the adult population might be generally related to the immense disparity in the presence of comorbidities, frailty or antithrombotic medication.

Nevertheless, alarming numbers have very recently been published concerning age-adjusted TBI mortality for patients aged 0–19 years in the US: Despite an initial decline from 1999 to 2012, pediatric TBI mortality has been raising again since 2013 (32). And although functional outcomes early after TBI might be better in children, there is growing evidence that they are more vulnerable to long-term cognitive deficits compared to adults (33). Therefore, and as disabilities and deficits are a huge burden in surviving patients with pediatric TBI, every effort should be made to prevent the occurrence of this condition.

With the findings in the CENTER-TBI core study and their validation in the CENTER-TBI registry, our analysis displays the most common injury causes of pediatric TBI in Europe at present. Also, it confirms known predictors for an unfavorable outcome after TBI in children. While neurosurgeons, pediatricians, and other health practitioners should be especially aware of the risks associated with secondary insults, legislators are reminded that further preventive efforts such as advertising the use of safety helmets or building safer infrastructure might still be needed to reduce the incidence of severe TBI.

CONCLUSION

TBI in pediatric patients within the CENTER-TBI study that were admitted to the regular ward or ICU were most commonly caused by road-traffic incidents and incidental falls. Injury severity was serious especially in ICU patients and concurrent injuries in other body parts were common. GCS and the occurrence of secondary insults were identified as predictors for an unfavorable outcome (GOSE 1–4) at six months follow-up. The current analysis suggests, that preventive efforts could still be very effective in decreasing the incidence of TBI.

LIMITATIONS

There are several limitations to this analysis. Recruitment to the CENTER-TBI core study was conducted at the discretion of the participating centers and thus influenced by local logistics and academic interests which might be a potential source of selection bias. Because of data anonymization reasons, no information on the specific countries where the TBI patients were recruited can be obtained from the CENTER-TBI database. The data used for our analyses might, therefore, be derived from only a

subset of countries and the results should be generalized with caution. Moreover, although the CENTER-TBI study included pediatric as well as adult patients, the participating centers were mainly general hospitals and not specialized pediatric centers and might thus not have primarily managed pediatric TBI in some regions or countries. Because data on the type of ICU is not available within the CENTER-TBI database, a possible bias from the treatment of pediatric patients in specialized ICUs cannot be ruled out. In addition, not all participating centers enrolled pediatric patients. This might be the reason why pediatric TBI was underrepresented in comparison to adult TBI in the CENTER-TBI study. While we can therefore not comment on the absolute incidence of pediatric TBI in Europe, we still provide a large multi-center pediatric patient cohort that can give important insights into injury causes and patterns. Furthermore, although the data were prospectively collected, missing data was still present especially regarding to long-term outcomes with GOSE ratings being only available for 90% of patients.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author and with permission of the CENTER-TBI management committee.

ETHICS STATEMENT

The CENTER-TBI study is compliant with all relevant EU- and national laws of recruiting centers in regard to privacy, data protection and ethical standards and in accordance with the Declaration of Helsinki ("Ethical Principles for Medical Research Involving Human Subjects"). Informed consent was obtained from all patients and/or their legal representatives, according to the local legislations, included in this study. Ethical approval was obtained for each recruiting site (see https://www.center-tbi.eu/project/ethical-approval for the list of sites, ethical committees, approval numbers and approval dates).

AUTHOR CONTRIBUTIONS

LR and AY designed the study, conducted the data analysis, interpreted the data, and co-wrote the manuscript. KZ, AU, and AE helped with data interpretation and critically revised the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00345/full#supplementary-material

