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Advancement and New Understanding in Brain Injury

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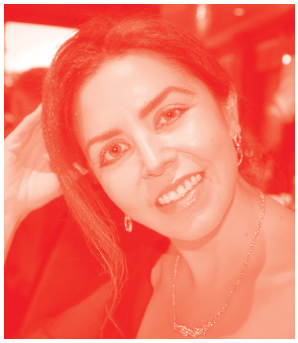

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Contributors
Nikolay Zavadenko, Alexey Kholin, Yuriy Nesterovskiy, Irina Vorobyeva, Sabrina Araujo de França, Wagner M. Tavares, Wellingson S. Paiva, Manoel J. Teixeira, Andrew Macnab, Michelle Theus, Amanda Hazy, Elizabeth Kowalski, Nathalie Groot, Gustavo Frigieri, Sérgio Brasil, Nicollas Nunes Nunes Rabelo, Ricardo De Carvalho Nogueira, Robert Louis Louis Beckman, Maria Teresa Botti Rodrigues dos Santos, Vanessa Lira Siqueira, Ana Cristina Ferreira, Marcelo Freire, Carolina Ferreira, Cintya Yukie Hayashi, Mehdi Chihi, Ulrich Sure, Ramazan Jabbarli, Dyah Wati, Ermias Koricho, Elizabeth Dimsdale

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Meet the editor

Prof. Dr. Zamzuri Idris graduated from the University of Wales College of Medicine, Cardiff, UK, and then pursued his post-graduate career in neurosurgery. His further training was in Belgium under Prof. J. Caemaert and Prof. D. Van Roost. He is currently the head of the Neuroscience Department, Malaysia Neurosurgical Teaching and Education, Neurosurgical-Board Examination, and serves on the Executive Committee for the Neurosurgical Association of Malaysia. In addition, he is a member of the Society of Brain Mapping and Therapeutics (SBMT), USA, and the European Society for Stereotactic and Functional Neurosurgery (ESSFN). His major interests are in brain trauma, minimally invasive neurosurgery, epilepsy, brain mapping, and quantum brain dynamics. He is a regularly invited speaker at many scientific meetings and has published numerous papers and chapters internationally.

Contents

Preface

The brain is an interesting and fascinating organ. It is commonly viewed as an organ with complex anatomy and physiology. Lately, however, some scientists do not regard the brain as an organ! This is mainly because of their belief that the brain cannot be transplanted. The scientific reason for that is probably related to the quantum concept of the brain. From the perspective of quantum physics, the atom can exist in either particles or waves. This is the dual existence of an atom. Thus, besides the anatomical brain, the brain can also be viewed as whole waves, which interact meaningfully with the cosmological waves, forming a part of the cosmological quantum field (onefield). This concept highlights the importance of the brain for optimal human body function, which encompasses the whole of the universe. Any injury to the brain may give rise to nonoptimal or dysfunctional human body function. As a result, a brain injury is a real concern to a person who suffers from it and is commonly associated with an intrauterine, traumatic, ischemic, or hemorrhagic type of injury. The new information and understanding in traumatic brain injury gathered in this book from various field scientists may provide important insights into the pathophysiology, treatment, and ultimate advancement of brain injury knowledge.

Chapter 1 covers the historical aspect of intracranial pressure, waveforms, and compliance. The authors have touched upon the various waveforms for the ICP and the importance of each.

Chapter 2 is a superb review of the peripheral immune response following a traumatic brain injury. The detailed review also covers prevalence, pathology, and current methods in studying traumatic brain injury. Chapter 3 discusses brain injury and neuroinflammation of the gut-brain axis in individuals with cerebral palsy. Brain–gut or spinal cord–gut axis is currently a hot topic in neuroinflammation. Various diseases are related to this, including the current Covid-19 pandemic, which is rightly discussed by the authors. Chapter 4 comprehensively reviews the pathogenesis and prevention of fetal and neonatal brain injury with an emphasis on pathogenesis, prevention, management, and treatment. Chapter 5 presents the interesting topic of traumatic brain injury in children, which is uncommonly discussed in detail. Chapter 6 details noninvasive monitoring and diagnostic methods by using the transcranial Doppler, optic nerve sheath diameter, and intracranial pressure waveform. The various indexes used in these methods are well depicted in the tabulated forms. Chapter 7 concerns hyperbaric oxygenation in the treatment of traumatic brain injury. The chapter covers the mechanisms of head injury and potential positive mechanisms of hyperbaric oxygen therapy. The neuroprotective effects are stated clearly by the authors–increasing tissue oxygenation, reducing inflammation, decreasing apoptosis, reducing ICP, and promoting neurogenesis and angiogenesis. Based on these pathophysiological understandings, the authors went further in discussing the scientific studies that have been completed, including some with conflicting results. The added values of this chapter are the economic argument and a discussion of the chronic sequelae of head injury. Chapter 8 is an excellent review of the engineering aspect of head injury. It gives additional understanding to the clinician on the pathophysiology for "diffuse" head injury. As correctly stated at the conclusion, this chapter provides alternative insights in

understanding the correlation between a vehicle's interior padding, various types of head form models, materials modeling, and output parameters such as acceleration, strain, and pressure that can be correlated to TBI resulting from a vehicle crash. Chapter 9 contains a systematic review of the benefits of early tracheostomy with details on the epidemiology and pathophysiology and added emphasis on oxygen management. Chapter 10 details the demographic, clinical, and radiographic characteristics of cerebral aneurysms in the tuberous sclerosis complex. It is a chapter that focuses on the hemorrhagic aspect of brain injury and the distinct characteristics of these aneurysms. The final chapter in this book outlines the neurobehavioral, cognitive, and paroxysmal disorders in the long-term period of pediatric traumatic brain injury. The subject is rarely studied by scientists or clinicians; thus, it is not commonly presented. Therefore, this chapter is a gift to all scientists and clinicians hoping to better understand the pathogenesis of pediatric traumatic brain injury and related cognitive and neurobehavioral sequelae.

This book is the result of vigorous work and invaluable contributions by many researchers. Thus, I gratefully acknowledge their efforts and also the assistance provided by the InTech editorial team, with specific thanks to Ms. Sandra Maljavac and Ms. Marijana Francetic.

Dr. Zamzuri Idris
Professor,
Head, Neurosurgeon and Senior Lecturer,
Department of Neurosciences and Brain and Behaviour Cluster (BBC),
School of Medical Sciences,
Universiti Sains Malaysia (USM),
Kelantan, Malaysia

Chapter 1

Intracranial Pressure Waveform: History, Fundamentals and Applications in Brain Injuries

Gustavo Frigieri, Cintya Yukie Hayashi, Nicollas Nunes Rabelo and Sérgio Brasil

Abstract

Intracranial pressure (ICP) can be analyzed for its absolute value, usually in mmHg or cmH2O, its tendency over time and the waveform of its pulse. This chapter will focus on the waveform of the ICP pulse (ICPwf), already observed since 1881, and for a long time not understood. Studies conducted in recent decades show the correlation between the ICPwf and intracranial compliance (ICC), another important clinical parameter added to the practice in the second half of the last century. ICC allows physicians early analyzing patients' neurological conditions related to disorders resulting from variations in cerebrospinal fluid (CSF), blood and intracranial tissue volumes. This chapter is an invitation to dive into the history and development of ICPwf analysis, clinical uses already adopted and others still under study.

Keywords: intracranial pressure waveform, intracranial compliance, ICP

1. Introduction

Technological development has brought the opportunity for significant advances in the health area. As new sensors have been developed, tools for image acquisition and treatment are improved and analytical methods using modern algorithms and artificial intelligence are developing, the set of tools available to assist in the diagnosis and monitoring of patients has been expanded.

ICP is a good example of how technological advancement has led to clinical understanding. Initially, only the number corresponding to the mean ICP was used to guide clinical procedures. Until then, there was only one number, and the information was punctual, it was as if we looked at a photo.

Advancing in understanding disclosed the value of having available real time information on early stages of intracranial hypertension (ICH), thus, techniques that show the pressure trend curve proved to be remarkable for the follow-up of critically ill patients.

The information resulting from morphology will be treated in greater detail in this chapter, and today it is known that monitoring ICP is far over knowledge of a mean value, but also its trend over time, and the morphology of the pressure pulse recognition.

2. History

The history of ICPwf is centuries-old. For understanding, it is necessary to go back to the year 1783, after researcher Alexander Monro [1], who started studies of intracranial structures. His work was later completed by George Kellie [2], giving rise to the Monro-Kellie doctrine. This doctrine showed that the volume of intracranial components (blood, CSF and brain tissue) and the bone box that contains them is fixed. The volume of these components needs to be under balance, if there is an increase in one, the others need to compensate by reducing their volumes. Thus, intracranial hypertension (ICH) emerges when this compensation ceases to happen [3]. The stiffness of the skull was later challenged by the work of Sérgio Mascarenhas in 2012 [4].

Angelo Mosso, at the end of the 19th century, presented results showing the influence of brain activity on its blood flow. For the first time, it was possible to observe the brain pulses, through a system that captured these pulses and recorded them on paper. These figures can be seen in Zago's manuscript [5]. Many years later these pulses were related to ICP and CSF [6].

Langfitt [7] brought an important contribution showing the mathematical hypothesis for the relationship between ICP and intracranial volume, making it easier to understand the importance of intracranial compliance (ICC=ΔV/ΔP) in critical care. Marmarou [8] in 1975 added to the pressure-volume curve the information about the increase in the amplitude of ICPwf as the mean value of ICP increases, and demonstrated that ICPwf contains unique information on intracranial contents, this data has already proven useful in several diseases such as stroke, hydrocephalus, idiopathic intracranial hypertension and brain injuries. It is important for gathering information on cerebrovascular hemodynamics and also of the cerebrospinal compensatory system. In 1983, Cardoso [9] showed that with the increase in ICP, in addition to the increase in the amplitude of its pulse, there was also a change in its configuration, as morphology became pyramidal with an increase in amplitude in the middle region of the pulse. Cardoso also shows the ICPwf configuration: P1 - systolic peak, P2 - tidal wave and P3 - venous return (explained in detail below).

Hu [10], understanding the possibility of using ICPwf as information to aid in diagnosis, created an algorithm called MOCAIP (Morphological Clustering and Analysis of Continuous Intracranial Pressure). This software is able to turn the waveform into numbers to facilitate the interpretation of the medical team. Nucci [11], in 2016, presented results of a software to calculate ICPwf parameters and clusters of waveforms for different stages of pathology.

Ballestero [12] and Bollela [13], in 2017, presented studies with hydrocephalus and meningitis respectively, that showed the applicability of a new noninvasive sensor to monitor the ICPwf, in the Ballestero study the ICPwf was analyzed through the relationship between the amplitude of the P2 and P1 pulses.

ICPwf is an important information, increasingly disseminated among physicians. New methods and analyses facilitate the use of this parameter, which is useful and disseminating over clinical institutions. The next chapters will provide more details and clinical applications of ICPwf.

3. Intracranial pressure- waveform pathophysiology

3.1 Waveform components

ICP is determined by the intracranial components volumes, as the brain tissue, the vascular or cerebral blood flow (CBF) and cerebrospinal fluid (CSF) [14, 15], and relations between them in a semi-rigid skull box, the Monroe-Kellie doctrine. Each cardiac beat corresponds to an ICP waveform composed of three peaks; arterial pulsation- P1, cerebral venous flow, secondary to autoregulation-derived cyclic fluctuations of arterial blood volume, reflecting intracranial compliance- P2, and the aortic valve closure- P3 (**Figure 1a**).

These cardiac-derived pulsatile signals are overlapped in time domain with the respiratory cycle, with influence in the cerebral venous pulsation by means of intrathoracic pressure generated by breathing, disclosed as slow waves [16] (**Figure 1b**). Moreover, ventilation plays a direct and remarkable role over CBF [17]. Thus, ICP is influenced by many physiological factors from extra and intracranial compartments. Moreover, factors as age, body posture, time of day as well as the clinical condition also are considerable variables, although in absence of disturbances, mean ICP is kept mostly within a range between 7 and 15 mmHg for adults, 3 and 6 mmHg in children, and between 1.5 and 6 mmHg in term infants [18].

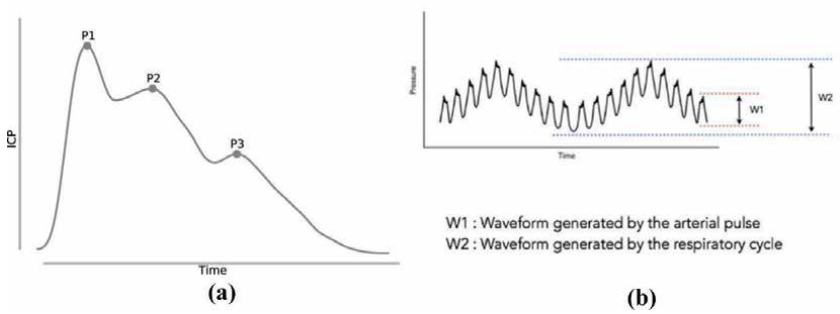

Figure 1.
(a) One single arterial pulse transmitted to the intracranial compartment, with three peaks observed; systolic peak (P1), tidal peak (P2) and aortic valve closure peak (P3). (b) Respiratory slow waves overlapping cardiac intracranial pulses spectrum (from Hall et al. [16]).

There is an existing volume of reserve in the brain which is around 60–80 mL in young persons and approximately 100–140 mL in geriatric population, because of ongoing cerebral atrophy with age. However, in normal conditions and for short time observations, the brain volume is typically static, with mean ICP varying mainly according to the CBF and the balance between production and absorption or outflow of the CSF. The relation observed between these intracranial components is named intracranial compliance (ICC). Compensatory mechanisms exist to maintain intracranial volume homeostasis by extrusion of the CSF or venous blood, in order to preserve ICC, otherwise, these efforts may be insufficient in pathological conditions (i.e. traumatic brain injury) with intracranial hypertension (ICH) and ICC impairment producing primary or secondary brain tissue damage [19, 20].

Langfitt et al. characterized the transmission of pressure across the intracranial compartments as the intracranial elastance curve, observing an exponential behavior between ICP and intracranial volume [21], from a stable ICP vs. volume relation until

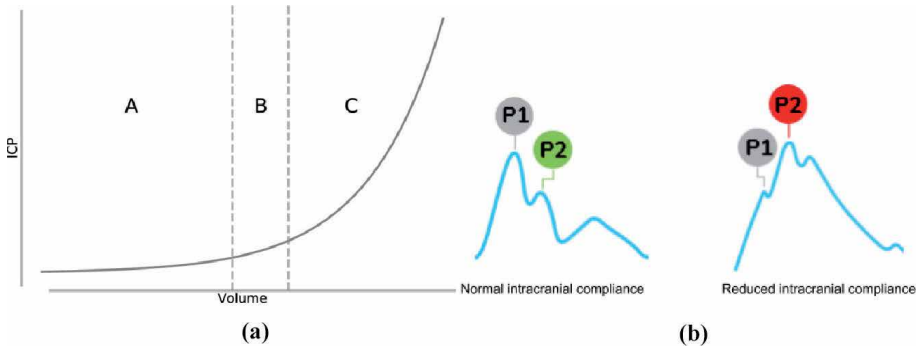

Figure 2.
(a) Langfitt curve representing volume x ICP exponential behavior with A- normal ICC, B- intracranial buffering capacity begins to exhaust and C- ICC impaired with rapid ICP elevation (from Canac et al. [18]) (b) representation of altered ICP curve with ICC impairment.

when a change in volume of any component will result in a commensurate change in ICP (**Figure 2a**). When ICP raises and compromises ICC, an inversion in ICP peaks relations may be observed [9], with ICH transmitted to the venous and ventricular compartments, affecting the buffering mechanisms (**Figure 2b**).

When mean ICP is elevated, the vascular (cardiac) waveform amplitude increases while the respiratory waveform amplitude decreases, associated with changes in the relationship between peaks P1, P2, and P3 [19, 22]. Different waves morphologies could reflect the residual compensatory capacity of the brain, since changes in the ICP wave shape are informative on an incoming or established alteration of the intracranial system (**Figure 3**) [11].

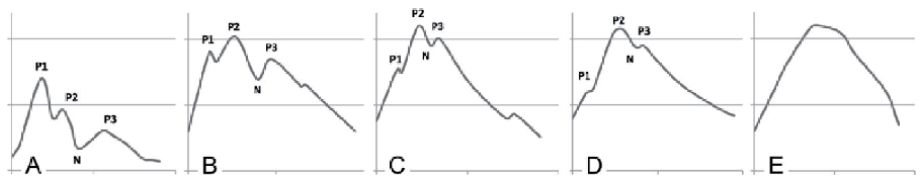

Figure 3.
A - Normal, if the first peak (P1) exceeds the other two; B - potentially pathological, if the tidal peak (P2) equals or slightly exceeds the systolic one (P1) and the dicrotic peak equals or is slightly inferior to P1; class C - likely pathological, if the tidal and the dicrotic peaks exceed the first one; D and E- pathological, if the tidal and the dicrotic peaks surmount the first one or if the shape of the curve is so rounded as not to permit the identification of the three peaks (from Nucci et al. [11]).

3.2 Slow waves

Additionally to all that was explained above, further phenomena in the observance of ICP waveforms may occur with high importance on alerting the neurophysician to initiate ICP control measures on an urgent basis. These phenomena were named slow waves by Lundberg et al., typically described as A, B and C waves (**Figure 4**). The A waves are denoted as plateau waves or vasogenic waves occurring during very high ICP (>50 mmHg), the B waves are short-duration elevations in ICP (1 to 2 per minute) with variable pressure levels up to 30–50 mmHg. C waves are more frequent (about 4–8 waves per minute) elevations of mean ICP (up to about 30 mmHg). A waves are clearly severe and with elevated risk of poor prognosis, whereas the clinical implication of the B waves is a research question that remains to be determined, since they are non-specific

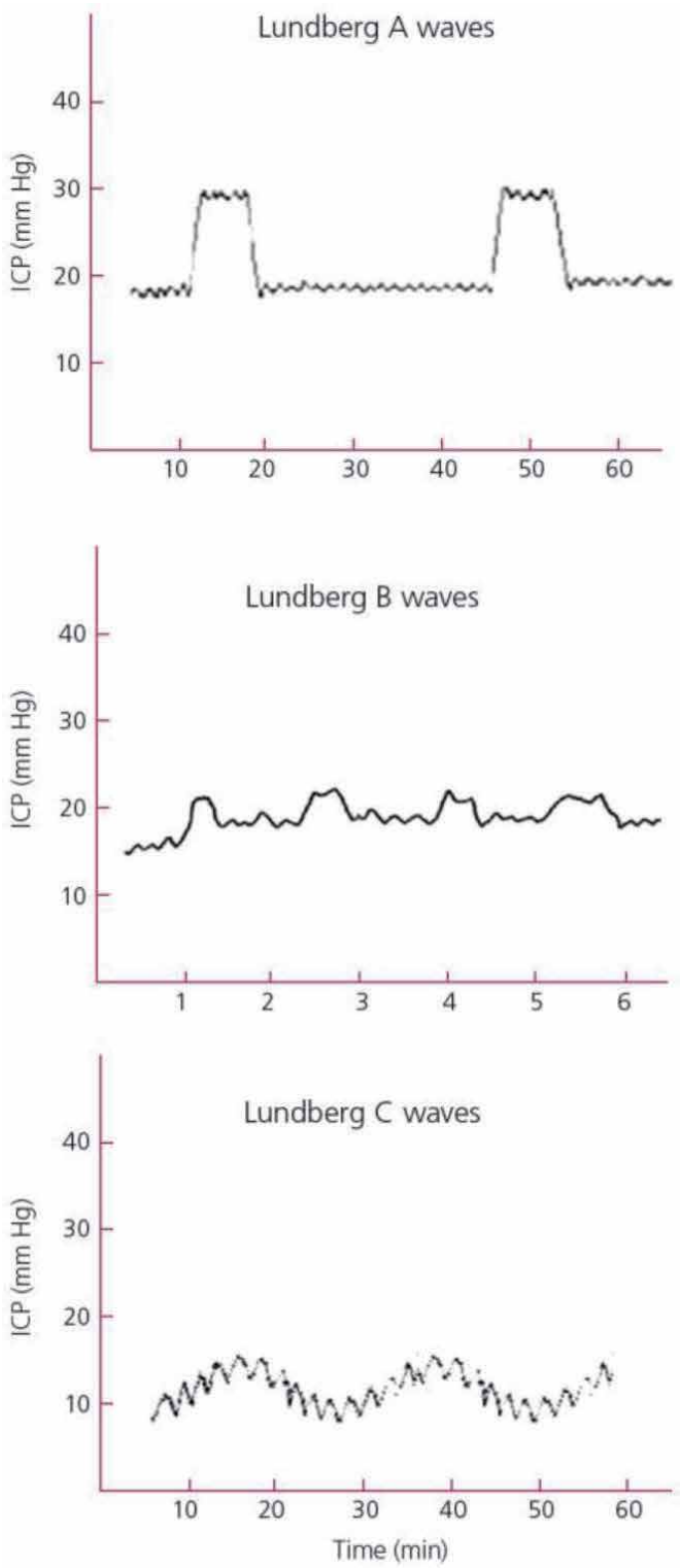

Figure 4.
Lundberg A, B and C waves (from Hirzallah et al. [23]).

indicators of diminished compliance and can also be present in patients with normal ICP [24]. Finally, C waves are products of cardiac and respiratory cycles interactions.

4. Intracranial compliance in real world

The next paragraphs will provide information on how to incorporate waveform information of ICP into clinical daily life, adding this information to the clinical set and adjunct with other diagnostic methods in different pathologies. It is worth mentioning that this information has been shown to be useful in situations where subjects present suspicion, risk or diagnosis of changes in ICC.

4.1 Aneurysm

Non-traumatic subarachnoid hemorrhage (SAH) is a situation that often results from the rupture of an intracerebral aneurysm [25]. SAH is associated with high morbidity and mortality and requires a multidisciplinary treatment, because of its high risk of complications [26].

Upon recognition, improved outcomes are dependent upon treatment by qualified high-volume centers with adequate neurovascular teams. Expeditiously determining the precipitating factor and subsequent mitigation of the cause(s) are the initial primary focus. Treatment involves early securing of a ruptured aneurysm, whether a surgical procedure or endovascular. Prior to securing the aneurysm, securing the airway, maintaining proper circulation, treating hydrocephalus, and managing blood pressure remain top priorities. After intervention, ICU observation and routine exams are compulsory.

Once patients presenting with aneurysmal SAH are acutely stabilized, they are evaluated for pathology-specific complications such as development of hydrocephalus and re-hemorrhage. Various grading scales are employed early in management to communicate the severity and prognosis of the pathology. Following stabilization and initial evaluation, patients should be transferred and admitted to intensive care units with a multidisciplinary team. Interim/short-term acute care strategies are employed to prevent rebleeding, assess hydrocephalus, maintain normotension, and reverse anticoagulant/antiplatelet agents. The risk of acute rebleed and long-term prevention of rebleed is not completely attenuated until aneurysm exclusion is performed.

Concurrent to the those risks above mentioned, in the extreme acute phase (first 48 hours) of SAH, the encephalic microvascular constriction promoted by hemoglobin degradation in the subarachnoid space may lead to a low cerebral blood flow (CBF) phenomena, with potential for brain swelling and ICC impairment. Techniques for monitoring ICC and CBF (such as transcranial Doppler) may play a crucial role in this phase.

Later, in the subsequent SAH phase, an inverse behavior is commonly seen in accordance with bleed severity, the so-called hyperemic phase. In this situation subjects present microvascular dilation, this time leading to ICC impairment for excess of CBF. An optimal therapy here is adapting CBF for satisfactory neuronal supply, under ICC adequate limits.

An additional threat for patients in this phase is the development of vasospasm, a complication which elevates risk of delayed cerebral ischemia, in opportunities needing endovascular management. The latter, associated with medical complications including fever, hyperglycemia, hyponatremia, cardiac and pulmonary complications, deep venous thrombosis and anemia may raise risk of ICC impairment. While scores classifications exist to determine an admission grade in order to provide prognostic information, outcomes are influenced by many additional

items, including a patient's values and preferences, comorbidities, social support, resilience, and time for recovery [27–31].

4.2 Tumor

The incidence and survival of patients with neuro-oncologic conditions have been increasing. Both primary central nervous and other types of cancer patients live longer due to early diagnosis and better treatment options. Global Burden Disease Study in 2016, there were 330,000 incident cases of CNS cancer and 227,000 deaths worldwide that year. It reflects the 17.3% increase in incidence between 1990 and 2016.

Extension of life expectancy and on the incidence of cancer itself predisposes to an increment in the occurrence of a variety of neurologic complications that can result in high morbidity and mortality [32, 33].

These conditions often result in hospital admissions, generally in an ICU bed, creating a heavy burden to the health care system since primary cancer patients' treatment costs 20-times more than age-matched controls without cancer [33].

The complications could occur due to a direct result of the tumor itself, to an indirect effect of cancer, or as a result of chemotherapy, radiotherapy, and other medical interventions. Recognizing the mechanism might help one early diagnosis and initiate treatment. As a mass effect directly, or even a compromise of CSF transit because of ventricle compression, intracranial neoplasm may lead to ICC impairment.

4.3 Traumatic brain injury

The World Health Organization considers traumatic brain injury (TBI) an important global health priority as it is a critical public health problem involving young adults worldwide. The leading causes of TBI are road traffic collisions, falls and interpersonal violence. This injury not only causes a large number of deaths, impairments and disabilities for individuals and their families, but also incurs great economic cost to healthcare systems due to required long-term care, rehabilitation, and loss of productivity [34].

TBI can be classified by clinical severity (mild, moderate, or severe) according to the Glasgow Coma Scale (GCS); pathoanatomic type (focal or diffuse) according to the extent of damaged area; and mechanism of injury (penetrating or blunt) according to the kinematics (**Table 1**) [35–38].

The TBI-related cellular injury involves two different processes. The primary damage occurs on the moment of trauma, immediately by the direct impact and/or structural lesion. It includes vascular and tissue tearing that causes various types of hemorrhage and nerve fibers disruption (axotomy). The secondary damage involves cellular reactive processes such as inflammation and biochemical cascades that gradually develop over the course of hours, days, even weeks after the trauma. It causes metabolic changes potentially leading to brain swelling or hydrocephalus but can also be caused by low blood pressure, hypoxia, seizures, or central nervous system infection [37, 38].

Both processes are intertwined and can contribute to complications, for instance, hemorrhagic progression of a contusion, a breakdown in the blood–brain barrier (BBB), and increased intracranial pressure (ICP). The expansion of an intracranial bleeding not only alters the dynamic shared space of encephalic parenchyma, vascular structures, and cerebral spinal fluid (CSF) inside cranial cavity – inferred intracranial compliance – but also triggers cytotoxic responses of brain cells. In addition, if there is a dysfunction of BBB its permeability changes letting plasma, proteins and proinflammatory mediators influx into the interstitial compartment causing edema, neurotransmitters imbalance, compressing all structures [38, 39].

Classification	Categories	Examples
Clinical severity	Mild	GCS: 13–15
	Moderate	GCS: 9–12
	Severe	GCS ≤ 8
Pathoanatomic type	Focal (one concise area)	Skull fracture Contusion Epidural hematomas Subdural hematomas Subarachnoid hemorrhage Intraparenchymal hemorrhage
	Diffuse (widespread area)	Diffuse axonal injury Concussion Chronic traumatic encephalopathy
Mechanism of injury	Penetrating	Gunshot wound/projectile Pierced object/weapons (knife, etc.)
	Blunt	Head rotation Jolt/blast Acceleration-deceleration

Table 1.
Different classifications of TBI.

As a result of this intricate association the ICP may rise if intrinsic compensatory mechanisms are not preserved and the sustained hypertension can prevent adequate perfusion depriving the brain of oxygen and nutrition. The combination of all situations related to TBI mentioned above need specific and adequate management through the whole trauma assistance from the pre-hospital setting to the critical care unit (CCU) and subsequent rehabilitation [36, 40].

The main method of assessment and management of severe TBI is monitoring and treatment of ICP. It is a level II-B of evidence recommended to reduce in-hospital and 2-week post-injury mortality [23, 41].

Neurocritical care specialists routinely base their clinical reasoning looking at the absolute value of ICP – measured in mmHg or cmH2O – combined with imaging exams – CT-scan or MRI. However, the numbers may not translate the entire complexity of intracranial dynamic. It is suggested that the ICP waves and the study of its morphology could bring differential evidence of altered intracranial compliance and changes of pressure regimen [14, 23, 42, 43].

A qualitative analysis of the ICP waveform [44] described the relationship between amplitude of ICP pulse wave, values of ICP, values of cerebral perfusion pressure (CPP), and the outcome of severe head-injured patients. Intracranial hypertension was evidenced by absolute values of ICP and CT-scan parameters. In those with fatal outcomes there was an increase in the ICP waveform amplitude along with an increase of ICP value up to 25 mmHg, however, above this value the amplitude began to decrease. This breakpoint trend in the amplitude-value relationship was not present in patients with good/moderate outcome. Thus, it is suggested that the physics involving ICP, CPP and parenchyma dynamics inside intracranial cavities was somehow translated into the waveforms, and its analysis and correlations could be a useful additional tool for outcome prediction.

Another study [45] involving TBI patients described the ICP plateau waves characteristics using multimodal brain monitoring as well as calculated indices of brain compensatory reserve and cerebrovascular reactivity. Plateau waves are associated with working cerebrovascular reactivity and occur in situations of

decreased volume-pressure compensatory reserve such as TBI and many other brain pathologies. It consists of sudden increases in ICP to peaks of 40-100 mmHg that persists for 5–20 minutes [14, 45, 46]. The study observed plateau waves in 44% of the patients and that abrupt increase of ICP above 40 mmHg was associated with an increase in amplitude of ICP pulse waveform and also with important decrease in CPP, cerebral blood flow and oxygenation, despite stable cardiovascular variables of arterial blood pressure and heart rate (**Figure 5**) [45].

When analyzing ICP pulse waveform during plateau waves, a statistically significant increase in amplitude and a change in its shape were noted. The ICP pulse components (P1 < P2 > P3) showed altered ICC [45] (**Figure 6**).

Although slight increases in ICP that last for short period are not usually associated with poor outcome, if plateau waves are sustained over 30 minutes it could have a negative impact on patient's recovery as intracranial hypertension compromises cerebral perfusion and implicates neuronal deterioration [14, 23, 42, 43, 46]. The analysis of ICP absolute values and waveform patterns over time could provide important information for early detection of ICH in TBI patients of the mentioned study [45].

The debate about how ICP waveform analysis could provide improved clinical benefit and a more actionable evidence to bedside addresses integrated metrics on brain's intrinsic compensatory capacity (autoregulation) and oxygenation, besides computational analysis of multiple continuous streams of neuro-monitoring data and equipment development to easily display this information [14, 23, 42–46].

In this way, non-invasive techniques are coming forward to give quick ICP information to neurocritical care team, including transcranial Doppler, optic nerve sheath diameter, near-infrared spectroscopy, tympanic membrane displacement, visual-evoked potentials, some other measurements of the optic nerve,

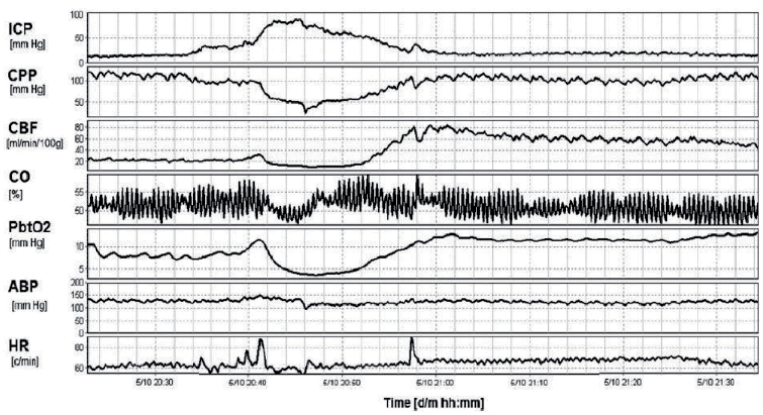

Figure 5.
Example of multimodal brain monitoring recording during plateau wave, extracted from Dias et al. [45].

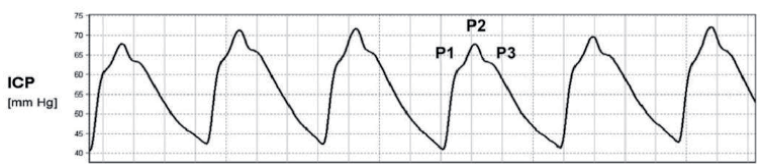

Figure 6.
Altered ICP pulse waveform indicating compromised intracranial compliance, extracted from Dias et al. [45].

retina, and pupil, besides the routinely used imaging exams of CT-scan and MRI [23, 42, 43, 45]. There is also a new non-invasive method of ICP monitoring that provides morphological data of ICP waves and intracranial compliance, adding celerity to this multimodal scenario [47, 48].

It is well established that ICH is an important issue after TBI because of its relationship to overall outcomes and all guidelines recommend a comprehensive ICP assessment – either invasively or non-invasively. Information about absolute values and waveform characteristics of ICP may together contribute to direct optimal management of TBI and good patient care [23, 42, 43, 45, 47, 48].

4.4 Increased ICP outside ICU environment

The brain constitutes approximately 80% of intracranial volume, and blood and CSF each account for 10% [49–51]. The first compensatory mechanism for maintenance of normal ICP involves displacement and reduction of the CSF compartment, reduction of CBF, and lastly, displacement of cerebral parenchyma causing herniation. The slower the increment in ICP, the more useful this regulatory system. Therefore, rapidly growing masses like malignant gliomas have a higher risk of causing brain herniation than slow-growing tumors like meningiomas or nerve sheath tumors [52].

Transient elevation in ICP, generally from 50 to 100 mmHg and 5 to 20 minutes, leads to plateau wave phenomena. It can occur spontaneously or start after coughing, sneezing, or changes in position. This transient intracranial hypertension period may be accompanied also by transient headache, transient alteration of the level of consciousness and focal deficits [49, 50].

Obesity and its relation with sleep apnea obstructive syndrome may show ICC impairment due to overnight hypercarbia leading to cerebral vasodilation. Also, this population is likely to develop chronic idiopathic intracranial hypertension. Moreover, hydrocephalus patients of any etiology, migraineurs, progressive neurological focal and/or gait disorders, all these situations mentioned here for outpatients practice raise the yellow sign on the need for ICC evaluation.

5. Conclusions

Advances on cerebral hemodynamics and intracranial compliance understanding brought to light by recent researches have made monitoring of these properties an essential practice in critical care. Likewise, advances in technology may convert intracranial compliance in a new vital sign present in daily practice in a near future.

Author details

Gustavo Frigieri[1*], Cintya Yukie Hayashi[2], Nicollas Nunes Rabelo[2] and Sérgio Brasil[2]

1 Scientific Department, Brain4care, São Paulo, Brazil

2 Department of Neurology, University of São Paulo, São Paulo, Brazil

*Address all correspondence to: gustavo.frigieri@brain4.care

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Chapter 2

Peripheral Immune Response Following Traumatic Brain Injury

Amanda Hazy, Elizabeth Kowalski, Nathalie Groot and Michelle Theus

Abstract

Traumatic brain injury (TBI) represents a leading contributor to long-term neurological damage. Though TBI is a leading cause of death and neurological damage worldwide, there exists no therapeutic treatments to alleviate deleterious secondary injury due to neuroinflammation. The continuum of pro- and anti-inflammatory response elicited by TBI is suggested to play a key role in the outcome of TBI; however, the underlying mechanisms remain poorly defined. This chapter explores rodent models of injury used to study the disease pathology of TBI, as well as the major contributions of the peripheral immune response following injury. Further, this chapter discusses the influence of individual immune cell types on neuroinflammation following TBI, focusing on peripheral monocyte/macrophages, their polarization state, and the current literature surrounding their behavior within the TBI milieu. Finally, cell-to-cell contact regulators that effect peripheral-induced neuroinflammation and may serve as novel targets for therapeutics will be highlighted.

Keywords: inflammation, monocytes, traumatic brain injury, blood-brain barrier

1. Introduction

Traumatic brain injury (TBI) is a leading cause of morbidity and mortality in the United States and worldwide [1–4]. TBI results from an injury to the brain following exposure to external physical forces including falls, car accidents, explosive blasts, and assault [5, 6]. These injuries often have long-term consequences to the health of injured individuals, and few effective treatments are currently available [6]. The pathophysiology is characterized by damage to the neuronal and glial cells of the brain as well as the associated vasculature [6], and the role of inflammation as a causative agent of tissue injury has emerged as a focus of TBI research [7]. Preclinical research focusing on the mechanisms underlying secondary inflammation and treatment of TBI employs various animal models [8]. This review will discuss TBI as a public health problem, the pathology of TBI and the significance of the peripheral immune response in the outcome of TBI in human and animal models.

2. Prevalence of TBI

Traumatic brain injury is a major cause of death and disability in the United States and worldwide [1–4]. An estimated 69 million people sustain a TBI each year

around the world [9]. In the United States, incidence of TBI has risen steadily over recent years. An average of 1.7 million TBIs occurred per year from 2002 to 2006 [1], but an estimated 2.8 million TBIs occurred in 2013 [4]. There is a gender disparity in groups most affected by TBI—in the United States, males are more commonly affected than females. Age group differences are also evident in TBI prevalence, with young children, young adults, and the elderly most frequently suffering from TBI. The specific age groups that most commonly sustain TBIs are ages 0–4 years, 15–24 years, and 75 years and older [4]. Traumatic brain injuries arise from a variety of causes including traffic accidents, falls, abuse, sports injuries, and traumatic impact with an object [4, 5]. The most prevalent causes of injury vary predictably with patient age. Injuries in younger patients are most commonly associated with sports activities or high-risk behaviors such as distracted driving, while injury in the older population of patients is more frequently associated with falls [5]. These events cause injuries of a range of clinical severities including mild, moderate, and severe TBI. In the clinical setting, these injuries are most frequently classified using the Glasgow Coma Score (GCS) [10]. The GCS assesses overall consciousness of the patient and classifies injury severity based on eye, motor, and verbal responses to stimuli [5, 10]. Scores range from 3 to 15. Higher scores correlate with decreased injury severity—for clinical classification purposes, a GCS range of 13–15 has been used to demarcate mild injury, 9–12 for moderate injury, and 8 or less to indicate severe TBI [5]. Imaging modalities including CT and MRI are also used to further assess the severity of TBI and inform prognosis [10].

3. Pathology of TBI

A traumatic brain injury may be defined as an injury to brain tissue caused by direct external force [10]. The physical impact of TBI initiates a plethora of downstream processes with deleterious effects on neuronal and glial tissue. Overall, the pathophysiology of a TBI can be divided into primary and secondary phases of injury [5, 10–12]. The primary phase of injury includes the cellular damage caused at the instant of injury by the direct mechanical impact of trauma. Primary injury can manifest as cell death, hemorrhage, and/or diffuse axonal injury. First, neurons and supporting vasculature can be directly torn by the shear forces of injury. This damage to the neurovascular network results in intracranial hemorrhage, which can lead to increased intracranial pressure as blood builds up inside the skull. Intracranial bleeding can also generate hematomas. Both increased intracranial pressure and hematoma formation have negative impacts on neural recovery [11, 13]. Primary injury can also encompass diffuse axonal injury. Diffuse axonal injury is damage to neurons going beyond the initial lesion area, caused by dynamic forces spreading through the brain from the primary impact [11]. These physical forces resulting from traumatic brain injury can be either linear accelerational forces or rotational forces. Since neural tissue is elastic and does not have a strong internal structure, the brain has little tolerance for this disruption and is very susceptible to injury from these forces [12]. Primary injury also disturbs autoregulation of cerebral blood flow and cellular metabolism. Normal control mechanisms for blood flow and metabolism fail due to the cellular damage of TBI, resulting in cellular effects similar to those seen in ischemic stroke. As the massive damage overwhelms cellular metabolism, ATP production cannot match demand, and neuronal and glial supplies of ATP become inadequate to fuel cellular ion pumps. The resulting dysregulation of ion flow initiates various downstream pathways leading to necrosis, apoptosis, and oxidative damage [14]. Additional mechanisms of secondary injury have been described and

include the long-term changes resulting from the physiological processes triggered by the primary phase of injury [12].

3.1 Neuroinflammation

Neuroinflammation plays a major role in the secondary phase of injury. While all resident brain cells are involved in some way in the response to TBI, the role of microglia, the resident immune cells of the brain, in neuroinflammation has been particularly well-studied. When brain injury occurs, cells damaged in the primary phase of injury release cell signals known as damage-associated molecular patterns (DAMPs). In the early stages of injury, resident microglial cells are activated by these DAMPs and migrate to the injury site [7, 15]. These cells have a profound effect on both acute and chronic injury processes as they secrete both pro- and anti-inflammatory cytokines and can remain activated for up to 18 years after TBI [7, 16]. Cytokines released by microglia have a plethora of effects including alteration of local blood flow and modification of the blood-brain barrier (BBB) [15]. Microglia also assist in walling off the injured area in a protective effort to prevent the spread of bleeding and cellular damage. However, these cells can also generate additional reactive oxygen species (ROS) with damaging effects on cells [17]. While glial cell activation is a key part of the secondary phase of TBI, there is also an important role for the peripheral immune system in TBI recovery. The central nervous system is typically viewed as an immune-privileged site, with few or no peripheral-derived immune cells present. However, following TBI, the blood-brain barrier is damaged, allowing infiltration of peripheral-derived circulating immune cells including neutrophils, macrophages, and lymphocytes [17]. Glutamate excitotoxicity, oxidative stress, and neuroinflammation all contribute to the cellular damage observed in the secondary phase of injury, and the long-term damage resulting from these processes can be extensive. This secondary phase of injury is the primary target for TBI therapeutics—while efforts can be made to reduce TBI incidence, once a TBI has occurred nothing can be done to treat primary injury. Therefore, potential TBI treatments are aimed at reducing damage from the secondary phase of injury [14].

4. Rodent models of TBI

Multiple rodent models have been used to study the role of inflammation in TBI. Due to the variety of injury causes and individual patient health effects, human TBI exhibits multifaceted disease processes, and different animal models are used to recapitulate different aspects of human injury. Here, we discuss three common mouse models of TBI: weight drop, fluid percussion injury (FPI), and controlled cortical impact (CCI). All three of these models generate TBI by direct impact, either applied directly to the brain through a craniectomy or applied to the intact skull. While each of these models replicate certain features of human TBI, no one model fully expresses the varied picture of clinical TBI.