REFERENCES

1. Schneier AJ, Shields BJ, Hostetler SG, Xiang H, Smith GA. Incidence of pediatric traumatic brain injury and associated hospital resource utilization in the United States. *Pediatrics.* (2006) 118:483–92. doi: 10.1542/peds.2005-2588
2. Araki T, Yokota H, Morita A. Pediatric traumatic brain injury: characteristic features, diagnosis, and management. *Neurol Med Chir.* (2017) 57:82–93. doi: 10.2176/nmc.ra.2016-0191
3. Dewan MC, Mummareddy N, Wellons JC, Bonfield CM. Epidemiology of global pediatric traumatic brain injury: qualitative review. *World Neurosurg.* (2016) 91:497–509.e1. doi: 10.1016/j.wneu.2016.03.045
4. Maas AIR, Menon DK, Steyerberg EW, Citerio G, Lecky F, Manley GT, et al. Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study. *Neurosurgery.* (2015) 76:67–80. doi: 10.1227/NEU.0000000000000575
5. R Core Team. *R: A Language and Environment for Statistical Computing.* Vienna: R Foundation for Statistical Computing (2018). Available online at: http://www.r-project.org/
6. The Lancet T. The burden of traumatic brain injury in children. *Lancet.* (2018) 391:813. doi: 10.1016/S0140-6736(18)30547-6
7. Amaranath JE, Ramanan M, Reagh J, Saekang E, Prasad N, Chaseling R, et al. Epidemiology of traumatic head injury from a major paediatric trauma centre in New South Wales, Australia. *ANZ J Surg.* (2014) 84:424–8. doi: 10.1111/ans.12445
8. Bowman SM, Bird TM, Aitken ME, Tilford JM. Trends in hospitalizations associated with pediatric traumatic brain injuries. *Pediatrics.* (2008) 122:988–93. doi: 10.1542/peds.2007-3511
9. Schrieff LE, Thomas KGF, Dollman AK, Rohlwink UK, Figaji AA. Demographic profile of severe traumatic brain injury admissions to Red Cross War Memorial Children's Hospital, 2006 - 2011. *South African Med J.* (2013) 103:616. doi: 10.7196/samj.7137
10. Parslow RC, Morris KP, Tasker RC, Forsyth RJ, Hawley CA, UK Paediatric Traumatic Brain Injury Study Steering Group, et al. Epidemiology of traumatic brain injury in children receiving intensive care in the UK. *Arch Dis Child.* (2005) 90:1182–7. doi: 10.1136/ADC.2005.072405
11. Steyerberg EW, Wiegers E, Sewalt C, Buki A, Citerio G, De Keyser V, et al. Case-mix, care pathways, and outcomes in patients with traumatic brain injury in CENTER-TBI: a European prospective, multicentre, longitudinal, cohort study. *Lancet Neurol.* (2019) 18:923–34. doi: 10.1016/S1474-4422(19)30232-7
12. Sarioglu FC, Sahin H, Pekcevik Y, Sarioglu O, Oztekin O. Pediatric head trauma: an extensive review on imaging requisites and unique imaging findings. *Eur J Trauma Emerg Surg.* (2018) 44:351–68. doi: 10.1007/s00068-017-0838-y
13. Wani AA, Sarmast AH, Ahangar M, Malik NK, Chhibber SS, Arif SH, et al. Pediatric head injury: a study of 403 cases in a tertiary care hospital in a developing country. *J Pediatr Neurosci.* (2017) 12:332–7. doi: 10.4103/jpn.JPN_80_17