- Weight drop and fluid percussion injury are both used to produce diffuse injury in rodent models of TBI. Weight drop injury relies on gravity-driven fall of the weight to generate injury. Injury severity can be controlled by adjusting both the height of the drop and the mass of the weight used. Modification of injury severity allows this model to reproduce features of mild, moderate, or severe TBI. Weight drop injury results in cortical cell death, cerebral edema, neuroinflammation, and blood-brain barrier compromise, and this method of

injury is relatively time-efficient to perform [18, 19]. In addition, weight drop injury results in demonstrable cognitive deficits, which may reproduce features of human TBI [20].

- FPI can also reproduce certain histological features of human TBI and can be modified to generate different severities of injury. The FPI method is one of the most commonly used models of experimental TBI and can be adjusted to generate mild, moderate, or severe TBI [21]. Fluid percussion injury is performed using the injection of fluid into the cranial cavity, generating injury as a pressure wave spreads through the fluid applied to the brain [8, 22]. This model results in cortical contusion, hemorrhage, inflammation, diffuse axonal injury, and gliosis, with accompanying memory and motor deficits [21, 23, 24]. Application of FPI causes both focal and diffuse damage to the brain and has been used to assess multiple prospective TBI therapeutics [25].

- CCI generates injury by application of a mechanical focal impact to the brain using a controlled piston. This technique was initially developed to replicate features of injuries caused by automobile accidents but is now commonly used to study multiple aspects of focal TBI pathology [26]. Controlled cortical impact machines allow modification of the depth, velocity, dwell time, and angle of the impact, as well as variation of the size and shape of the impactor tip. These highly reproducible features make the CCI model especially well-suited to induce a wide range of injury severities, and the tight control of injury parameters is an important advantage of this model [26, 27]. The CCI method of experimental TBI typically includes a craniotomy before impact to the intact dura mater, although this method can also be used to produce closed-head injury [27]. Injury induced by CCI replicates many histopathological changes seen in human TBI, including cortical contusion, blood-brain barrier compromise, inflammation, and oxidative stress [26]. Corresponding to the histological features observed in this model, CCI results in functional deficits, including memory, learning, and motor deficits similar to those observed in human TBI patients [26]. These deficits are observed in both the acute and chronic periods, while other models including FPI less frequently report the chronic persistence of cognitive deficits [27]. The CCI model also has an overall higher survival rate compared to the fluid percussion model [26]. The reproducibility, tight control of experimental parameters, persistence of cognitive deficits, and high survival rate induced by CCI make it an excellent model for TBI research. For these reasons, the work outlined in this dissertation takes advantage of the CCI model.

5. Peripheral-derived immune cell response to TBI

The peripheral-derived immune cell response is a key feature of the physiologic response to traumatic brain injury, which can have both positive and negative effects. The central nervous system is typically regarded as an immune-privileged site due to the action of the blood-brain barrier (BBB), which prevents peripheral immune cells from readily entering CNS tissue [7, 15]. However, following TBI, the integrity of the blood-brain barrier is compromised by a variety of mechanisms, allowing infiltration of peripheral-derived immune cells into brain parenchyma [28]. Various immune cells including neutrophils, macrophages, and lymphocytes have been shown to infiltrate the lesion area following injury, releasing cytokines that influence recovery [17]. These peripheral immune cells have a profound effect on injury recovery—impact of these infiltrating cells can be either beneficial or

deleterious to recovery depending on the specific cells and mechanisms involved. While all of these cell types may affect TBI recovery, macrophages in particular have been a focus of TBI research [29]. This review will discuss the general mechanisms of blood-brain barrier compromise after TBI and survey the effects of peripheral immune cell infiltration, with a focus on macrophages.

5.1 Blood-brain barrier compromise and immune cell infiltration in TBI

The blood-brain barrier (BBB) forms a protective layer separating the CNS from the surrounding environment, including circulating peripheral immune cells. The brain is typically regarded as an immune-privileged site due to the operation of the BBB—under normal physiologic conditions, peripheral immune cells in the vasculature cannot enter CNS tissue [7, 15]. The healthy brain exists in a tightly regulated system, and proper operation of the BBB is critical in maintenance of the correct microenvironment for healthy neural function [30]. Multiple cell types including brain endothelial cells, astrocytes, and pericytes compose the BBB [30]. Traumatic brain injury compromises the BBB by direct damage to the cells composing this barrier. The direct damage to cerebral vasculature and disruption of endothelial tight junctions allows entry of immune cells and proteins from the vasculature into cerebral tissue [28, 31]. Rising calcium concentrations activate caspases in endothelial cells, initiating apoptosis of brain endothelial cells and resulting in additional damage to the BBB [28]. The glutamate excitotoxicity observed in TBI also has been shown to increase production of reactive oxygen and nitrogen species (known as oxidative stress), causing further apoptosis of brain endothelial cells [31]. Reactive oxygen species can also increase migration of peripheral monocytes through up-regulation of cellular adhesion molecules [31]. The physical damage to brain endothelial and glial cells combined with the activation of apoptotic and stress-related pathways in the endothelium that disrupt tight junctions can increase BBB permeability, allowing circulating peripheral immune cells to enter the brain. Massive influx of peripheral immune cells, induced by brain-derived cytokine release (IL-6, TNF, IL-1β, etc.) at the lesion area over time, further contributes to BBB damage. Additional cytokine, matrix metallopeptidase (MMP), and reactive oxygen species (ROS) released by activated neutrophils and monocyte/macrophages further disrupt the BBB via down-regulation of tight junction proteins as well as through recruitment of additional inflammatory cells [28, 31–34]. An overview of the major peripheral immune cell response is depicted in **Figure 1**.

5.2 Immune cell-specific contribution to TBI

Neutrophils: Neutrophils arrive at the lesion area in the early stages of injury—these cells migrate to the area of injury and infiltrate damaged brain tissue within the first 24 hours postinjury [33]. These cells are recruited by the release of IL-8, a chemoattractant cytokine known to be generated in the early stage of TBI [35]. Numbers of circulating neutrophils rise significantly in the acute phase of TBI. One study found that neutrophils present following TBI appear to be less susceptible to apoptosis than neutrophils in uninjured patients, which may contribute to the increased numbers observed [36]. In contrast to the few studies implicating a positive role for neutrophils in TBI recovery [33, 37], numerous show deleterious effects. One study, using the CCI model, found that neutrophil depletion improved tissue recovery. Neutrophil-depleted mice in this study showed decreased cell death and tissue loss following TBI [38]. Another study assessed the effects of decreased immune cell infiltration following TBI via administration of anti-intercellular adhesion molecule 1 (ICAM1) antibody in a fluid percussion model of rat TBI. Rats given anti-ICAM1

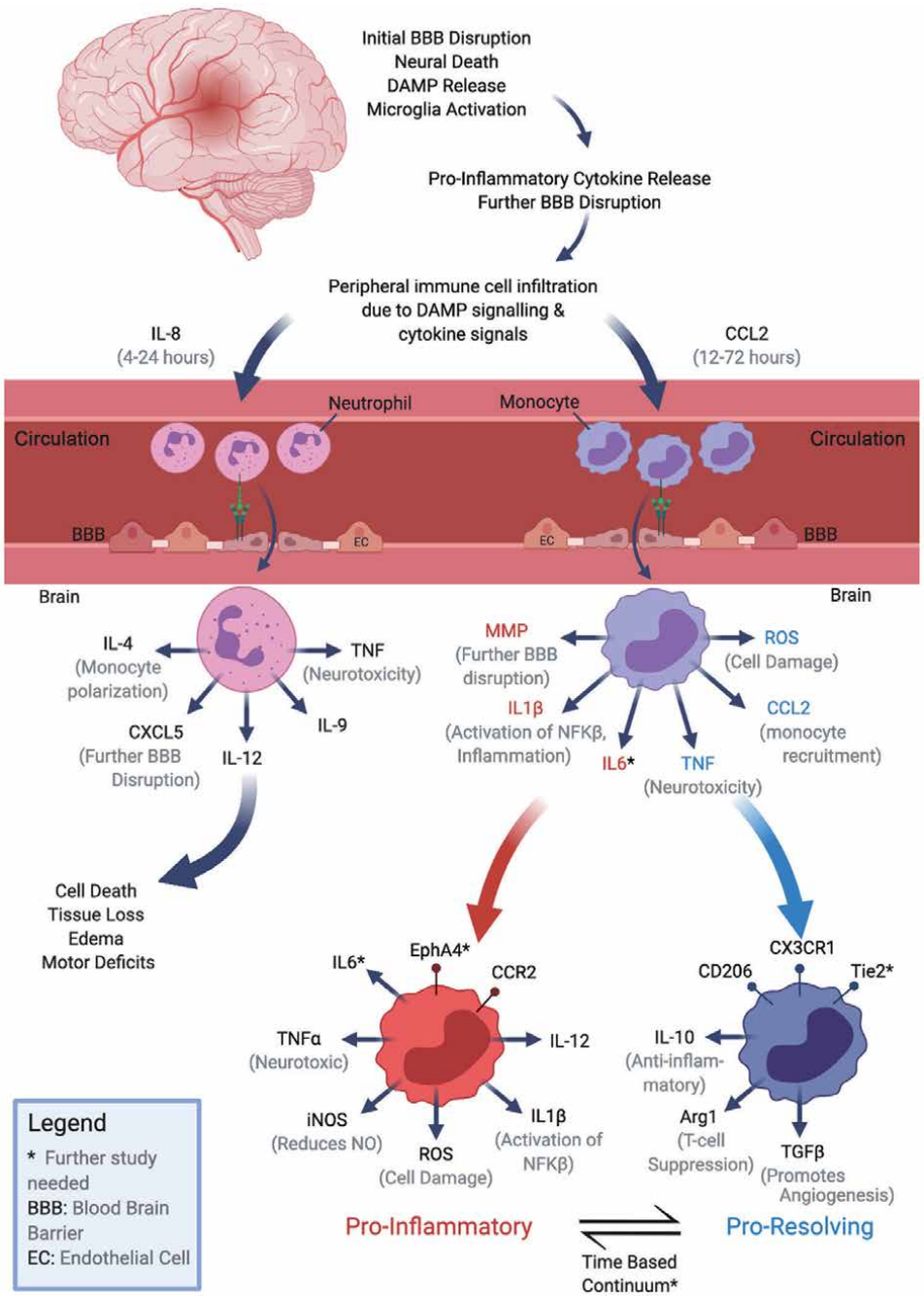

Figure 1.
Overview of major peripheral immune cell response to TBI.

showed decreased neutrophil infiltration following injury 26 hours following TBI, which correlated with increased motor recovery [39]. Several mechanisms have been suggested to explain these negative effects. Some studies have indicated that neutrophils bind endothelial cells and platelets after TBI, decreasing blood flow and promoting ischemia [33]. As previously mentioned, neutrophils can also damage the BBB through release of MMPs and reactive oxygen and nitrogen species [33]. In addition, many of the cytokines generated by neutrophils following TBI have been

shown to have negative effects on neural recovery. These cytokines include IL-9, IL-12, CXCL5, and TNFα. IL-9 can increase the damage caused by excitotoxicity following TBI, and high levels of IL-12 have been correlated with poor postinjury outcome (**Figure 1**). CXCL5 contributes to BBB compromise, and TNFα plays a role in neurotoxicity [33]. However, other studies have found that infiltration of peripheral cells in the acute stage of injury has little effect on recovery, suggesting instead that infiltration of peripheral-derived monocytes in the later stages of injury (greater than 48 hours after injury) has the greatest influence on injury progression [7].

Monocytes: The role of monocyte/macrophages has been particularly well-studied in regard to the effects of infiltrating peripheral-derived immune cells after TBI. Although a minority in terms of numbers of circulating immune cells, composing only 5–10% of the peripheral immune cell population, monocytes play an important role in TBI recovery [36]. Monocytes are the primary infiltrating immune cells observed at 3–5 days following injury [29]. While some studies have even argued that peripheral monocytes are the most prominent infiltrating immune cell at 24 hours postinjury as well [40]. Circulating monocytes can display pro- or anti-inflammatory properties. When monocytes migrate into affected tissue, they mature into macrophages with pro- or anti-inflammatory characteristics [36]. These cells can have a neuroprotective effect via phagocytosis of dead cell debris, release of growth factors, and production of anti-inflammatory cytokines. Monocyte/macrophages also release granulocyte-macrophage colony-stimulating factor (GM-CSF), which may have a neuroprotective effect through promotion of stem cell differentiation and suppression of apoptotic pathways [41]. However, monocyte/macrophages may have differing effects on TBI recovery depending on their inflammatory profile.

While monocyte/macrophages may be beneficial in some aspects of TBI recovery, other studies have found that these cells may also negatively affect neural recovery through different mechanisms. One study assessed the influence of macrophages on TBI recovery using a chemokine CC ligand-2 (CCL2) knockout mouse model. This study found increased levels of CCL2 following TBI in both human patients and in a murine weight drop injury model. CCL2 knockout mice showed decreased macrophage accumulation and smaller lesion volumes at 2 and 4 weeks after injury [42]. One study showed that depletion of monocytes using clodronate liposomes decreased neutrophil infiltration and edema and resulted in improved neurobehavioral recovery [43]. Several mechanisms have been suggested by which macrophages could exert neurotoxic effects. Infiltrating macrophages may release reactive oxygen and nitrogen species, increase additional recruitment of neutrophils and monocytes, and generate multiple pro-inflammatory cytokines including TNF, IL-1β, and IL-6 (**Figure 1**) [41]. The apparent discrepancy between the neurodegenerative and pro-resolving effects of macrophages following TBI is most likely due to the release of both pro- and anti-inflammatory signals from these cells, with corresponding positive or negative effects [29]. As previously mentioned, monocytes are capable of maturing into macrophages with either pro- or anti-inflammatory characteristics [36]. These two populations are traditionally defined as M1 (pro-inflammatory) and M2 (anti-inflammatory) macrophages. Although the overall balance between these phenotypes is driven by injury processes [44], their differential characteristics and the mechanisms underlying their fate choice remain under investigation.

6. The M1/M2 continuum in TBI

Monocyte/macrophages display different phenotypes depending on the cellular microenvironment. Classical macrophages, called M1 macrophages, specialize in promoting inflammation and phagocytosing pathogens. The second class of

macrophages, called M2 macrophages, serves to promote tissue recovery [45]. Macrophages are a critical part of the tissue repair process following injury, but these cells can be either helpful or damaging depending on M1/2 status. Following TBI, macrophage polarization toward the M1 phenotype has been associated with neurodegeneration, while polarization toward the M2 phenotype has been shown to reduce oxidative stress [46]. However, these classes are not absolute—macrophages respond to their cellular environment to become more or less M1/2, existing on a continuum with M1 and M2 subcharacteristics at either end [45]. The varied expression of M1 pro-inflammatory vs. M2 pro-recovery traits can be a critical factor in recovery during the peripheral-derived inflammatory response to TBI.

6.1 Classical role of macrophages as pro-inflammatory cells in TBI (M1 phenotype): time course

The classically activated or M1 phenotype macrophages are known to function as pro-inflammatory cells. Early studies indicated that these cells become activated by a combination of IFNγ signaling and either direct TNF signaling or Toll-like receptor-induced production of TNF, usually triggered by lipopolysaccharide (LPS) [47]. In the typical response to wound healing outside the CNS, these cells are important in protection against bacterial infection. M1-polarized macrophages generate reactive oxygen species and also activate inducible nitric oxide synthase (iNOS) to generate nitric oxide as well as an array of pro-inflammatory cytokines including IL-12, TNFα, IL-6, IL-1β, and nitric oxide [47, 48]. Identification of M1 macrophages is typically done by measuring gene expression of characteristic markers including IL-12, IL-1β, iNOS, TNFα, and IL-6 [46]. High levels of CCR2 with low CX3CR1 expression have also been used as an indicator of pro-inflammatory status in macrophages [49]. Bystander tissue damage from M1 macrophages can be catastrophic in the normally immune-privileged setting of the CNS.

Peripheral-derived macrophages have been shown to rapidly infiltrate the injured brain within the first 1–3 days postinjury [46]. Although both M1 and M2 macrophages are likely present at this stage, early studies of macrophage polarization following TBI indicated that the M1 phenotype predominates in the *initial response* to brain trauma [48]. CCI-induced increase in expression of pro-inflammatory markers has been demonstrated as early as 6 hours following injury, suggesting that macrophages expressing M1 traits are a key part of the acute response to TBI [46]. One study found that increases in the number of IL-12-expressing macrophages/microglia were evident by 24 hours following CCI injury, and the number remained increased compared to sham controls out to 7 days postinjury [46]. Other work demonstrated that either macrophages polarized toward the M1 phenotype or a transitional phenotype between M1/2 (to be discussed later) become predominant over M2 phenotype by 7 days following CCI injury. This phenomenon correlates with neurodegeneration [46].

Based on these reports, macrophages seem to be skewed toward the M1 phenotype for an extended period following CNS injury, with corresponding negative effects on recovery. This contrasts with the typical immune response outside neural tissue, where an early increase in M1 macrophages gives way to pro-recovery M2 macrophages [46]. The neurotoxic effect of M1 macrophages is most likely mediated by pro-inflammatory cytokines. Levels of M1-associated pro-inflammatory cytokines transiently increase in brain tissue during the acute response to injury. Specifically, IL-1β, IL-6, and TNFα levels have been shown to significantly increase in brain tissue by 12 hours postinjury in a mouse model. These cytokines return to sham levels by 7 days postinjury [50]. Support for the importance of these cytokines as mediators of M1-induced secondary neural damage following TBI is provided by a study targeting

these cytokines as a potential TBI therapeutic. For example, treatment with Minozac, an inhibitor of pro-inflammatory cytokines, ameliorated the TBI-induced increase of pro-inflammatory cytokines in cortex and hippocampus and resulted in decreased neuronal damage and improved neurocognitive function following TBI [50].

6.2 Pro-resolving macrophages in TBI (M2 phenotype): time course

The alternatively activated or M2 phenotypic macrophages are known to serve as pro-recovery or anti-inflammatory cells. These cells are activated by IL4 and serve an immunoregulatory function, in contrast to the microbe-killing function of their M1 counterparts [47]. Like M1 macrophages, identification of M2 macrophages employs gene expression levels of a wide array of characteristic markers. Markers commonly used for this purpose include CD206, Fizz1, Ym1, IL1-RN, Arg1, TGFβ, SOCS3, and IL4-RA [46]. Low levels of CCR2 with high CX3CR1 expression have also been used as a marker for pro-repair macrophages [49]. Studies using these markers have demonstrated an important role for M2-polarized macrophages at multiple time points following TBI. Increases in M2 markers have been shown as early as 6 hours following CCI injury [46]. The reported timeline of M2 influence varies depending on the specific markers assessed. For example, the number of TGFβ-expressing macrophages/microglia has been demonstrated to increase by 24 hours post-CCI injury and remain elevated compared to sham out to 7 days following injury [46]. Increase in expression of Arg1 has also been demonstrated in macrophages/microglia following CCI. Interestingly, the increase in Arg1 expression in macrophages/microglia, which first becomes evident at 24 hours post-CCI, continues to rise out to 7 days postinjury rather than decreasing back toward normal levels as was observed for TGFβ [46]. Expression of CD163, another marker of the pro-resolving M2 phenotype, has also been investigated following TBI. One study showed increased expression of $CD163^{+}$ macrophages following weight-drop TBI in a rat model. This may have anti-inflammatory effects following TBI through suppression of the pro-inflammatory macrophage phenotype [51]. While timing of expression of specific markers can vary, these studies indicate that macrophages expressing M2 phenotypic traits are a significant factor in TBI recovery.

Macrophage polarization toward the alternatively activated or M2 phenotype has beneficial effects on recovery following TBI through a variety of mechanisms. M2-polarized macrophages are characterized by expression of multiple markers including arginase 1 (Arg1), CD206, CD301, resistin-like α, and PDL2 [48]. Alternatively activated macrophages have been shown to decrease T-cell proliferation, promote angiogenesis, assist in generation of extracellular matrix components, and benefit wound healing and tissue repair [47]. In addition, the anti-inflammatory cytokines TGFβ and IL10 secreted by alternatively activated macrophages help to decrease activation of classical macrophages, reducing bystander tissue damage [47]. One study demonstrated that experimentally altering macrophage/microglia phenotype to favor M2 polarization by inhibition of NOX2 results in decreased oxidative damage [46]. In another report, inhibition of high-mobility group box 1 (HMGB1) decreased M1 and increased M2 polarization of macrophages/microglia, which correlated with decreased lesion volume and improved recovery [52]. Moreover, activation of the cannabinoid receptor CB2R decreased M1 and promoted M2 macrophage polarization, accompanied by decreased edema and improved blood flow and behavioral recovery [53]. These studies employed different methods to influence macrophages toward the M2 phenotype with similar results—*increased expression of M2 traits has a positive impact on TBI recovery.* Additional studies are needed to confirm this beneficial role of M2 macrophages in TBI.

7. Continuum of expression between M1/2 and influence on TBI

As previously mentioned, macrophages *in vivo* do not always show a sharply demarcated M1 or M2 phenotype. Several studies have shown expression of both M1 and M2 traits in macrophages following TBI, while others have demonstrated that macrophages can switch between phenotypes [54, 55]. One study using the CCI model demonstrated co-expression of iNOS, a classical M1 marker, with Arg1, an M2 marker, in perilesional macrophages/microglia following injury [46]. Another study assessed expression of a wide array of pro-inflammatory (associated with M1) and anti-inflammatory (associated with M2) genes in mouse cortical tissue following CCI injury and found that both sets of genes are co-expressed at 1, 2, and 7 days postinjury. This study also showed that perilesional microglia/macrophages co-labeled with both M1 and M2 markers at all three time points [56]. A different study using flow cytometry to sort Arg1-positive and Arg1-negative brain macrophages following TBI demonstrated that neither $Arg1^+$ or $Arg1^-$ cells displayed gene expression profiles consistent with the M1 or M2 patterns defined by *in vitro* studies, although two distinct populations of macrophages did seem to exist in this context [48]. These findings suggest that the classic M1 and M2 traits may actually coexist in the same macrophages following TBI. To confirm this at the level of the individual macrophage, one study employed single-cell RNA sequencing to assess the expression of classical and alternative markers in individual macrophages 1 day following TBI. This work demonstrated that traditional M1/2 markers are frequently co-expressed at high levels in the same cell [55]. This study also demonstrated that high expression of well-known M1 or M2 markers did not seem to down-regulate expression of markers of the opposite class. Some macrophages with high expression of Arg1, an established M2 marker, also displayed high expression of TNF and/or IL-1β, known M1 markers [55]. This type of M1/2 combination profile was displayed in a variety of genes, demonstrating that macrophage polarization *in vivo* can widely differ from the traditional M1/2 paradigm established primarily by *in vitro* studies [55]. Surprisingly, this study actually failed to find any macrophages that fit entirely within the M1 or M2 category, suggesting that all macrophages responding to TBI respond to injury stimuli along a continuum of expression [55]. Intermediate macrophage phenotypes with traits of both M1 and M2 have also been found in studies of spinal cord injury and Alzheimer's disease [46]. The results of these studies indicate the existence of a continuum between M1 and M2 macrophages in the setting of brain injury and disease.

The specific stimuli and mechanisms involved in the continuum of M1/2 expression are currently areas of active research. Some authors have suggested that dual expression of M1 and M2 characteristics is a necessary part of the macrophage response to TBI, as these cells must respond to both pro- and anti-inflammatory environmental signals simultaneously in the setting of brain trauma [54]. This concept is supported by the results of the previously mentioned study demonstrating concurrent expression of both pro- and anti-inflammatory gene signatures [56]. The function of infiltrating monocyte/macrophages, therefore, appears to depend more on the specific gene expression and cytokine profile than on overall classification as M1 or M2. These findings underscore the importance of improving our understanding of the pathways involved in regulation of expression on the M1/2 continuum. Data from multiple studies have indicated that the Tie2/Angiopoietin pathway is an important factor in the continuum of expression between M1 and M2 macrophages. In addition, data from our project, to be discussed in the following chapters, have specifically implicated this pathway in the context of M1/2 polarization after TBI.

8. Tie2/Angiopoietin signaling in immune cells

The Tie2/Angiopoietin signaling axis was first identified for its key role in the regulation of angiogenic pathways, but this receptor complex is also gaining increasing recognition for its importance in peripheral immune cells. The receptor tyrosine kinase Tie2 (also known as Tek) interacts with its ligands, the angiopoietin family of proteins, to influence vascular development [57]. Studies in endothelial cells have shown that Tie2 is differentially regulated by its ligands Angiopoietin 1 (Angpt1) and Angiopoietin 2 (Angpt2). Angpt1 typically acts as an agonist for Tie2, while Angpt2 serves as an antagonist with several exceptions [58, 59]. Although Tie2/Angiopoietin signaling has been most studied for its role in regulation of vascular function, Tie2 is also expressed in a subpopulation of monocyte/macrophages called Tie2-expressing monocytes (TEMs) implicated in tumor formation and inflammation [60]. This review will discuss the mechanisms involved in the Tie2/Angiopoietin signaling axis and investigate the function of TEMs in various cellular contexts.

8.1 Overview of the Tie2/Angiopoietin axis

Tie2 is a receptor tyrosine kinase first identified on vascular endothelial cells [61]. There are multiple components to the Tie2 signaling pathway where the angiopoietin ligands serve as binding partners [59]. In addition to its expression on endothelial cells, Tie2 is expressed in TEMs, hematopoietic stem cells, neutrophils, eosinophils, and some muscle satellite cells [59, 62]. Angiopoietin 1 (Angpt1) is primarily expressed in platelets and perivascular cells, while Angiopoietin 2 (Angpt2) is expressed in endothelial cells [63]. Expression of both Angiopoietins has also been demonstrated in hematopoietic stem cells and some immune cell types including monocyte/macrophages [64, 65]. Angpt1 serves as a Tie2 agonist, activating this receptor and increasing endothelial vessel stability [59]. However, the function of Angiopoietin 2 (Angpt2) is more variable. Some studies have shown that Angpt2 can act as either an agonist or antagonist of Tie2 depending on cellular context, and increased expression of Angpt2 has been demonstrated in multiple disease states [59]. Angpt2 has been found to act as a Tie2 agonist in the context of decreased Angpt1 signaling, absence of Tie1/Tie2 heterocomplexes, or inhibition of vascular endothelial protein tyrosine phosphatase (VE-PTP) in the endothelium [59, 66, 67]. However, the dominant role of Angpt2 and/or these co-complexes in TBI has not been established. This ligand has repeatedly been shown to act as an antagonist in the setting of inflammation [68]. Although less studied than its counterpart, Tie1 has also been found to interact with Tie2 to promote Tie2/Angiopoietin interactions in vascular remodeling [59, 69]. The interactions between Tie2, Tie1, Angpt1, and Angpt2 have a profound influence on cell survival and vascular permeability [59, 61].

The downstream cellular effects of Tie2 binding with an Angiopoietin ligand can vary widely with cellular context. This is partially due to the differing effects of Angpt1 vs. Angpt2—Angpt1 binding has been shown to oppose the effects of inflammatory cytokines and decrease vascular permeability, while Angpt2 has been found to increase vascular permeability in a number of inflammatory models [59]. Binding patterns of these two ligands with Tie2 are distinct from each other, which may contribute to their differing effects. The fibrinogen-like domain of Angpt1 binds an immunoglobulin domain of Tie2, which may help Angpt1 increase cluster formation and cross-phosphorylation of Tie2 upon binding [68]. In contrast, Angpt2 has a slightly different amino acid sequence in the fibrinogen-like domain

and is also more likely to form dimers than oligomers. These structural differences may contribute to the different effects of the two ligands [68]. The central importance of clustering in Tie2 activation is confirmed by the results of one study that used an anti-Angpt2 antibody to cluster Angpt2. The clustering of Angpt2 caused it to act as an agonist to Tie2 rather than an antagonist, resulting in decreased vascular permeability and increased organ protection in the setting of sepsis [70]. Once Tie2 is activated, multiple downstream signaling pathways could be involved as effectors. Specifically, the Akt/PI3K (phosphatidylinositol 3 kinase) pathway has been implicated as a downstream effector of Tie2. This pathway is critical for cell survival and M2 macrophage polarization [61, 71, 72]. In the context of inflammation, Tie2 activation is decreased by a variety of mechanisms, (1) Angpt2 can be released from endothelial cells and competitively inhibits Angpt1/Tie2 binding, (2) overall expression of Tie2 and Angpt1 may be decreased, or (3) the extracellular domain of Tie2 can be cleaved [68]. The decrease in Tie2-Akt/PI3K signaling up-regulates Angpt2. This creates a feedback loop that further decreases Tie2 signaling [68]. The overall effect of the increasing endothelial-derived Angpt2 signaling is an increase in vascular permeability and amplification of inflammatory processes; however, these effects in the brain have not been established following TBI-induced neuroinflammation [63].

While expression of Tie2 has been most studied in endothelial cells, Tie2 has also been shown to be expressed in hematopoietic cell types. The role of Tie2 has been studied in hematopoietic stem cells and a subset of monocytes in addition to vascular and lymphatic endothelial cells [59]. Interestingly, Tie2 expression has also been demonstrated on neutrophils—Angiopoietin 1 has been shown to interact with Tie2 on neutrophils to promote neutrophil migration [73]. The role of Tie2 in macrophages has been increasingly recognized for its importance in tumorigenesis and inflammation. This critical function of Tie2 signaling will be discussed in the following sections of this review.

8.2 Tie2-expressing macrophages

Tie2 has been shown to play an important role in a subset of monocyte/macrophages known as Tie2-expressing monocytes or macrophages (TEMs). TEMs have been most studied in the setting of tumorigenesis and have been found to promote tumor development through a variety of mechanisms. In addition to potentiating overall tumor growth and metastasis, TEMs have been demonstrated to directly promote tumor angiogenesis [74]. Other research has shown that TEMs not only promote tumorigenesis but are necessary for tumor angiogenesis and tumor recurrence following chemotherapy [75]. Several mechanisms have been proposed as effectors of this process. The interaction of Angpt2 with Tie2 in TEMs has been implicated in the pro-angiogenic effect of TEMs as well as in metastasis. One study found that inhibition of Angpt2 blocked the pro-angiogenic function of TEMs in tumors, and another study suggested that inhibition of Angpt2 could help to limit metastasis [59]. Tumor-associated expression of Angpt2 has also been shown to increase expression of pro-angiogenic factors in TEMs [76]. In addition, TEMs in tumors display increased expression of the anti-inflammatory cytokine IL-10. Stimulation of these cells by Angpt2 can work through IL-10 to influence activity of T cells by decreasing T-cell proliferation and increasing regulatory T cells for an overall immunosuppressive effect [77]. Angpt1-Tie2 interaction may also influence tumor development. TEMs are known to express Angpt1 [78], indicating that they may be able to activate Tie2 through autocrine signaling. Angpt1 expression in tumor-infiltrating TEMs has been suggested as a mechanism of increasing tumor angiogenesis through interaction with

endothelial cells [78]. While both Angpt1 and Angpt2 may influence the tumor-promoting activity of TEMs, studies agree that the protumorigenic activity of these cells is under control of Tie2/Angiopoietin signaling. This discovery has established the Tie2/Angiopoietin signaling axis as a target of interest in tumor therapeutic research. Several treatments aimed at blocking Tie2/Angiopoietin signaling are currently in development, with three Tie2/Angiopoietin inhibitors currently in clinical trials as cancer therapeutics [79]. No trials are currently underway for brain injury.

The origin and M1/2 polarization status of TEMS is currently under active investigation. Some studies have found that these cells seem to be polarized toward the M2 phenotype [80]. TEMs have been shown to display increased expression of arginase 1 (Arg1) and scavenger receptors accompanied by decreased expression of pro-inflammatory and anti-angiogenic mediators compared to tumor-associated macrophages that lack Tie2 expression. This expression pattern is consistent with an M2 polarization state [78]. In addition, TEMs exert an anti-inflammatory effect in the context of tumorigenesis. These cells release IL-10 and VEGF, decrease T-cell proliferation, inhibit antigen presentation by dendritic cells, and promote T-cell conversion to regulatory T cells [80]. However, TEMs may also play important roles in a variety of disease settings aside from tumorigenesis. Specifically, many studies have implicated TEMs as key regulators of inflammation.

9. TEMs in inflammation

An influential role of TEMs under inflammatory conditions remains under investigation. In the setting of inflammation, Tie2 expression may influence macrophage phenotype on the M1/2 continuum [45]. While TEMs have been shown to favor the M2 phenotype in the context of tumor infiltration, Tie2 expression has been demonstrated in monocytes polarized to both M1 and M2 phenotypes [60, 78]. Investigations of whether Tie2 expression in inflammatory disease correlates with M1 or M2 phenotype have shown conflicting results. One study showed Tie2 activation in synovial macrophages of human patients with autoimmune rheumatoid arthritis. In this study, Angpt2/Tie2 signaling interacted with TNF to up-regulate IL-6 and macrophage inflammatory protein 1α (MIP-1α), and antagonizing this pathway reduced synovial inflammation in a mouse model of disease [81]. Exogenous Angpt1 application to human monocyte cultures has been shown to up-regulate TNF and possibly regulate their polarization state [45]. Another study found that Angiopoietin binding works synergistically with TNF to drive expression of pro-inflammatory cytokines in human-cultured monocytes under several polarized conditions [60]. In contrast, previous studies showed anti-inflammatory effects of Angpt1 binding in TEMs and found that Angpt1 blocks LPS-induced TEM migration and ameliorates LPS-induced TNF expression via NF-KB [82]. Angpt2 has also been shown to augment immunosuppressive cytokines and T-reg chemokines expressed by TEMS *in vitro* [77]. These conflicting results suggest that Tie2 signaling may serve differential functions depending on acute and chronic conditions and may be dependent upon the activation state of the cells. Furthermore, the role of clustering and oligomerization of angiopoietin molecules on Tie2 binding and activation [83] raises the possibility that Tie2 may be differentially regulated under these conditions, although individual studies failed to confirm p-Tie2 states directly. Therefore, the role of Tie2 activation in the M1/M2 continuum remains unclear. While Tie2 signaling has been implicated in promoting injury-induced and tumor-promoting vascular health in numerous non-CNS models [59, 74, 75], its role

in regulating monocyte/macrophage polarization in CNS inflammation remains unexplored. Furthermore, limited data exist regarding novel pathways that may regulate Tie2 function in TBI-induced peripheral immune response.

10. Cell-to-cell contact in TBI-induced inflammation

Many cell-to-cell interactions become key in the regulation of inflammation following TBI. As previously mentioned, one of the most detrimental results of TBI is the breakdown of the BBB. Adhesion molecules contribute to cell-cell and cell-extracellular matrix (ECM) interactions that mediate inflammation by promoting peripheral leukocyte infiltration across the BBB and aggregation to the site of injury. This represents the initiation of the inflammatory response [84]. After tissue injury, circulating immune cells will recognize signals released from injured tissue, will stop on the luminal surface of blood vessels, transmigrate paracellularly across the endothelial layer, and enter the injured milieu [85, 86]. This process is referred to as the leukocyte adhesion cascade, which involves tethering, rolling, activation, firm adhesion, and transmigration. Numerous preclinical models have determined the detrimental role of leukocyte migration and accumulation during neuroinflammation in TBI [39, 87].

10.1 Adhesion molecules involved in TBI-induced inflammation

Adhesion molecules involved in these processes include three major families: selectins, integrins, and immunoglobulins. Selectins are a group of transmembrane glycoproteins expressed on the surface of leukocytes, which express L-selectin, and endothelial cells, which express P- and E-selectins following activation [88]. These glycoproteins mediate the initial tethering of leukocytes to the vessel wall by binding to counter-receptors and rolling within moments of tissue injury [89]. Integrins are a family of adhesion molecules broken into subclassifications of α and β subunits that are responsible for cellular attachment to the ECM and leukocyte-endothelial cell adhesion and are denominated by the β subunit CD18. These molecules include CD11a/CD18 (LFA-1), CD11b/CD18 (Mac-1), CD11c/CD18, and CD11d/CD18 [90, 91]. Immunoglobulins are a superfamily in which some members are glycoprotein adhesion molecules that regulate the adhesion and migration between leukocytes and endothelial cells during the inflammatory process. These molecules include ICAM-1, ICAM-2, VCAM-1, and PECAM-1 [92]. Key adhesion molecules involved in TBI inflammatory response are summarized in **Table 1**. Eph receptors and their ephrin ligands have also been implicated in the migration step of leukocyte infiltration into injured tissue and subsequent inflammation and will be discussed further.

10.2 Overview of membrane-bound Eph receptors and ephrin ligands

Eph receptors tyrosine kinases and their membrane-bound ephrin ligands function as mediators of cell migration and a wide-range of cellular functions across different cell types. Eph receptors are the largest family of receptor tyrosine kinases that are activated following cell-to-cell contact [107]. The Eph receptors are classified as either EphA or EphB receptors based on ligand binding. EphB receptors typically bind to transmembrane ephrin B ligands [107–109], while some Eph receptors, such as EphA4, can bind to both A and B ephrins [110]. Eph receptors play critical roles in axon guidance, synaptogenesis, neuromuscular junctions, and vascular remodeling among other roles [107, 109, 111]. Importantly, multiple

Adhesion molecule family	Molecule	Involvement/association with TBI	Expression	Mediates
Selectin	E-selectin (CD62E, ELAM-1)	Up-regulated 2–24 hrs in percussion model of TBI in rats, activated by IL-1 and TNFα [93].	Activated endothelial cells	Slow leukocyte rolling
	P-selectin (CD62P)	Increased CSF levels in children with severe TBI and associated with poor outcome [94]. Stimulated by TNFα and IL-1 [95].	Secretory granules of platelets and endothelial cells	Leukocyte rolling
Integrins	CD11b	Depletion of CD11b macrophages in diphtheria toxin receptor mice increased inflammatory signaling during TBI [96]. This may be due to critical mechanisms for TBI recovery being impaired.	Macrophages and microglia	Pathogen and DAMP recognition, phagocytosis, and cell survival [97]
	CD18/CD11b (Mac-1)	Blockade attenuates neutrophil accumulation following TBI in rats [98].	Neutrophils, monocytes/ macrophages, and NK cells	Firm adhesion during transmigration of leukocytes
	CD18/CD11d	Blockade reduces lesion volume and macrophage infiltration 3 d post-TBI in rats [99].	Neutrophils and monocyte/ macrophages	Adhesion of leukocytes
Immunoglobulin	ICAM-1	Increased significantly in TBI up to 72 hours postinjury, and blockade reduced leukocyte accumulation and improved neurological function following TBI [100, 101]. Soluble ICAM-1 in CSF was found in patients with severe cerebral injuries and BBB impairment [102]. Stimulated by IL-8, IL-1, and TNFα.	Endothelial cells	Leukocyte passage across vascular endothelial cell layer to injured tissue. Promotes leukocyte adhesion and migration [103]
	VCAM-1	Significantly decreased in children suffering from inflicted TBI [104].	Activated endothelial cells [105]	Promotes leukocyte adhesion through VLA-4 receptor [106]

Table 1.
Adhesion molecules involved in TBI inflammatory response.

Eph receptors and ephrins play a critical role in inflammation [111]. Ephrin A1 in endothelial cells responds to TNF stimulation, and multiple Eph receptors and ephrins respond to LPS [111]. EphA4 has been demonstrated to influence both spinal cord injury and TBI [111, 112].

10.3 Eph signaling in immune cells

Eph/ephrin signaling contributes to immune cell function. For example, EphA4 expression influences multiple different immune cell types including T cells, B cells, platelets, monocyte/macrophages, and dendritic cells [113–115]. Both $CD4^+$ and $CD8^+$ T cells have been shown to express EphA4 [116], and EphA4 expression in $CD4^+$ T cells has been implicated in T-cell migration [117, 118]. EphA4 is also critical in migration of memory T cells in response to ephrin A1 stimulation [116]. EphA4 expression in monocyte/macrophages effects their polarization status by mediating their pro-inflammatory (M1-like) state [115]. Moreover, ephrin A1 stimulation increased monocyte adhesion in a cell culture model through interaction with EphA4 on endothelial cells [119]. While these studies highlight that Eph/ephrin signaling is important in peripheral-derived immune cells, a significant research gap exists concerning the specific mechanisms involved in bi-direction signaling and its role in the function of peripheral immune cells following TBI.

11. Conclusions

Understanding the role of the peripheral-derived immune response to TBI is an important unmet need in TBI research. TBI is a leading cause of death and disability worldwide, and the secondary phase of injury is a critical target for therapeutics. Infiltration of peripheral immune cells through the compromised blood-brain barrier forms a major component of this phase, which can have both beneficial and deleterious effects. Monocyte/macrophages impact the response to TBI by a variety of mechanisms. These cells can cause tissue damage through pro-inflammatory traits or exert pro-recovery effects through anti-inflammatory traits, and the continuum of M1/2 expression is a growing research focus. Tie2 and cell-to-cell contact signaling is gaining attention for its role in peripheral immune cells, which provides additional opportunity for developing novel therapeutic treatments following TBI.

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Conflict of interest

The authors declare no conflict of interest.

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Author details

Amanda Hazy, Elizabeth Kowalski, Nathalie Groot and Michelle Theus*
Virginia Tech, Blacksburg, VA, USA

*Address all correspondence to: mtheus@vt.edu

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Chapter 3

Brain Injury and Neuroinflammation of the Gut-Brain Axis in Subjects with Cerebral Palsy

Ana Cristina Ferreira, Marcelo Freire, Vanessa Siqueira, Carolina Ferreira and Maria Teresa Santos

Abstract

Cerebral Palsy (CP) is a limiting deficiency, characterized by a permanent neuromotor disorder which affects movements, resulting in non-progressive lesions of the immature brain during the neuro psychomotor stages. Epidemiological studies of premature births correlated with the presence of high levels of inflammation in the umbilical cord, amniotic fluid, and fetal blood, being that one of the most relevant underlying physiopathological mechanisms includes inflammation and intra-amniotic infection, with inflammatory response and damage to the developing brain. Recently attributed to the excessive production of cytokines, CP inflammation is mostly modulated through diet restriction, intestinal dysfunction, and drug intake. The high prevalence of convulsive crises in individuals with CP (77%) on its own does not bring about post inflammatory and post convulsive cytokine synthesis, treated with antiepileptic medication. In these individuals, there is high incidence of intestinal constipation (47%), besides oral dysbiosis, gingival bleeding and even greater increase in chronic inflammation. The dysbiosis causes an increase in mucous permeability (leaky-gut) of the gut-brain axis, and increase in seric endotoxin, demonstrating a persistent inflammatory state, and supporting the emergence of new side effects, which can become the object of future research.

Keywords: cerebral palsy, brain injury, neuroinflammation, inflammation, cytokines, constipation, antiepileptic drugs

1. Introduction

Cerebral Palsy (CP) covers a group of disorders in the relative development of movement and posture, causing limitation in task execution, attributed to non progressive disturbances of the central nervous system (CNS), occurring during fetal development or in the immature brain. It is the most common cause of physical incapacitation in childhood [1–3].