14. Slovis JC, Gupta N, Li NY, Kernie SG, Miles DK. Assessment of recovery following pediatric traumatic brain injury. *Pediatr Crit Care Med.* (2018) 19:353–60. doi: 10.1097/PCC.0000000000001490
15. Luerssen TG, Klauber MR, Marshall LF. Outcome from head injury related to patient' age. *J Neurosurg.* (1988) 68:409–16. doi: 10.3171/jns.1988.68.3.0409
16. Bahloul M, Chabchoub I, Dammak H, Ksibi H, Rekik N, Bouaziz M, et al. Outcome analysis and outcome predictors of traumatic head injury in childhood: Analysis of 454 observations. *J Emerg Trauma Shock.* (2011) 4:198. doi: 10.4103/0974-2700.82206
17. Coates BM, Vavilala MS, Mack CD, Muangman S, Suz P, Sharar SR, et al. Influence of definition and location of hypotension on outcome following severe pediatric traumatic brain injury. *Crit Care Med.* (2005) 33:2645–50. doi: 10.1097/01.ccm.0000186417.19199.9b
18. Samant UB, Mack CD, Koepsell T, Rivara FP, Vavilala MS. Time of hypotension and discharge outcome in children with severe traumatic brain injury. *J Neurotrauma.* (2008) 25:495–502. doi: 10.1089/neu.2007.0491
19. Volpi PC, Robba C, Rota M, Vargiolu A, Citerio G. Trajectories of early secondary insults correlate to outcomes of traumatic brain injury: results from a large, single centre, observational study 11 medical and health sciences 1103 clinical sciences. *BMC Emerg Med.* (2018) 18:52. doi: 10.1186/s12873-018-0197-y
20. Alali AS, Temkin N, Vavilala MS, Lele A V., Barber J, Dikmen S, et al. Matching early arterial oxygenation to long-term outcome in severe traumatic brain injury: Target values. *J Neurosurg.* (2020) 132:537–44. doi: 10.3171/2018.10.JNS18964
21. McHugh GS, Engel DC, Butcher I, Steyerberg EW, Lu J, Mushkudiani N, et al., Marmarou A, Maas AIR, Murray GD. Prognostic value of secondary insults in traumatic brain injury: results from the IMPACT study. *J Neurotrauma.* (2007) 24:287–93. doi: 10.1089/neu.2006.0031
22. Butcher I, Maas AIR, Lu J, Marmarou A, Murray GD, Mushkudiani NA, et al. Prognostic value of admission blood pressure in traumatic brain injury: results from the IMPACT study. *J Neurotrauma.* (2007) 24:294–302. doi: 10.1089/neu.2006.0032
23. Hoffmann M, Czorlich P, Lehmann W, Spiro AS, Rueger JM, Lefering R. The impact of prehospital intubation with and without sedation on outcome in trauma patients with a GCS of 8 or less. *J Neurosurg Anesthesiol.* (2017) 29:161–7. doi: 10.1097/ANA.0000000000000275
24. Denninghoff KR, Nuño T, Pauls Q, Yeatts SD, Silbergleit R, Palesch YY, et al. Prehospital intubation is associated with favorable outcomes and lower mortality in proTECT III. *Prehospital Emerg Care.* (2017) 21:539–44. doi: 10.1080/10903127.2017.1315201
25. Sabrina A de F, Tavares WM, Salinet ASM, Paiva WS, Teixeira MJ. Early tracheostomy in severe traumatic brain injury patients: a meta-analysis and comparison with late tracheostomy. *Crit Care Med.* (2020) 48:e325–e331. doi: 10.1097/CCM.0000000000004239
26. Robba C, Galimberti S, Graziano F, Wiegers EJA, Lingsma HF, Iaquaniello C, et al. Tracheostomy practice and timing in traumatic brain-injured patients: a CENTER-TBI study. *Intensive Care Med.* (2020) doi: 10.1007/s00134-020-05935-5. [Epub ahead of print].
27. Spaite DW, Hu C, Bobrow BJ, Chikani V, Sherrill D, Barnhart B, et al. Mortality and prehospital blood pressure in patients with major traumatic brain injury: Implications for the hypotension threshold. *JAMA.* (2016) 2016:360–8. doi: 10.1001/jamasurg.2016.4686
28. Fuller G, Hasler RM, Mealing N, Lawrence T, Woodford M, Juni P, et al. The association between admission systolic blood pressure and mortality in significant traumatic brain injury: A multi-centre cohort study. *Injury.* (2014) 45:612–7. doi: 10.1016/j.injury.2013.09.008
29. Greene NH, Kernic MA, Vavilala MS, Rivara FP. Variation in pediatric traumatic brain injury outcomes in the United States. *Arch Phys Med Rehabil.* (2014) 95:1148–55. doi: 10.1016/j.apmr.2014.02.020
30. Robertson BD, McConnel CE, Green S. Charges associated with pediatric head injuries: A five-year retrospective review of 41 pediatric hospitals in the US. *J Inj Violence Res.* (2013) 5:50–60. doi: 10.5249/jivr.v5i1.205
31. Ghajar J, Hariri RJ. Management of pediatric head injury. *Pediatr Clin North Am.* (1992) 39:1093–25. doi: 10.1016/S0031-3955(16)38409-7
32. Cheng P, Li R, Schwebel DC, Zhu M, Hu G. Traumatic brain injury mortality among US.children and adolescents ages 0 – 19 years, 1999 – 2017. *J Safety Res.* (2020) 72:93–100. doi: 10.1016/j.jsr.2019.12.013
33. Purcell LN, Reiss R, Eaton J, Kumwenda K, Quinsey C, Charles A. Survival and functional outcomes at discharge after traumatic brain injury in children versus adults in resource-poor setting. *World Neurosurg.* (2020). doi: 10.1016/j.wneu.2020.02.062 . [Epub ahead of print].

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