Motor disturbance is the fundamental alteration caused by CP and must be present. However, other multiple comorbidities are observed such as intellectual deficit, learning difficulties, communication problems (language disturbances, delay in speaking),

ophthalmic (strabismus, visual deficit), otorhinolaryngological, (hearing deficit, mouth breathing), pneumological (recurrent pneumonias), gastroenterological (oropharyngeal dysphagia, gastroesophageal reflux), nutritional (diet, deglutition), neurological (epilepsy, hydrocephalus), orthopedic (limbs, spine deformity, osteoporosis), behavioral disturbances and proprioception (disturbances in sensorial integration) and impact on the secondary musculoskeletal, constipation and epilepsy **Figure 1** [1]. Although the structural damage to the immature brain is static and permanent, the consequences vary and can of change during the child's growth and development through physical rehabilitation and assisted individualized therapy [1].

The estimated prevalence of CP varies from 2.3 to 2.9 per 1000 live births in the United States. (National Infant Health Research 2011–2013) **Figure 1** [4]. About 80% of the causes of CP are attributed to intrauterine events such as inflammations, congenital infections, reduced oxygen delivery, and encephalic strokes [5]. The remaining 20% are due to occurrences at birth, such as peripartum suffocation, low birth weight, acute maternal viral infections during pregnancy and postnatal and early childhood factors caused by accidental and non accidental traumas, hypoxia, and infections like meningitis [5–7].

Individuals with CP can be classified according to the most dominant clinical characteristic [3]:

- Dyskinetic: the lesions are located in groups of neurons at the base of the brain and present atypical movements, which are more evident when the individual makes a voluntary movement [8].

- Ataxic: caused by a dysfunction in the cerebellum, presents generalized hypotonia with a loss of muscular coordination, characterized by abnormal force, rhythm and control or precision of movement [8].

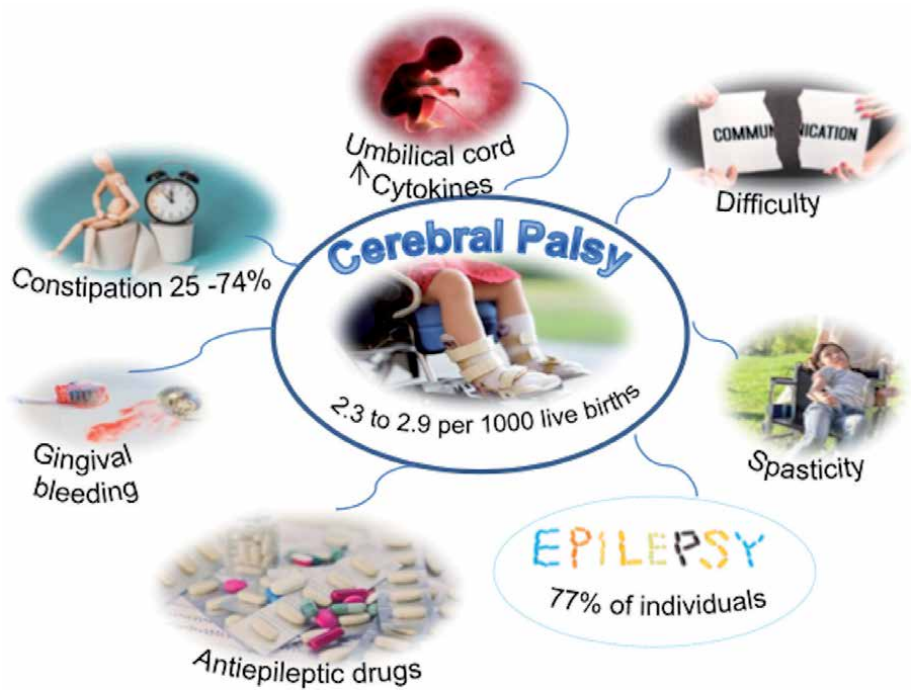

Figure 1.
Characteristics that accompany the subject's life with Cerebral Palsy. (Figures Source: Adobe stock).

- Spastic: presents hypertonia, hyperreflexia, clonus, and signs of inadequate coordination, and insufficient selective muscular control. The spasticity causes a reduction in the joint movement, secondary contractions, bone deformity, joint dislocations, and chronic pain. The conditions of spasticity must also be classified according to the anatomical distribution: unilateral (monoplegic and hemiplegic) and bilateral (diplegic, triplegic, quadri/tetraplegic and with double hemiplegia) [8].

The deambulation classification form is based on the Gross Motor Function Classification System, which is widely and internationally used, categorizing individuals with CP in one of five levels based on functional mobility or limitations in activity: Level I (walking without limitations), Level II (walking with limitations), Level III (walking using a hand-held mobility device), Level IV (self-mobility with limitations) and Level V (transported in a wheelchair) [9].

Even though CP has diverse etiology, in the center of the disease's development, the effect of the inflammation regulates CP's clinical phenotypes.

2. Inflammation early in life

Intrauterine inflammation is observed in approximately 20% of all pregnancies and a surprising 85% of premature child-birth and is associated with a series of neurodevelopment disturbances [10]. Maternal respiratory and genitourinary infections which occur during prenatal hospitalizations and at the moment of birth, emphasize the role of the maternal inflammatory medium in CP's pathogenesis, even though one should not discard an additional causal path involving hypoxemia in the scenario of respiratory infections. Intrauterine infections, extra-uterine infections, and maternal extra-amniotics diagnosed in the hospital during a pregnancy are also associated with a moderately increased risk of pathology in the child [11].

Epidemiological studies of premature births correlate the presence of high levels of inflammatories in the umbilical cord, amniotic liquid and fetal blood with white matter injury, CP and damaged development. In truth, premature babies are born in a serious state of inflammation [12–14].

When there is an association between inflammation and infection, premature delivery may be initiated with ramification of the corona amniotic membranes to the amniotic liquid, resulting in systemic fetal inflammation, which can affect several organs, including the brain. Mothers in premature labor display elevated concentrations of Interleukin (IL)-6 and IL-8 in the amniotic liquid [12]. The most commonly found cytokines were: Tumor necrosis factor alpha (TNF-α), Interferon (IFN)-gamma, IL-1, IL-6 and IL-18 and the imbalance in these cytokines in the beginning of development can have deep and long-term impact on several illnesses, such as CP. These alterations can occur starting in the intrauterine life to early infancy. The cytokines probably exert their effects, and may include modulation of other immunological mechanisms [15]. These cytokines coordinate the host's immune response and mediate normal signalling between immune and non immune cells, including in the CNS [16]. Pro-inflammatory cytokine induction in the maternal infectious process or in the beginning of life demonstrated an adverse effect on neurodevelopment [17]. While certain cytokines are considered pro or anti-inflammatory, certain types may exhibit both properties in different situations [17]. Strategies must be elaborated to inhibit the imbalance effect of cytokines as a therapeutic way of preventing or treating neurological diseases [15]. Recently, attributed to deregulated production of cytokines, CP inflammation is mainly

modulated through dietary restrictions, intestinal dysfunction, and medication intake. Convulsions alone stimulate the pro-inflammatory and pro-convulsive cytokine synthesis in epileptic individuals [18].

3. Epilepsy

Epilepsy is a chronic cerebral disease characterized by recurrent unprovoked epileptic crises [19] of diverse etiology with consequences for the neurobiological, cognitive, psychological, and social planes/plans, negatively impacting the affected individual's quality of life [20, 21].

In the history of epilepsy there are accounts that in the neolithic period (Historical Period of Polished Stone X Millennium a. C.) trepanations were performed in skulls in order to free the bad spirits. Skulls scarred from these interventions were found in Egypt, Greece, Rome, the Orient, Equatorial Africa, in Mayan, Aztec and Brazilian indians, with curative objectives. In ancient Rome people with epilepsy were avoided for fear of contagion of the illness, and in the Middle Ages, they were pursued as witches [22].

In 1494, Malleus maleficarum, the witch hunting manual written by dominican priests linked to the Catholic Inquisition, was published. In this treatise, epileptic crises were a characteristic of witchcraft [23, 24]. This treatise's orientation led to the the persecution, torture, and death of more than 100.000 women, being that the majority were epileptics [23, 24].

Worldwide prevalence of active epilepsy is estimated around .5% to 1.0% of the population. The prevalence of epilepsy differs among ages, sex, ethnic groups, and socioeconomic factors [25]. The incidence of epilepsy adjusted for age in North America varies between 16 in 100,000 and 51 in 100,000 people per year. The adjusted prevalence by age varies from 2.2 in 1000 to 41 in 1000, depending on the country.

Partial epilepsy may constitute up to two thirds of incident epilepsies. The incidence increases in populations of lower socioeconomic status [25]. It is estimated that near 25–30% of the recently started crises are provoked or secondary to another cause. The incidence of epilepsy is higher in younger groups and continually increases after 50. The most common cause of convulsions and epilepsy in seniors is cerebrovascular disease [25, 26].

Among epilepsy's etiological factors, those that stand out are: electrolytic (hypoglycemia, hyponatremia, hypernatremia, hypocalcemia, use of drugs like Teofilina, Aminofilina, antidepressants, Ciclosporina, Cocaine, Crack, amphetamines, Lidocaine); acute toxic effects (antidepressants, sympathomimetics, others); irregular intake of prescribed antiepileptic medicine; Sepse, infections in the CNS; hypoxic cerebral lesions; cranial traumatism; ischemic or hemorrhagic stroke; inflammatory neoplasma (lupus cerebritis); fever and sleep deprivation [27].

Epilepsies can be classified according to the axes: topographic and etiological. On the topographic axis, generalized epilepsies occur that are manifested by epileptic seizures that start in both hemispheres simultaneously. In general, they are genetically determined and accompanied by altered consciousness; when present, motor manifestations are always bilateral. Absence seizures, myoclonic seizures and generalized tonic–clonic seizures (GTC) are its main examples [28].

In focal epilepsies, the epileptic crises begin locally in a specific area in the brain, and their clinical manifestations depend on the starting point and the speed of the spread of the epileptogenic discharge. The crises are divided into simple focals (without affecting consciousness) and complex focals (at least partially affecting consciousness during the episode). Finally, a focal crisis, be it simple or complex,

when propagated throughout the cerebral cortex, can end up in a GTC, and denominated a secondarily generalized focal crisis [29].

The symptomatic convulsions occur during the course of many clinical and neurological diseases, are generally self limited and do not persist if the subjacent disturbance is corrected. There may occur a reaction in the brain to physiological stress like sleep deprivation, fever, and abstinence from alcohol or other drugs such as sedatives. Other causes of symptomatic convulsions are hypertensive encephalopathy, renal insufficiency, sickle cell anemia, idiopathic thrombocytopenic purpura, systemic lupus, erythematosus, meningitis, encephalitis, traumatic brain injury and stroke. In these situations the cerebral function is temporarily compromised [21].

It must be pointed out, regarding characteristics of symptomatic convulsions, that fever is the most common cause of convulsions in children between six months and four years of age, with 30% chance of another convulsion, increasing the risk of subsequent epilepsy, though not associated, and do not cause intellectual deficit [21].

The objective of epilepsy treatment is to provide the best quality of life possible for the person with epilepsy, through adequate control of crises, and a minimum of adverse effects. Seventy percent of people that have epilepsy take control of the crises with the appropriate use of anticonvulsant medicine [30].

Epilepsy is one of the most common comorbidities associated with motor damage in individuals with CP, and affects close to 77% of that population [30]. Clinical treatment for epilepsy is based on long term antiepileptic drug therapy which reduces the frequency of crises, raising the threshold of motor neurons in the cortex, reducing abnormal electrical discharges of the brain and limiting the dissemination of the excitement of the abnormal foci [29].

The antiepileptic pharmaceuticals act through different mechanisms which may or may not be favorable for the treatment [31]. The antiepileptic pharmaceuticals act through one or several mechanisms such as increasing gabaergic inhibition, blocking sodium channels, blocking calcium channels or connecting to protein SV2A of the synaptic vesicle [32].

Regarding gamma-aminobutyric acid, (GABA) it was possible to identify specific benzodiazepine receptors in the CNS structures, principally in the limbic system, allowing the comprehension of the action mechanism of these medications. By connecting to these receptors, the benzodiazepines facilitate GABA's action, which is the primary inhibitory neurotransmitter of the CNS. The specific activation of GABA receptors induces the opening of chloride channels in the neuron membrane, amplifying the influx of this anion into the cell, which results in decreased excitability and the spread of excitatory impulses. Among the effects observed for these drugs are described the reduction of salivary flow, the vomiting reflex and the relaxation of skeletal muscles [33].

Voltage-dependent Na + is one of the principal channels responsible for the rapid depolarization of the widely and disorganized presence and neuronal membrane in the epileptic processes [34]. These channels represent the important site of connection for several antiepileptic drugs such as hydantoin, carbamazepine, valproic acid, lamotrigine, among others [33].

The first evidence of the possible participation of channels Ca + 2 dependent on voltage in epilepsies came from the verification that the accentuated reductions in extracellular concentration of this ion can create epileptic activity in cerebral tissue such as the dentate gyrus and other hippocampal structures. It is known that the acute increase in Ca + 2 influx is important to maintain the reflex hyperexcitability, which occurs in convulsive processes. In this context, the Ca + 2 channels dependent on voltage have an important role in the functional processes of the nervous system. For example, the presynaptic Ca + 2 entry is associated with the liberation

of these neurotransmitters and to their postsynaptic entry with sustained neuron depolarization. Blocking the Ca + 2 channels can produce several effects on the neuronal functioning: (a) blocking Type T channels (associated to absence crisis treatment); (b) blocking type L channels (associated with partial crisis treatment); (c) blocking Ca + 2 channels can prevent the liberation of excitatory neurotransmitters such as glutamate and (d) blocking these channels reduces the concentration of Ca + 2 ions in the neuronal cytoplasm, reducing the possibility of excitotoxic cellular damage [33].

The first study, which evaluated the association between intestinal constipation, use of antiepileptic drugs (AEDs), and gingivitis in subjects with spastic CP, was published by our work group (**Figure 2**) [35]. It was clearly demonstrated an association between intestinal constipation and the use of GABA antiepileptic drugs (phenobarbital, primidone, benzodiazepines including diazepam, lorazepam, and clonazepam; topiramate, felbamate, ezogabine); GABA transporter tiagabine GABA transaminase (vigabatrin); synaptic release machinery SV2A (levetiracetam, brivaracetam α2δ gabapentin, gabapentin enacarbil, pregabalin).

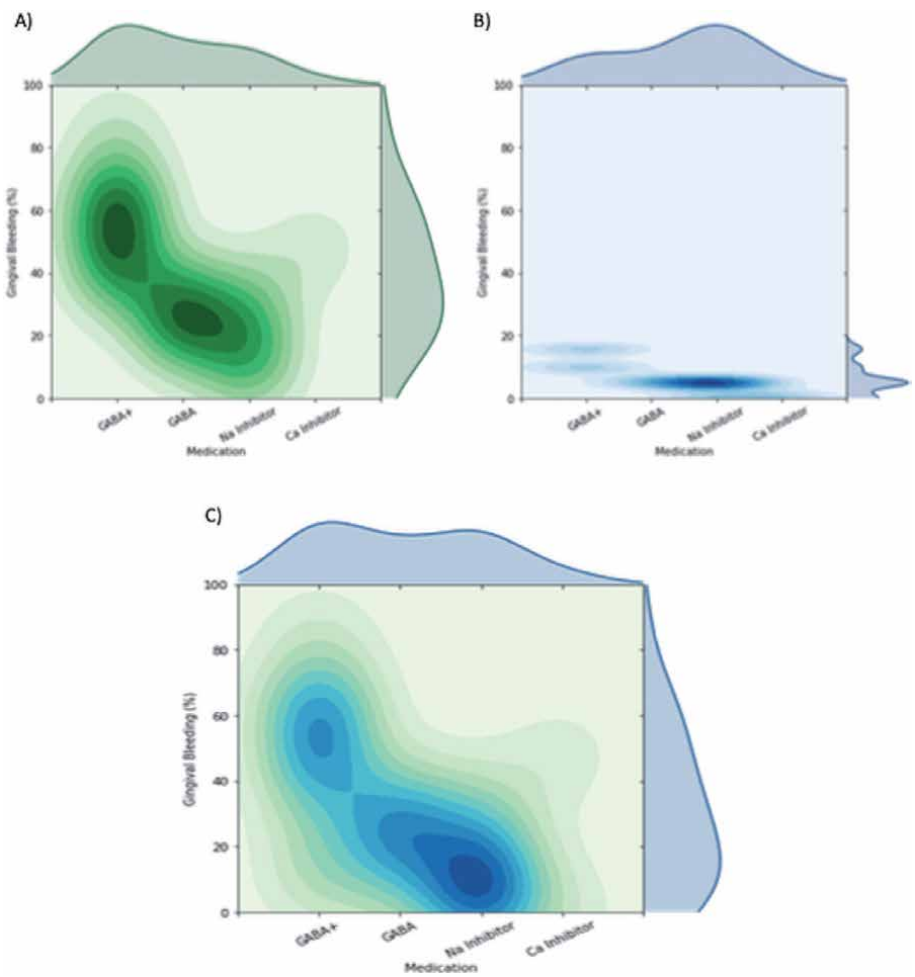

Figure 2.
Gingival bleeding and medication type: bleeding is measured by the percentage of teeth which bled after periodontal probing. Each kernel density estimation plot shows clustering by the type of medication taken by subjects. (A) Green figure show constipated subjects; (B) blue figure show non-constipated subjects; (C) Green-to-Blue figure show the full population.

It was described that the use of AEDs should be considered as a causal factor of constipation in CP subjects. A wide range of AEDs has been used either in the form of monotherapy or polytherapy for seizure control. Monotherapy has the advantage of lowering the potency of toxicity and side effects. Nevertheless, polytherapy may be recommended for the most neurologically compromised, despite its greater side effects and toxicity to the users of this treatment modality. GABA is localized in the gastrointestinal tract and is present in enteric nerves [35].

Regarding those people with epilepsy, it is necessary to emphasize the caution needed in the occurrence of a GTC in an odontological office. It characteristically occurs in two phases: Initially there is loss of consciousness followed by muscular convulsions. The steps to be taken are to immediately stop the odontological procedure, position the patient in lateral decubitus, and activate the medical emergency system.

Another situation to be observed is the possibility of leukopenia and thrombocytopenia induced by antiepileptic drugs such as phenytoin, carbamazepine, and valproic acid, requiring the request for additional tests (blood count).

Another prevalent condition refers to drug-induced gingival overgrowth, also referred to as drug-induced gingival enlargement, and previously known as drug-induced gingival hyperplasia, is a side-effect of certain drugs where the gingival tissue is not the intended target organ. The key offending drug classes are anticonvulsants, immunosuppressants, and calcium channel blockers [36]. Gingival overgrowth impedes proper dental hygiene and, apart from the cosmetic damage, causes painful chewing and eating. Therefore, patient education and information about the condition and its management are essential.

4. Gut-brain axis

The gut-brain axis is an information exchange platform which allows bidirectional communication between the host's intestine and nervous system. The information can be exchanged through a neural network, hormones, and immunological system [37].

The enteric nervous system consists of approximately 200 million neurons which control the entire digestive tract. It is composed of a web of intrinsic nerve fibres and ganglia, the myenteric and the submucous plexus. The myenteric plexus mainly controls motility of the digestive tract (peristalsis) and is located deep between the longitudinal and the circular layers of the entire digestive tract. It is mainly composed by a network of ganglia connected by unmyelinated fibres which are connected to the vagus nerve and to sympathetic ganglia. The submucous plexus (Meissner plexus) is located more superficially and closer to the intestinal lumen. It is mainly composed by nerve fibres and ganglia which control the mucous secretions, vascular flow and absorption [38]. The vagus nerve allows the direct connection between the intestine and the brain. By controlling motility and intestinal secretion, the vagus nerve can alter the intestinal environment and the response to the enteric immunological system with direct consequence to the intestinal microbiota. On the other hand, the intestinal bacteria produce metabolites which can influence the CNS and enteric and affect the production of neurotransmitters, such as GABA, acetylcholine, and the serotonin precursor, tryptophan [39].

Intestinal microbiota composition is regulated by extrinsic factors, such as lifestyle, precocious exposure to microbiota and diet, and intrinsic factors, such as metabolism, genetic history and the host's immunological and hormonal systems activity [40]. Intestinal dysbiosis can have an infinite amount of consequences for

the CNS. Microbes can stimulate the liberation of small molecules, like cytokines, and produce metabolites which work as neuromodulators, such as short-chain fatty acids (SCFAs), GABA and serotonin precursors [41–43].

One of the most studied extrinsic factors is diet, since it can alter the intestinal microbiota. Epidemiological studies show a positive correlation between the increase in risk of cognitive decline and high ingestion of animal protein, refined sugar and foods with high content of saturated fats [44]. Patients with refractory epilepsy can benefit from a ketogenic diet, since it can influence the intestinal microbiota [39]. The commensal bacteria in the intestine degrade the dietary fibre and lead to the production of SCFA, which are beneficial to the brain [44].

SCFAs are important bacterial metabolites which can reduce the inflammatory response, promote CNS plasticity, and increase the hematoencephalic permeability [45]. An exacerbated inflammatory response in the hippocampus is associated with a diet rich in fructose, and can be a consequence of alterations in intestinal bacteria [46].

Colonization with Akkermansia Mucinophilia e Parabacteroides bacterias offers protection against convulsions, altering the level of cerebral neurotransmitters in the hippocampus, including GABA and glutamate. Intestinal microbiome dysbiosis can alter GABA, which is the main inhibitory neurotransmitter in the brain, and the reduced levels have been known to exacerbate convulsions [47–49]. But the reduction of Prevotellaceae and increase of Lactobacilliaceae are related to neuroinflammation and were discovered in neurodegenerative diseases such as Parkinson's Disease [49]. An increase in Proteobacteria and Cronbacteria was found in patients with epilepsy [50]. Individuals with epileptic CP (CPE) exhibited lower proportions of Anaerostipes, Faecalibacterium e Bacteroides [51] which can produce butyrate with acetate [52] since butyrate can stimulate the differentiation of regulatory T cells (Treg) and relieve the neuroinflammation charge [53]. Nevertheless, great quantities of acetate would accumulate in these individuals, which could activate the parasympathetic nervous system [54] and unchain a convulsion. Besides that, the reduction of Bacteroids would also reduce butyrate secretion and attenuate its neuroprotector effect in patients with CPE [53]. On the other hand, a greater abundance of Enterococcus, Bifidobacterium, Clostridium IV and Akkermansia were discovered in patients with CPE [51]. A deeper analysis of the microbial functions revealed an increased systemic immunological and neurodegenerative diseases in patients with CPE [51], and that neuroinflammation probably carried out a fundamental role in CPE pathology [55].

Dysbiosis and frequency of epileptic events are frequently correlated, suggesting that the drugs can interact directly with the intestinal microbiota, modifying their metabolism and, therefore, affecting the efficacy and toxicity of the drugs [56]. Drugs are transformed into bioactive metabolites, inactive or toxic through direct microbial action or host-microbial co-metabolism. These metabolites are responsible for therapeutic effects or collateral effects induced by these medications [57]. Alteration in the microbiome can affect absorption and medicine metabolism, influencing their efficacy and resistance to the drug [58].

The antiepileptic medication is normally used in long-term clinical treatment, and for this reason can cause serious collateral effects in the childhood development of patients with CP and epilepsy, such as: gastrointestinal complications including oral dysbiosis, gingival bleeding (GB) and increase in systemic inflammation [35, 59].

CP's inaccessibility and vulnerability to oral care and consequently the development of caries and gingival diseases can also phenotypically affect the intestine

through the microbiome's oral-intestine axis. These facts do not alone indicate alterations in the microbiome, but indicate that the gingival bleeding index suggests dysbiosis in the host-microbial interactions in the oral mucosa interface which then can influence an individual's systemic inflammatory profile.

Current literature indicates that intestinal disturbances play a prominent role in inflammatory responses and neurological conditions [60]. This line of evidence is fundamental in identifying the effects of dysbiosis in mucosa inflammation in the entire digestive tract. Significantly higher levels of IL-1β, IL-6, IL-8 and IL-10 were found in constipated individuals with GB (**Figure 3**), besides this, presence of chemokine IL-8 induces the secretion of lymphocytes, monocytes, epithelial cells, fibroblasts, tumor cells, bone reabsorption and IL-1β [61, 62], indicating a continuous inflammatory process and progression of the periodontal disease [61–64]. The use of this medication caused individuals with CP to present reduced salivary flow, increase in the salivary osmolarity, dry mouth and gingivitis, which is represented by elevated levels of inflammatory cytokines in tetraplegics [59].

There is an elevated risk of immunological system diseases in these vulnerable individuals, and oral and intestinal dysbiosis is attributed to an exacerbated increase of Akkermansia in patients with CPE [51]. The excessive increase in Akkermansia would degrade the mucin in the mucous layers and would increase the mucous permeability [65], which allows for more bacterial antigens to be exposed to the host's immunological system, unchaining systemic immune reactions in individuals with CPE.

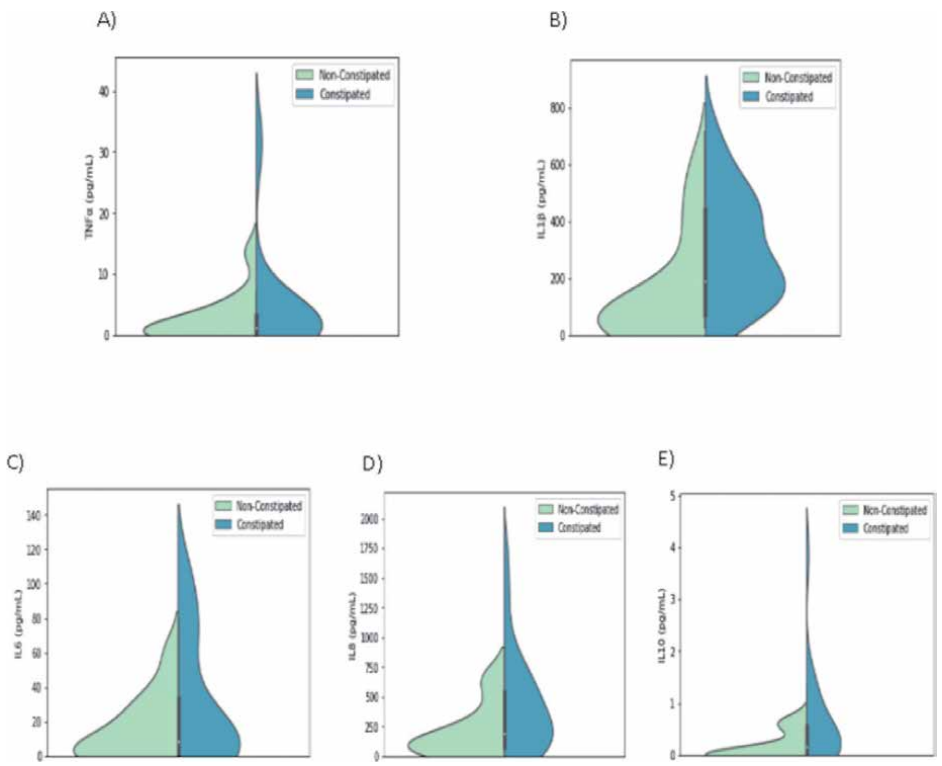

Figure 3.
Constipation actions on Inflammatory Cytokine Levels. Distributions of each measured cytokine—(A) TNFα, (B) IL1β, (C) IL6, (D) IL8, and (E) IL10— in constipated subjects (blue) and non-constipated subjects (green) are mapped using a violin plot. White dots mark the means, bars show the inner quartiles, and whiskers mark the 5% confidence interval.

5. Correlation between covid-19, brain injury and neuroinflammation

Vulnerable children are those with neurological diseases and lung problems, requiring respiratory care [66]. This situation is currently a priority with the advent of the new coronavirus disease of 2019 (COVID-19). This is a zoonotic virus, an enveloped RNA, which can be transmitted from a sick person to another by close contact through touch, handshake, droplets of saliva, sneeze, cough, phlegm and contaminated objects or surfaces [67, 68].

It was first detected in December 2019 and became an epidemic in Wuhan, Hubei province, China and quickly spread to several countries on six continents [69]. On March 11, 2020, the World Health Organization announced that COVID-19 was characterized as a pandemic, threatening global public health and creating a record economic burden. Coronaviruses are a large family of viruses that cause diseases such as the common cold to more serious diseases, such as Severe Acute Respiratory Syndrome (SARS). A new coronavirus is typically a new strain of infectious disease that has not been previously identified in humans [70].

The new 2019 coronavirus, coronavirus 2 of the severe acute respiratory syndrome (SARS-CoV-2) appeared after six other human coronaviruses. Four common human coronaviruses which cause light to moderate illness of the superior respiratory tract, including 229E (coronavirus alpha), NL63 (alpha coronavirus), OC43 (beta coronavirus) and HKU1 (beta coronavirus), were registered for the first time in the 60's [71]. Two other human coronaviruses are SARS-CoV and MERS-CoV, which cause grave infections to pulmonary lesions, known as Severe Acute Respiratory Sickness (SARS-C0V) and Middle East Respiratory Syndrome (MERS-CoV), respectively. The MERS-CoV outbreak occurred in 2012, starting in Saudi Arabia and spreading to other countries with a mortality rate of 37% [71, 72].

These are the diagnostic criteria [73]:

1. Asymptomatic Infection: without symptoms and clinical signs and normal thorax image, while the 2019 nCoV nucleic acid test is in a positive period.

2. Light: Acute symptoms of infection of the superior respiratory tract, including fever, fatigue, myalgia, cough, sore throat, coryza and sneezing. The physical exam shows pharyngeal congestion and absence of auscultatory abnormalities. Some cases may not have fever or only present digestive symptoms such as nausea, vomit, abdominal pain and diarrhea.

3. Moderate: with pneumonia, fever and frequent coughs, especially dry cough, followed by productive cough, some may have a chest wheezing, but no obvious hipoxemia, with lack of air or dry wheezing and or wet wheezing. Some cases may not have signs or clinical symptoms but the Computerized Tomography of the thorax shows subclinical pulmonary lesions.

4. Serious: precocious respiratory symptoms, such as fever and cough, can be followed by gastrointestinal symptoms, such as diarrhea. The disease generally progresses for about one week and dyspnoea occurs, with central cyanosis. Oxygen saturation is inferior to 92%, with other manifestations of hypoxia

5. Critical: Children can rapidly progress to acute respiratory distress symptom or respiratory insufficiency and can also present shock, encephalopathy, myocardial or cardiac injury, coagulation dysfunction, and acute renal lesion. The organic dysfunction can be fatal.

The majority of discussions based on evidence demonstrate the power of privilege during a pandemic, where it is indicated that the most vulnerable, such as seniors, people with deficiencies and aborigenes, will be the most impacted [74].

Children of all ages are sensitive to Covid-19, and there is no significant difference between the sexes. The clinical manifestations of cases of children with Covid-19 were less serious than those of adult patients. Nevertheless, small children, especially babies, are also vulnerable to infection by Covid-19 [75]. Many families have to live in just one room with shared bathrooms and kitchen, causing overcrowding and making self isolation impossible in confined spaces. Many times, the children have inadequate space to crawl or play, and no access to fresh air. The duration of the outbreak is not clear and these children are more vulnerable both to the primary as well as the secondary effects, it is absolutely vital that they are no longer marginalized [76].

Antiviral immunity includes innate and adaptive immune responses. There are different innate immune receptors, the Toll like receptors (TLRs) are more intimately related to adaptive immune responses, therefore the TLRs are important antiviral immunity elements [77]. After a virus is recognized, the TLR signaling positively regulates the expression of pro-inflammatory cytokines and co-stimulatory molecules, through the accumulation of interferons (IFNs). Consequently, the adaptive antimicrobial immunity is processed by co-stimulatory molecules [78].

Patients with serious SARS-CoV infection show an aberration of the innate immune system. Particularly, the induction of proinflammatory cytokines, IFNs type I and genes stimulated by interferon (ISG) would suffer oscillations clearly favorable to SARS-CoV. The liberation of cytokines and pro-inflammatory chemokines occurs on the first day of infection. High levels of proinflammatory cytokines in patients with SARS-CoV are correlated to symptoms of respiratory discomfort in old animals. The IFNs can help to control the replication of SARS-CoV. Therefore, it is possible to suppose that other innate immunological mechanisms will have an essential role in immunity against SARS-CoV [79].

A certain subgroup of the population of T cells develops a cytokine storm during initial stages of the SARS-CoV-2, involving cytokines and chemokines from the beginning until the other phases of the illness. In its initiation phase, SARS-CoV-2 would increase the plasma concentration of different cytokines, including IL-1β, IL-1Rα, IL-7, IL-8, IL-9, IL-10, basic FGF G CSF, GMCSF, IFNγ, IP10, MCP1, MIP1A, MIP1B, PDGF, TNF-α and endothelial vascular growth factor. Critical patients interned in intensive care units (ICUs) presented higher levels of IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A and TNFα compared to those who did not need to be in the ICU. In SARS-CoV-2, there appears to be an interaction between different subsets of the population of T-helper cells (Th), for example, Th1, Th2 and Treg [80].

Both winter and low humidity act as stressors for the immune system. Evidence shows an association between cold temperatures and low humidity with respiratory tract infections whereby the lower the temperature/humidity, the greater the infections in the respiratory tracts of the population [81].

Precocious induction of interferon-gamma (IFN-γ) in viral infections, indicates a battle between innate immunity and the virus, so the immune system would start with a fever, to allow the expression of TLR4, and would unchain a series of antiviral immune responses characterized by the production of cytokines. In almost 99% of cases, the most common initial symptom of SARS-CoV-2 is fever [82].

Evidence points to the effect of this new coronavirus in inhibiting antiviral immune responses and, therefore, its powerful capacity to replicate in the host cells. On the other hand, SARS-CoV-2 demonstrated a greater rate of incidence of

mortality in the senior population and in people with certain comorbidities which are known since they have differences in their immune profile [83].

Comorbidity is present in more than 30% of cases of infection with SARS-CoV-2 [80]. Organized by related mortality rates, the chronic conditions in victims with the virus include cardiovascular diseases, diabetes, chronic respiratory diseases, hypertension and cancer. All of these conditions, in the long run, tend to make the immune system imperfect, both in innate and adaptive terms in the immune functions [84].

Brain injury caused by hypoxia increases the risk of developing epilepsy that is difficult to control. In the presence of infection by SARS-CoV-2, there is greater susceptibility to the occurrence of convulsions, increasing their vulnerability.

6. Conclusion

Dysbiosis causes an increase in mucous permeability (leaky-gut) of the gut-brain axis, and increase in serum endotoxin, demonstrating a persistent inflammatory state, and supporting the emergence of new side effects, which can become the object of future research.

Abbreviations

CP	Cerebral Palsy
CNS	Central nervous system
IL	Interleukin
TNF-α	Tumor necrosis fator alpha
IFN	Interferon
GABA	Gamma-aminobutyric acid
AEDs	Antiepileptic drugs
SCFAs	Short-chain fatty acids
CPE	Cerebral Palsy epileptic
GTC	generalized tonic–clonic seizures
GB	Gengival Bleeding
COVID-19	Coronavirus disease 2019
SARS	Severe Acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
MERS	Middle East Respiratory Syndrome
TLR	Toll like receptor
ICU	intensive care unit
Th	T-helper cells

Author details

Ana Cristina Ferreira[1*], Marcelo Freire[2,3], Vanessa Siqueira[1], Carolina Ferreira[1] and Maria Teresa Santos[1]

1 Department of Individuals with Special Needs, Postgraduate Program in Dentistry, Cruzeiro do Sul University, São Paulo, Brazil

2 Department of Genomic Medicine and Infectious Diseases, J. Craig Venter Institute, 4120 Capricorn Lane, La Jolla, California, USA

3 Department of Infectious Diseases School of Medicine, University of California San Diego, La Jolla, California, USA

*Address all correspondence to: anacristina.ferreira@gmail.com

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Chapter 4

Pathogenesis and Prevention of Fetal and Neonatal Brain Injury

Andrew Macnab

Abstract

Recent advances in the clinical management of at-risk pregnancy and care of the newborn have reduced morbidity and mortality among sick neonates, and improved our knowledge of factors that influence the risks of brain injury. In parallel, the refinement of imaging techniques has added to the ability of clinicians to define the etiology, timing and location of pathologic changes with diagnostic and prognostic relevance to the developing fetus and newborn infant. Abnormalities of brain growth, or injury to the developing brain can occur during pregnancy; during labor and delivery, hypoxia, acidosis and ischemia pose major risks to the fetus. Defined practices for the management of pregnancy and delivery, and evidence-based strategies for care in the newborn period are influencing outcome. However, newborn infants, especially those born prematurely, remain at risk from situations that can cause or worsen brain injury. The literature reviewed here explains the mechanisms and timing of injury, and the importance of hypoxia, ischemia, hypotension and infection; describes current diagnostic strategies, neuroimaging technologies and care entities available; and outlines approaches that can be used to prevent or mitigate brain injury. Some show particular promise, and all are relevant to lowering the incidence and severity of brain damage.

Keywords: encephalopathy, hypoxia, ischemia, magnetic resonance imaging, prematurity, ultrasound, umbilical cord blood gases

1. Introduction

> *"This work must begin with the conception of man, and describe the nature of the womb and how the foetus lives in it, up to what stage it resides there, and in what way it quickens into life and feeds. Also, its growth and what interval there is between one stage of growth and another. What it is that forces it out from the body of the mother, and for what reasons it sometimes comes out of the mother's womb before the due time."—Leonardo da Vinci (1452-1519) [1].*

In a prior review (2012), literature describing the etiology of fetal brain injury, and its presentation, evolution and management in the neonate was summarized [2]. However, recent advances have considerably increased our knowledge of the nature and prognosis of brain injury, and what can be done to treat and prevent it.

The importance of maternal and fetal health throughout the nine months of intrauterine life remains. But the vulnerability of the fetus to adverse events related to labor and delivery is better understood, and more readily anticipated. Substantial progress has also been made in the care of neonates, our

understanding of the pathogenesis of injury, and protective strategies which can help to prevent or mitigate permanent injury. It is now clear that acute brain injury is a continuum; hypoxia and ischemia in particular generate a sequence of physiologic consequences where the acute phase of injury is followed by a period of latency, and then brain cells undergo secondary energy failure where a cascade of disruptive events occurs which leads ultimately to programmed cell death. This understanding is particularly valuable, as it now guides investigation linked to both the diagnosis and prognosis of injury, and provides critical opportunities for novel care strategies.

The birth and care of infants born prematurely remains challenging. The inherent immaturity of their organ systems and complex therapies they require makes them vulnerable physiologically to a spectrum of potentially adverse events; the result is a significant incidence of long-term cognitive and motor deficits. In spite of advances in obstetric and neonatal care lowering the overall prevalence of complications, the incidence of cerebral palsy has not reduced significantly. But it is clear now that a strong relationship exists between gestational age at delivery and the probability of both survival and discharge without major handicap, with every additional week in utero tending to improve the chances of a good outcome [3].

Fetal and neonatal brain injury, and the long-term neurodevelopmental handicap caused, is an extremely important problem, and especially so in premature infants, because of the large absolute number born. Research documents that infants born very prematurely (<32 weeks gestation), and those with an extremely low birth weight (<1000 g), are at increased risk for neurobehavioral impairments (cerebral palsy, blindness, deafness), lower general intelligence, specific cognitive defects, learning disabilities, and behavioral and emotional problems [2, 3]. Modern neonatal care does now enable an increasing number of these infants to survive and escape significant handicaps. Survival of extremely preterm infants (<25 weeks gestation) remains rare, but in Europe and the USA 75-90% of infants who weigh <1500 g at birth now survive, however 5-10% of them develop cerebral palsy subsequently, and many have cognitive, behavioral, attention-related or socialization deficits.

Normal fetal growth is a continuum that must be appreciated in order to fully understand the causes, evolution, and consequences of abnormalities in brain development. Key factors have been reviewed previously [2]. Genetic anomalies are the principal cause of fetal loss, and structural abnormalities are commonly evident at a macroscopic and microscopic level. Advances in genetic screening and analysis have led to genetic studies becoming an integral part of the workup of an increasing number of infants. Genetic counseling is central to prevention in situations where there is a family history of a genetic brain abnormality, birth of a prior infant with an anomaly, or predisposition to a genetic problem due to racial or age-related factors. An autopsy and placental pathology are important after fetal loss.

Embryonic development progresses rapidly after conception, so that a large proportion of the brain's structure is already formed by the time many women become aware that they are pregnant. By the end of the first trimester (3 months of gestation), all the main structures of the central nervous system are formed and so brain growth alone follows between this time and fetal maturity (40 weeks). Hence the relevance of more people understanding the concepts currently articulated in the developmental origins of health and disease (DOHaD) [4] and the importance of:

- health at the time of conception (both paternal and maternal);
- the detrimental effects on the fetal brain of drugs, alcohol and nicotine;

- the beneficial effects of a maternal diet that provides essential nutrients
- maternal nutrition and weight gain that avoids fetal stunting or overweight

Impaired fetal growth secondary to poor maternal nutrition or placental insufficiency can be associated with reduced brain development; growth retarded infants are at increased risk of hypoxic stress and hypoxic ischemic (HI) brain injury due to altered placental blood flow and sub-optimal fetal oxygenation, particularly at the time of delivery. Suboptimal nutrition also poses the risk of hypoglycemic brain injury immediately after birth; the impact of this form of brain injury can now be defined through neuroimaging [5]. At the opposite end of the spectrum, being large for gestational age, post mature, or the product of a multiple pregnancy poses unique challenges, and increases the risk of HI injury [2]. In addition, surviving infants born small or large for gestational age are at increased risk of developing adult-onset chronic diseases (e.g. hypertension, cardiovascular disease, stroke, type 2 diabetes, obesity); the current epidemic of non-communicable diseases has been shown to be linked to early stunting of growth and excessive infant weight gain [4].

Importantly many of the causes of brain damage are now avoidable or amenable to treatment. Neuroimaging protocols help to define both the timing and geographic location of injury, and document the evolution of neuronal changes through defined phases over time [6, 7]. In the acute phase, damage follows decreased cerebral blood flow and reduced oxygen and glucose delivery and resulting ischemia and acidosis. A period of latency follows with transient recovery of energy metabolism. Then an 'excito-oxidative' cascade leads to cerebral energy failure and progression to cell death [8–10]. In this phase, reduced adenosine triphosphate (ATP) production affects membrane integrity; intracellular accumulation of sodium and water follows, and brain cell injury is caused by neuronal depolarization, glutamate release, an influx of calcium, and release of toxic nitric oxide free radicals. The 'therapeutic window' offered by the 'latent phase' now allows interventions to ameliorate the effects of HI injury, and hypothermia initiated within 6 hours of age shows particular promise.

2. Predisposing factors for brain injury

Hypoxia is central to the genesis of much of the brain injury that occurs in the fetus. Compromised oxygen delivery is a particular risk during labor and delivery, but the fetus is at risk whenever brain ischemia occurs due to impaired cerebral blood flow (CBF). After ischemic injury, reperfusion can potentially cause additional injury or complicate recovery, as can any situations that compromise normal brain perfusion further, including disturbance of oxygen delivery and/or carbon dioxide transport, acid base status, or the supply of energy and metabolites required for normal brain function. Resuscitation of a newborn neurologically depressed by intrapartum asphyxia is such a situation, and ongoing brain injury will occur until effective cardiac output, cerebral perfusion and oxygen transport are restored.

Clinical effects of hypoxia include a disturbance of acid base status. An unrelieved hypoxic event in the fetus causes progressive acidosis which leads to systemic organ dysfunction, including cardiac depression, where compromised contractility and filling reduce cardiac output leading to a reduction in CBF and high risk of brain insult when cerebral hypoxia and ischemia occur. Importantly, cardiac functional impairment can precede depression of fetal heart rate. Hypoxic insults depress brain

function, so following intrapartum insults infants are neurologically abnormal at birth, often require resuscitation to initiate breathing, and cardiovascular support can be needed to stimulate heart function and provide adequate blood pressure and circulation. Tone and behavior usually remain abnormal on admission to the nursery; encephalopathy developing in the hours or days after birth is confirmation that a significant HI insult resulting in brain injury has occurred.

Hypoxic ischemic brain injury is estimated to occur in about 3 out of every 1000 births [8]. Diagnostic features include problems with level of consciousness, tone, respiratory drive, and coordination of sucking and swallowing, and seizure activity which is commonly refractory. In the longer term, the consequences of injury vary between death (15-20%) and complete recovery, with the spectrum of permanent brain injury ranging from mild motor and cognitive defects, to cerebral palsy and severe cognitive disabilities. The pattern and consequences of injury depend on the severity and duration of the insult. The neurovascular and anatomical maturity of the brain relative to the gestational age of the fetus is also a primary factor; co-related elements include the adequacy of metabolic reserves available to the fetus to compensate for oxidative stress, the presence or absence of infection, and pre-existing abnormalities in brain growth and development. Different regions of the fetal brain and individual cell lines have gestation specific vulnerability to damage.

Prematurity: The 10% of infants born prematurely are at particular risk for brain injury; their neurovascular anatomy has limited development making them vulnerable to fluctuations in brain blood flow and oxygen delivery. In those very immature, the brain lacks both the duplication of blood supply that develops as a fetus matures, and the ability to auto-regulate CBF in response to fluctuations in systemic blood pressure. Vascular complexes in areas such as the germinal matrix are vulnerable to bleeding when blood pressure fluctuates, and perturbations insufficient to cause damage in a more mature fetus may generate injury; bleeding is often related to asphyxial stress, and can result from complications of treatment entities very preterm infants require. Mechanisms underlying this form of injury include: variations in cerebral venous pressure, major cerebral vasodilatation or constriction, altered distribution of CBF, systemic fluctuations in circulating blood volume, and significant changes in either oxygen or carbon dioxide tension [11].

Periventricular leukomalacia (PVL) is predominately a condition affecting the preterm infant. The primary causal mechanism is HI injury, with ischemia being the major component. PVL acquired intrapartum is usually associated with abnormal neurological findings at birth, but may manifest as lower limb weakness evident in the first weeks of life. PVL can be aggravated by, or generated as a result of postnatal events. Neurobiologic research has shown that maturational dependent oligodendroglial precursor cells are a major target in PVL, and these are exquisitely vulnerable to damage by free radicals generated during ischemia and reperfusion. PVL is associated with intraventricular hemorrhage (IVH) in approximately 25% of cases. The pathogenesis of IVH is usually multifactorial, and related to: fluctuating CBF; increased cerebral venous pressure; decreased CBF followed by reperfusion; and disorders of coagulation, platelet function and capillary integrity [11].

The commonest clinical situation where pathogenic factors combine to generate sufficient ischemia to cause PVL is when a sick preterm infant requires mechanical ventilation, and problems occur during 'uncontrolled' intubation, with 'fighting the ventilator,' or when a pneumothorax (air leak) compresses the lung, which raises intrathoracic pressure and disrupts normal blood return to the heart; in turn, this reduces cardiac output and brain blood flow. Vascular factors are also relevant; blood transfusion or rapid IV volume replacement pose potential risk due to the pressure passive nature of the immature cerebral circulation; systemic variations in blood pressure, sequelae of sepsis, and the cerebral effects of hypocarbia can render

an infant symptomatic. Many infants with PVL have a normal neurologic outcome. Those with permanent sequelae exhibit a range of problems with varying degrees of severity; including intellectual and visual deficits, usually superimposed on spastic paresis involving the extremities, where the lower limbs are predominantly affected.

In late prematurity (34 weeks to 36 weeks plus 6 days gestation), the vulnerability of the brain to injury, and the pattern of damage commonly seen are different, due to increased structural and functional maturation; at 34 weeks of gestation the brain has 65% of its term volume compared to 13% at 28 weeks, and a fivefold increase in white matter volume occurs between 35 and 41 weeks of gestation.

Low birth weight (LBW) infants are those born <2500 g. and comprise infants born prematurely but appropriately grown for gestational age, and those who are small because of intrauterine growth retardation (IUGR). LBW is further divided into very low birth weight (<1500 g) and extremely low birth weight (<1000 g). Globally 14.6% of infants born are LBW (5-10% in industrialized countries); UNICEF data indicate that LBW infants have a disproportionate death rate and high intrapartum morbidity. Brain injury is caused by many factors, e.g. placental dysfunction and acute compromise of placental gas exchange, and risks in the newborn period due to the causal factors for their small size. Long-term, neurodevelopmental problems occur.

Extremely low birthweight (ELBW) infants are often born close to the limit of viability. Many who survive are at risk of brain injury and neurodevelopmental handicaps; however, advances in care have led to a substantial reduction in severe morbidity, with clear benefits evident for ELBW infants of higher gestation [3]. Consequently, gestational age is a factor that continues to drive interventions aimed at prolonging pregnancy. Where such treatment is an option and fetal wellbeing can be sustained, there are clear benefits for the fetus of longer gestation. Data from a national, prospective, population-based cohort study conducted in all maternity and neonatal units in France in 2011 indicate that survival to discharge, and survival without any severe adverse outcome are both gestation dependent (**Table 1**).

Small and large for gestational age (SGA/LGA) infants are those born below the 10th and above the 90th centiles respectively. Hypoxic composite neonatal morbidity is more common among SGA neonates and traumatic–composite neonatal morbidity more common with LGA. In symmetrically growth-retarded SGA infants, brain size and function are affected; long-term deficits in neural connectivity and cognitive problems can result. Fetal glucose is determined by maternal levels, but impaired glucose metabolism occurs with SGA where hepatic glycogen stores are low at birth, and in LGA associated with maternal gestational diabetes [2].

Placental pathology underlies many causes of compromised fetal growth and development and intrapartum hypoxia, e.g. decreased maturation of the terminal villi is associated with injury to the white matter/watershed areas and basal ganglia [12]; also, conditions that can cause fetal death (toxemia in pregnancy, twin to twin transfusion syndrome (TTTS), hemorrhage from placenta previa and placental abruption and fetal stroke) [13, 14]. Strokes occur between 14 weeks gestation and delivery. Etiology is often obscure; ischemic, thrombotic or hemorrhagic injury occurs; causes include maternal platelet abnormalities, trauma, TTTS, medication (warfarin and some antiepileptic drugs decrease vitamin K dependent coagulation

Gestation in weeks	23	24	25	26	27-31	32-34
Percentage of survivors	0%	11.6%	30%	47.5%	81.3%	96.8%

Table 1.
Gestation-related survival without grade 3/4 intraventricular hemorrhage, cystic periventricular leukomalacia, retinopathy of prematurity stage 3 or higher, severe bronchopulmonary dysplasia, or necrotizing enterocolitis stage 2-3 [3].

factors), parvovirus B19 and cytomegalovirus infections, and protein C deficiency [15, 16]. Diagnosis in utero can be made by ultrasound (US); magnetic resonance imaging (MRI) is the optimal imaging modality [16].

Twin to twin transfusion syndrome (TTTS) occurs in up to 1:4 monochorionic diamniotic twin pregnancies; nearly 100% have placental vascular anastomoses; most are hemodynamically balanced, but severe complications result when there is a chronic net transfusion imbalance between fetuses. Hemodynamically significant shunts classically manifest in the mid trimester; while subtle initially, cardiovascular effects do impact both recipient and donor twins and are an important factor contributing to morbidity and mortality [13, 17]; 70% of recipient twins show echocardiographic evidence of cardiac compromise [18]. Protocols for frequent US of at-risk twins are the mainstay of management; these monitor onset/progression of complications through defined stages of evolution (Quintero stages 1–5), quantify the adverse effects of the altered hemodynamics on each twin, and allow perinatal management interventions that have the potential to improve fetal morbidity and mortality. US provides assessment of amniotic fluid status, measurements of fetal structures, and fetal weight estimates which identify growth disparity, and are predictive of birth weight discordance [19]. As the transfusion of blood from one twin to the other increases, the donor twin becomes oliguric due to decreased renal perfusion, with virtual absence of amniotic fluid; this can be so marked it prevents fetal movement giving rise to the term 'stuck' twin. In contrast, the recipient develops polyhydramnios due to increased urine production. Without intervention to treat TTTS, increasing polyhydramnios will ultimately result in preterm labor, due to the mechanical forces generated by overdistention of the uterus; overall, polyhydramnios is complicated by preterm labor in up to 26% of cases, and premature rupture of the membranes (PROM) in up to 19% of cases.

Ischemia is the principal mechanism underlying brain damage; lesions include white matter infarction, intra-ventricular hemorrhage, hydranencephaly, and porencephaly. In up to 58% of TTTS affected pregnancies combined US evidence is reported of antenatally acquired brain abnormalities and IVH, and periventricular echogenicity assumed to be perinatally acquired [20]. Fetal MRI can identify CNS injury; findings range from ischemic or hemorrhagic lesions in the brain to marked dilation of the cerebral venous sinuses secondary to central venous hypertension.

US can also evaluate flow in the umbilical vein (UV) and ductus venosus (DV). Normally, the UV blood flow velocity waveform has an even non-pulsating pattern, since the pulse waves caused by atrial contractions are not propagated backwards through the narrow ductus venosus. However, if the DV widens, the pulse waves propagate into the UV and result in a pulsating pattern. UV pulsations were first described in fetuses in imminent danger of asphyxia, then in those hydropic due to heart failure. In fetuses exposed to chronic hypoxia, UV pulsations predict poor outcome [21]. The presence of absent or reversed flow in the DV during atrial systole (defined as absent/reversed a-wave) is associated with poor perinatal outcomes because of compromise to mechanisms that normally preferentially supply the fetal brain with well oxygenated blood. The function of the DV is to shunt a portion of the oxygenated blood arriving from the placenta directly to the inferior vena cava, allowing oxygenated blood to bypass the liver. Consequently, DV flow plays a critical role in preferentially supplying oxygen to the fetal brain, in parallel with the other fetal shunts (foramen ovale and ductus arteriosus). And so, US evidence of an absent or reversed a-wave in the DV identifies those fetuses who are at the highest risk of hypoxic brain injury in utero [13, 22, 23].

The expectation of maternal treatment, even for severe TTTS, is for improvement, with probable resolution in utero [24], including regression of fetal cardiovascular pathology and improved myocardial performance. Recovery may take

longer in more severely affected pregnancies, but this is not the case in all series. Survival, particularly for the recipient twin, is likely to be compromised if treatment is delayed [25] hence the relevance of US surveillance and early diagnosis [17].

Maternal Illness during pregnancy: Some are specific to pregnancy such as gestational diabetes; others pre-exist; many have the potential to cause damage, or predispose the fetus to independent risks for neurological morbidity [2]. Some have well known associations with brain injury; rubella and the TORCH group of viruses are examples; TORCH viruses are also a potent cause of perinatal death and a particular burden in developing countries; some are amenable to treatment; early recognition, including maternal prenatal screening, is a key aspect in management [26]. Common upper respiratory tract infections and gastroenteritis, although often of concern to pregnant women, are not usually associated with brain injury [27].

Fetal inflammatory response syndrome (FIRS): Inflammatory mediators are known to precipitate premature rupture of the membranes (PROM) and preterm labor, inflame and cross the placenta, and have been linked to increased risk of fetal brain injury and cerebral palsy [28]. In FIRS, maternal systemic inflammation occurs with activation of the innate fetal immune system and elevation of fetal plasma cytokines. Cytokine production usually generates a normal immune response, but in the immature fetus and premature infant born after FIRS, the complex effects of cytokine activity have been linked to increased infant morbidity and mortality, perhaps because the balance of these agents is imperfectly controlled [11].

Many cytokines are vasoactive, so in the immature brain, focal variations in brain perfusion could result in local ischemia followed by reperfusion; such perturbations may cause cumulative injury to brain white matter due to the primitive neuro-vascular architecture, immature autoregulatory control mechanisms, and sensitivity of maturational dependent cells to free radical damage. The germinal matrix is also particularly vulnerable to variations in brain blood flow and blood pressure [11]; consequently, it has been hypothesized that periventricular hemorrhage would be more likely to occur in the preterm fetus exposed to FIRS.

The initial literature supported a role for inflammatory mediators in premature labor and delivery; linked maternal infection and pro-inflammatory mediators in the neonatal systemic circulation with increased risk of periventricular leukomalacia and/or spastic diplegia; emphasized the synergistic role of inflammation and hypoxia and ischemia when they occur together; and reported a higher incidence of HI brain damage where fetal exposure to maternal inflammation/infection occurred [2]. This literature also states: "For the premature fetus, once clinical chorioamnionitis occurs, rates of sepsis, pneumonia, respiratory distress syndrome and death are all increased by 2-4-fold and long-term neurologic injury is substantially more likely to occur" [29]. Strategies can be used to down-regulate the inflammatory response and treat mothers with signs and symptoms of infection; some antibiotic therapies reduce cytokine production; because of the independent association of elevated maternal temperature with worse fetal outcome, appropriate management to control fever is also cited as a treatment of potential benefit [30, 31].

Recent literature reappraises prior FIRS-related research. Isolated cytokine-mediated injury is not reported in term infants [11], and in the premature newborn, newer studies have found the relationship between chorioamnionitis and brain injury to be attenuated; this difference may result from heterogeneity of the studies, or possibly improved neonatal intensive care [32]. Current literature does conflict on whether or not histopathological chorioamnionitis is linked to an increased risk of white matter injury and intraventricular hemorrhage, or with abnormalities of brain development identifiable via MRI (e.g. variations in cortical thickness). But research continues to emphasize that postnatal complications from infections,

particularly when associated with hypotension in the premature newborn, are associated with an increased risk of white matter injury [33, 34].

Fetal and neonatal Infection significantly increases the risk of brain injury. Mechanisms promoting sepsis include PROM; the risk of fetal infection from membrane rupture beyond 18 hours increases (10-fold), as does the occurrence of perinatal asphyxia, maternal urinary tract infection and colonization with group B Streptococcus [35]. Maternal treatment and prophylactic antibiotics given in anticipation of sepsis to the infant at birth are essential, as by the time confirmatory tests (bacterial cultures) are positive, the risks of infection having disseminated into the blood stream (septicemia) or spread to the meninges (meningitis) are high. Hypotension secondary to sepsis can profoundly compromise brain perfusion and oxygen delivery, and dramatically increases morbidity; once present, it is often refractory to treatment as the underlying mechanisms are multifactorial, including the generation of cytokines, and release of toxic metabolites by bacteria.

Hypoglycemia: During transition to extrauterine life, fetal adaptation normally enables alternative fuels to be metabolized (lactate, ketone bodies, fatty acids) which ensures energy supply to vital organs when blood glucose concentration falls. But once born, this ability is down-regulated, especially by oral feeding [2], and transitional hypoglycemia can occur. While no single glucose value can define hypoglycemia, fully ensure an infant's safety or limit morbidity, management guidelines exist as hypoglycemia can have neurologic consequences [36–38], especially when accompanied by seizures, including: motor and/or psychodevelopmental delay, microcephaly, seizures, visual impairment, and spastic quadriplegia and hemiplegia.

Population data indicate that blood glucose levels as low as 2.0 mmol/L (or even 1.8 mmol/L at 1 hour of age) are not uncommon in healthy newborns. However, various syndromes and metabolic conditions cause or contribute to hypoglycemia. Importantly, HI injury can disrupt normal metabolic adaptation, as anaerobic glycolysis depletes hepatic glycogen and hyperinsulinism can also occur; there is a correlation between lower serum glucose levels and higher Sarnat stages in hypoxic ischemic encephalopathy (HIE).

For at-risk infants, outcome data support raising the intervention threshold from conventional levels. Current screening and management guidelines are that neonates with hypoglycemia persisting beyond the first 72 should be investigated further when levels remain ≤2.8 mmol/L, and ≥ 3.3 mmol/L should be the therapeutic glucose target level in symptomatic/at risk infants. Also, before discharge, those experiencing persistent hypoglycemia should have a 5-6 hour fast, while maintaining blood glucose levels ≥3.3 mmol/L, to ensure safety at home [39].

Differing patterns of damage now help to distinguish hypoglycemic from HI brain injury [5, 40, 41]; the combination on MRI of selective edema in the posterior white matter and pulvinar appears specific even in absence of hypoglycemic laboratory values. In neonates with concurrent hypoglycemia and HIE, injury is synergistic, and the imaging features of both HI injury and hypoglycemia may be detected [5].

Hyperglycemia: A blood glucose concentration > 125 mg/dL (6.9 mmol/L) is a common metabolic abnormality encountered in preterm and critically ill newborns [42]. Management varies; often iatrogenic, hyperglycemia can cause or aggravate brain damage, principally because of the hyperosmolar state that ensues [43].

Hyponatremia in the premature can cause sensorineural hearing loss, cerebral palsy, intracranial hemorrhage, and increase mortality following asphyxia [44, 45].

Hypernatremia/hyperbilirubinemia when extreme are neurotoxic. Inadequate fluid intake in immature infants and those primarily breast fed is contributory [46, 47]. Kernicterus selectively damages the globus pallidus and subthalamic nuclei [8, 48]; hazardous hyperbilirubinemia is often preventable; health care professional

compliance with best practices for screening, phototherapy and related treatment is required [49, 50].

Seizures: Major causes include brain malformation or structural injury, hypoxia, infection and reversible metabolic disorders. Clinical signs vary from subtle movement disorders to focal or generalized, brief or sustained convulsive activity. Abnormal movement often involves the eyes (blinking, staring, horizontal tonic deviation), mouth (lip smacking or sucking, tongue thrusting), and extremities ('bicycling', 'rowing' or jerking movement). Respiratory (apnea) and cardiac effects (tachycardia or bradycardia) occur, often with color change and significant oxygen desaturation. Focal clonic seizures may indicate brain damage due to arterial or venous infarction. Clinical signs suggesting seizures require confirmatory EEG. MRI can distinguish between seizures due to HI events and other causes. Preventable or reversible causes include hypoglycemia, hypocalcemia, hyponatremia, hypoxemia and acidosis. Seizures do not always imply poor neurodevelopmental outcome for affected infants. But the severity of seizures in human newborns with perinatal asphyxia is independently associated with brain injury, and not limited to structural damage detectable by MRI [51]. In term newborns, the predominant pattern of watershed and basal nuclei injury after hypoxic ischemic encephalopathy is a valuable predictor for later epilepsy; injury to the motor cortex, hippocampus and occipital lobe are also independent risk factors, and the severity of brain injury and recurrent neonatal seizures elevate risk [52]. Delayed treatment likely increases the probability of residual consequences, because of the stresses placed on the brain by the high oxygen and substrate requirements implicit when seizures are prolonged.

3. Hypoxic brain injury

As the physiologist Haldane said: "Hypoxia not only stops the machine it wrecks the machinery" [2]. A healthy fetus can respond to, and tolerate, the early effects of hypoxia, and the degree of acidosis that occurs initially in response to the associated retention of carbon dioxide. Acute hypoxia promotes adenosine release, which reduces fetal cerebral oxygen consumption via action on neuronal A1 receptors on the cerebral arteries, and initiates vasodilatation through activation of A2 receptors; release of nitric oxide and opioids and direct effects of hypoxia on the vascular endothelium also contribute [53]. As a result, while fetal vascular resistance can decrease up to 50%, the net effect is to maintain CBF with only minimal reduction in oxygen delivery; but normal or elevated mean arterial blood pressure is critical in parallel, and once hypotension ensues the brain suffers from the resulting ischemia.

With moderate HI stress and evolving acidosis, the fetus also has the physiologic ability to preferentially perfuse the deep structures of the brain that have higher metabolic rates (brainstem, cerebellum, basal ganglia). However, this compensatory redistribution of blood from the anterior to the posterior circulation results in the brain's cortical areas being less well perfused, and hence, if ongoing hypoxia remains unrecognized and unrelieved over the course of an hour or more, the end result is damage to cortical white matter, and the watershed areas of the cerebral hemispheres. In contrast to this partial prolonged pattern of injury, situations occur where the HI event is near total in nature and the effect profound. With such insults, acidosis develops relatively abruptly, and little or no compensatory redistribution of blood to the deep brain structures occurs, because there is no time for effective redistribution of CBF to maintain their perfusion. Hence it is the basal ganglia and thalami that are predominantly injured, and damage happens over a much shorter time frame [9, 54–56]. In the premature, mild to moderate HI injury results in periventricular leukomalacia and germinal matrix bleeds, and in full term

neonates parasagittal watershed infarcts are seen [55, 57]; severe injury in both term and preterm infants involves deep gray matter.

Distinction between partial/prolonged and near total/profound/patterns of injury is important from a diagnostic and prognostic standpoint, for understanding potential mechanisms for prevention, and over issues of causation in a medico-legal context. Modern neuroimaging is the definitive way to distinguish between them based on the selective geographic patterns of brain damage caused. Importantly however, mixed patterns of injury are also seen that involve both the cortex and deep structures [55, 57]. The mechanisms involved can be either superimposed insults involving periods of both partial/prolonged and near total/profound injury, or, situations where partial and prolonged injury is severe enough to extend to involve the deep brain nuclei, or vice versa, when a near total, profound event is extensive enough to also involve cortical damage [11, 58].

The time line of near-total HI events can be extrapolated from data obtained in animal studies, where fetal monkeys were exposed to complete (i.e. total) hypoxia and ischemia, generated by ligating the umbilical cord and preventing breathing. These animals could tolerate 10 minutes of HI insult without permanent effects if delivered and resuscitated immediately, but, where the HI event was continued beyond this 10-minute period for an additional 10 minutes, a progressive and cumulative increase in the level of neurological damage was then evident. Where the whole insult extended beyond 20 minutes, the fetal monkeys died, in spite of delivery and immediate resuscitation.

In applying these data to the human fetus, it is recognized that what occurs most often is a near total (profound) interruption of brain blood flow and oxygen delivery, rather than an event where hypoxia and ischemia are absolutely total in nature. Hence the time-line for tolerance of such events, and the period over which brain damage evolves, are accepted as being longer than in the landmark animal studies conducted by Myers [59–62]. For this reason, it is generally agreed that approximately 15 minutes, and possibly up to 20 minutes, of sudden profound asphyxia can be tolerated by the human fetus prior to brain damage beginning (in contrast to the 10 minutes seen in the animal model). Then, after this 'grace' period, damage to the brain begins to occur, and over a further period of 15 to 20 minutes the extent and severity of injury become progressively more profound over time. And beyond this time frame, a human fetus is usually born dead. It is important to recognize that the principal mechanism that causes fetal asphyxial brain injury is cerebral ischemia caused by the severe reduction in CBF that occurs as a result of hypoxic myocardial depression significantly reducing cardiac output (CO). The fetal heart has a fixed stroke volume, which means that CO, and the amount of blood supplied to the brain are a direct function of the rate of contraction; so, for example, with bradycardia where fetal heart rate slows to half normal, this equates to a 50% fall in CO, and a comparable reduction in CBF will result. CO also decreases where tachycardia accompanies hypoxic stress; at high heart rates poor contractility secondary to acidosis is then compounded by incomplete atrial filling in diastole.

The relationships between the geographic pattern of asphyxial brain injury and type of resulting disability have been defined [63], and the predictors of long-term morbidity delineated [64]. Near-total insults of moderate duration and degree which have the basal ganglia and thalamic pattern of damage, predominantly lead to athetoid or dystonic cerebral palsy, with intact or mildly impaired cognitive development. When severe, near-total insults damage the cerebral cortex in addition to the deep brain structures; and severe spastic quadriplegia results, with microcephaly, significant cognitive deficits and cortical visual impairment. The extent of injury is strongly associated with the intensity of resuscitation, the degree of encephalopathy, and severity of seizures [55, 65]. Prolonged partial insults of moderate degree with

injury confined to watershed regions cause variable degrees of cognitive deficit and epilepsy, and can be associated with spastic quadriplegia. But, when more severe or prolonged, injury causes extensive cortical brain involvement, or global brain injury; the end result is spastic quadriplegia, severe cognitive impairment, cortical visual impairment, and microcephaly. In addition, symptomatic brainstem involvement can be associated with severe patterns of injury, and lead to non-survival [66].

Hypoxic ischemic encephalopathy (HIE) is a clinically defined syndrome of disturbed neurological function in the earliest days of life, caused by intrapartum or late antepartum brain hypoxia and ischemia [67]. HIE evolves clinically following significant HI insult, and is a major predictor of neurodevelopmental disability. HIE develops in 1 to 8 per 1000 live births in developed countries, and up to 26 per 1000 worldwide [65, 67]; not all cases of neonatal encephalopathy are due to anoxia or HI injury [8, 58], but epidemiological studies confirm the association of HIE with pregnancy related risks, and intrapartum risk factors that predispose the fetus to hypoxia; 15-20% of affected infants die; in about 25% of survivors permanent neurologic deficits remain. Prospective studies employing MRI suggest that the majority of HIE occurs as a result of HI insult and brain injury at or near the time of birth [41]. Postnatal exacerbation of intrapartum acquired injury occurs relatively rarely (10%), but is a potentially preventable component in many instances [11, 67].

Hallmarks of neonatal encephalopathy are neurological depression, with altered level of consciousness and often respiratory depression, abnormal muscle tone and power, disturbances of cranial nerve function, and seizures. HI injury is strongly suggested in a neurologically depressed infant by associated acidosis, and further confirmed by concomitant multi-organ injury [58, 65, 68].

Acidosis has two components: respiratory - from retained carbon dioxide, and metabolic - from accumulation of fixed acids (lactic acid and β-hydroxybutyrate). While acidosis present at birth usually resolves in the first hours of life, HIE progresses with further depression of consciousness, abnormalities in tone and movement, and onset of seizures. Infants exhibit a range of behaviors and alterations of conscious level from lethargy and obtundation to irritability and a hyper-alert state. Similarly, disorders of tone range from a marked decrease to hyper-tonicity. Abnormal movements include tremors, jitteriness, mouthing and blinking, and 'bicycling' of the legs, through to frank seizures. Other manifestations include apnea, with bradycardia and impaired oxygen saturation, shrill cry, feeding difficulty (due to poor coordination of suck or altered peristalsis, and occasionally brain stem damage), absence of the Moro and/or gag reflexes, and exaggeration of deep tendon reflexes. Decerebrate or decorticate posturing may be seen. Sarnat et al. defined three levels of severity (mild, moderate and severe); these are linked to the probability that HIE will result in permanent neurological consequences [69].

The pathophysiology of HIE is now better understood and treatment with hypothermia has become the foundation of therapy [67]. All affected infants require supportive management that anticipates and limits the adverse effects on the brain of fluctuations in cerebral perfusion, metabolic instability, sepsis, suboptimal respiration, and any situation that increases oxygen and energy demands. This involves correction of hypotension, attention to glucose, fluid and electrolyte homeostasis, maintenance of $PaCO_2$ in the normal range, and treatment of seizures [58, 67]. Neuroimaging (US, CT, MRI) is best done at defined periods after injury [41, 57]; MRI in particular can then define the diagnosis, pattern, severity, timing and prognosis, and help rationalize hypothermia and other interventions, including the withdrawal of support. Several neuroprotective agents that can be combined with hypothermia have entered clinical trials; new biomarkers for HIE are being sought [70]. Affected survivors need follow up to manage their handicaps.

4. Multisystem involvement secondary to hypoxia

The effects of hypoxia extend beyond the brain [9, 11, 67, 68], associated injury to other organs principally occurs due to compensatory redistribution of blood during partial and prolonged insults, but can follow profound, near total episodes; 60-80% of affected neonates exhibit single or multiple organ injury [68].

The fetus often passes meconium (fetal bowel contents) in utero due to hypoxia; a combination of gut ischemia and reduced sphincter tone secondary to neurological depression is the likely mechanism, hence, the presence of meconium is a marker for probable HI. Following a recent event, meconium seen is usually thick and green; after a remote event, because mixing with amniotic fluid disperses and thins the meconium, the liquor is evenly discolored, and the fetal skin may be stained green.

In the neonate, multiple organs can show varying effects from hypoxia.

The lungs can be injured directly and indirectly; inhaled meconium, surfactant depletion, pulmonary hypertension and left ventricular failure can all result in impaired gas exchange and the need for assisted ventilation. The risks of brain injury increase where such effects are superimposed on the poorly compliant lungs of a preterm infant. A pneumothorax (air leak into the pleural space) causing lung compression and elevated intrathoracic pressure is less common with modern ventilation techniques, but when it occurs, major disturbances in cerebral perfusion pressure result that increase the risk of brain ischemia and hemorrhage.

The heart can suffer functional and structural damage; acidosis seriously impairs myocardial function, myocardial ischemia further compromises conduction and mechanical contractile efficiency; affected neonates often require fluid resuscitation at birth and inotropic agents (dobutamine/dopamine) to maintain their circulation. Abnormalities on ECG and echocardiogram, and elevated cardiac enzymes (creatine kinase–MB fraction/troponin T levels) reflect heart dysfunction and damage.

The kidneys: Absent or significantly reduced urine output in the 24 hours following HI is common, associated hematuria indicates renal tubular damage. Renal injury is the best systemic marker of potential brain injury when oliguria (urine output <1 ml/kg/h) is associated with an abnormal neurological exam [68]. Blood urea and serum creatinine rise progressively and peak in the days following injury. Inappropriate secretion of antidiuretic hormone (ADH) causes hyponatremia; hypoxia stimulates the carotid body chemoreceptors to secrete ADH which causes fluid retention, and a secondary fall in serum sodium concentration.

The liver: Elevated enzymes reflect hepatic cellular damage; lactate dehydrogenase (LDH) is the best hepatic predictor of HIE (sensitivity 100% and specificity 97%), and also of long-term outcome after HIE [71]; blood glucose concentration can fluctuate, with hypoglycemia being most common [72].

Bone marrow: Increased release of nucleated (immature) red blood cells (NRBC) and reduction in platelet numbers (thrombocytopenia) reflect hemopoietic effects. After HI, platelets numbers fall by 12 hours, with the nadir at 2-3 days [2], while NRBCs peak in the hours after birth and fall by 50% after 12 hours [73]; distinct patterns relate to timing of HI [74]. Hypoxic events likely induce exaggerated erythropoiesis as a compensatory response, with release of NRBCs into the fetal circulation. Elevated NRBCs are associated with intrapartum fetal distress and acidemia at birth secondary to hypoxia, with a direct correlation reported between decreasing UA pH and NRBC elevation in the term human fetus. Newborns with elevated NRBCs suffer a significant increase in both short-term morbidity and mortality and long-term disability [75]. NRBC counts are best given as an absolute number per unit volume rather than relative to 100 white blood cells as this avoids misleadingly low

values when wbc counts are high; published values indicate normal counts decrease with advancing gestation and increasing birth weight [73, 74]. A value >1000/mm^3 (or > 10-20/100 wbc) in the first hours of life is considered elevated [73]; A prospective case-controlled study identified that a NRBC count of >13/100 leukocytes had a sensitivity of 81.3% and a specificity of 94.4% in predicting adverse outcomes [76]. In neonates subsequently cooled, those with absolute NRBC counts >1324/mm^3 within 6 hours of birth had high risks of abnormal MRIs and adverse 2-year outcomes; the combination of NRBC count and other early markers, such as lactate levels and EEG, could increase the overall predictive ability [77]. The magnitude of increase in NRBCs is a function of the severity and duration of asphyxia, and a reliable index of perinatal brain damage [73–77].

Metabolic markers: Plasma lactate is an important marker for recent tissue hypoxia; lactate is a metabolite in aerobic metabolism, and measurements in arterial blood at 30 minutes of life show lactate to be as equally valuable as base deficit in assessing the severity of birth asphyxia; elevated concentrations >9 mmol/l are associated with moderate or severe encephalopathy and PVL (sensitivity 84% and specificity 67%) [78]. Low serum calcium and elevation of bilirubin can also occur.

Gastrointestinal tract: abnormal peristalsis underlies feeding intolerance after hypoxia, and the risk of necrotizing enterocolitis is increased [68]. Infants also feed poorly due to an impaired rooting reflex, reduced tone, diminished coordination and drowsiness; associated cranial nerve and brain stem lesions contribute.

5. Adjuncts to comprehensive care

Fetal ultrasound (US): Endovaginal ultrasonography has become the standard imaging measure in pregnancy. US uses pulsed high-frequency sound to produce images and employs terminology and standardized interpretations based on defined criteria to ensure safe maternal examination, and prevent inadvertent harm to early normal pregnancy [79]. US provides routine confirmation of gestational age/due date, detects fetal anomalies, oligo or polyhydramnios, and provides assessment of fetal growth parameters in early pregnancy [80]. Protocols also exist for the management of specific clinical scenarios that pose a risk for the fetus and require increased fetal surveillance; these allow for appropriate referral when complications are suspected, e.g. for intrauterine growth retardation, and monochorionic dichorionic twin gestation where there is a high risk of twin-to-twin transfusion syndrome developing [81].

Fetal scalp blood sampling: can assess the evolution of hypoxia and acidosis via blood gas measurement or lactate analysis, once the membranes have ruptured and the fetal head has descended into the birth canal during the later stages of labor.

Fetal heart rate monitoring (EFM): The physiologic perturbations in fetal oxygenation and hemodynamics that changes in fetal heart rate (FHR) reflect, provide the rationale for FHR measurement and EFM intrapartum [56]. With onset of hypoxia, physiological effects on the fetus usually generate detectable changes in fetal heart rate pattern, as the myocardium is sensitive to reduced oxygen tension, elevated carbon dioxide, and progressive evolution of acidosis. From a preventive standpoint the importance of EFM is that clinically relevant FHR changes are usually evident before the brain is affected sufficiently for permanent damage to begin.

Assessment at birth: Transition to extra-uterine life is physiologically complex. Where needed, resuscitation must mitigate any residual effects of compromised organ function or intrapartum events that have depressed or damaged the brain. A key element in reducing morbidity is the immediate availability of skilled personnel able to provide the well-established neonatal life support (NALS) priorities for resuscitation [68], assess the history, intrapartum events and clinical status of the

infant, and order the level of care and specific diagnostic and treatment entities required.

Apgar score: Named for Virginia Apgar, this is intended as an objective index to evaluate the condition of a newborn infant based on a rating of 0, 1 or 2 for each of the five components: color, heart rate, response to stimulation of the sole of the foot, muscle tone, and respiration. Scores are determined by observing/examining the newborn infant in real time at 1, 5 and 10 minutes of age. Scores principally gauge progress in response to resuscitation; persistently low scores equate with failure to respond, and imply the newborn has significant physiologic problems. Apgars were not meant to be an outcome parameter. Also, retrospectively estimated scores are problematic when they do not match contemporaneous event descriptors in the resuscitation record. Care with interpretation is also required where an infant is premature due to an associated degree of physical immaturity, and where active life support (e.g. assisted ventilation) is generating the improvements observed.

Umbilical cord blood gas analysis: Fetal oxygenation and acid base status can be assessed from paired blood samples collected from the umbilical vein (UV) and arteries (UA) at birth; this is an integral part of monitoring high-risk deliveries [82], but an understanding of fetal placental perfusion and how specific conditions affect values are necessary for accurate interpretation. Cord compression, for example, is associated with normal values when acute and complete, in spite of the infant being profoundly acidotic systemically, as they reflect fetal status when cord flow ceased. In contrast, partial restriction causes UA and UV values to progressively widen, and with impaired maternal placental perfusion UA/UV differences are small [82, 83].

Normally, oxygenated blood from the placenta flows through the UV and preferentially supplies the fetal brain and heart via shunts that bypass the liver; repeated uterine contractions during labor exert a significant, but manageable metabolic stress on the fetus. But when labor is precipitous, or contractions are abnormally frequent or prolonged, uterine artery blood flow becomes restricted, and intercontraction restoration of placental perfusion is delayed as it is dependent on uterine relaxation; in this and similar scenarios maternal to fetal oxygen transfer via the UV can suffer sufficiently for HI injury to occur. Where blood return through the UA is also affected, normal removal of carbon dioxide from the fetus is reduced.

Acidosis occurs as a consequence of cellular hypoxia (inadequate oxygenation), tissue ischemia (inadequate blood flow) and retention of carbon dioxide; the unit of measurement, pH, is on a logarithmic scale, so small differences represent a major change in the degree of acidosis. Bicarbonate naturally buffers acid production; as reserves are depleted, base deficit increases. With resolution of acidosis, PCO_2 values are restored first, followed by bicarbonate and pH; base deficit remains abnormal longest. Normal cell metabolism only occurs when pH is held within a narrow range, beyond these limits, cells progressively lose their ability to sustain normal function and maintain their metabolic integrity, and organs begin to fail.

Blood gas data are compared to the reference range of the testing laboratory. Significant, recent HI stress usually manifests with low oxygen, elevated PCO_2, low pH, low bicarbonate and high base deficit, with UA values most affected. However, it is most relevant clinically to define pathological acidosis as the threshold at which the incidence of adverse events starts to correlate strongly [83]. Criteria to define an acute intrapartum event as sufficient to cause cerebral palsy include UA pH <7.00 and base deficit of >12; infants with a pH <7.0 who are not vigorous are at high risk of adverse outcome [84], and the threshold for moderate or severe newborn complications is defined as a UA base deficit of >12 [85]. With worsening acidosis progression of adverse sequelae rises sharply; in one reported series, HIE occurred in 12% of infants with cord pH <7.0, in 33% with pH <6.9, and in 80% with pH

<6.7; a pH <6.8 equated with the probability of neonatal death [86]. Persisting lactic acidosis is associated with severe encephalopathy [82]. Identifying those at risk is especially important now, since neuroprotection strategies are available.

Hematology: White blood cell (wbc) counts can be strongly indicative (but not always diagnostic) of the presence of infection. Elevated total wbc numbers, a high proportion of neutrophils (granulocytes), and elevated primitive (band) cells indicate that stimulation of the bone marrow by inflammatory cytokines has occurred; very low counts often indicate inability to mount an effective immune response. Elevation of band cells is the earliest change in response to inflammatory stimuli, although hypoxia can also result in an increase in band cell number [87].

Hemoglobin concentration and hematocrit are used to identify anemia and polycythemia where too few or too many red cells are circulating respectively. Both circumstances compromise oxygen delivery; anemia by limiting the amount of oxygen that can be transported, and polycythemia by reducing the ease with which blood flows, which also increases the risk of blood vessel occlusion (thrombosis), and is one of the mechanisms underlying stroke. Also, by following serial measurements from birth, situations can be identified where bleeding occurred while the fetus was in utero. After significant blood loss, the volume of the blood in the circulation is reduced, but the hemoglobin concentration remains the same initially, then, as physiological compensation for the blood lost occurs, fluid is drawn into the circulation to restore blood volume and, as a consequence, hemoglobin concentration and the number of red cells per unit of volume (hematocrit) fall.

Blood chemistry: Electrolyte and glucose measurements, in parallel with blood gas analysis of pH, oxygen and carbon dioxide tension, bicarbonate and base deficit, plasma lactate, serum calcium and liver transaminases are the mainstays of clinical monitoring in brain injured infants, particularly when multisystem involvement complicates the course of neonatal encephalopathy. A small but complex group of congenital metabolic abnormalities causing neonatal encephalopathy exist [58]; these require expert assessment, comprehensive investigation and management.

Neuroimaging: Modalities include ultrasound, computerized tomography and magnetic resonance imaging [55, 88]. US provided the initial method for imaging brain structures and is still clinically attractive because of the ability to study sick pre-term infants in the nursery. The advent of CT greatly advanced knowledge of brain development and injury. But MRI is now the imaging modality of choice, in spite of cost, due to the lack of ionizing radiation and its superior sensitivity and specificity in detecting brain abnormalities. CT remains relevant for infants too sick for MRI. MR image interpretation needs to be as sophisticated as the technology.

Magnetic resonance imaging (MRI) is now invaluable in assessing the neonatal brain following suspected perinatal injury. Imaging during the first week of life is prognostic and can aid management decisions. MR imaging is an excellent predictor of outcome following perinatal brain injury; characteristic lesions and patterns of changes are at their most obvious on conventional imaging between 1 and 2 weeks from birth [7]. Diffusion-weighted imaging (MRI sensitive to water diffusion) allows early identification of ischemic tissue; associated restricted diffusion on day 3 of life implies injury was acquired around the time of birth, and is not the late manifestation of remote in utero injury sustained during the third trimester [6]. However, DWI may underestimate the final extent of injury, particularly in basal ganglia and thalamic lesions. The outstanding contrast resolution of MRI, superimposed on the ability to image in any plane, means even subtle brain malformations are identified.

Like US and CT, MRI scans are best done at defined intervals after birth (3-5 and 10-14 days of life) for accurate diagnosis, timing and evolution of injury [55, 57].

Pathology identified includes structural developmental abnormalities, edema, hemorrhage, early ischemic damage, localization of the predominant injury to either cortical tissue or deep brain structures, the evolution and end stages of scarring, and, onset and progression of hydrocephalus or microcephaly. Importantly, intrapartum and late antepartum HI damage can be distinguished from congenital structural effects or lesions due to acquired causes that occurred well prior to birth, so MRI scans can identify damage caused to an otherwise normal and pristine brain.

MRI, magnetic resonance spectroscopy, and diffusion-weighted MRI have identified the patterns of brain injury that evolve after HI insults. Studies also define the severity of the insult and can indicate the age at which it probably occurred. Injury evolves over days, if not weeks before the final stage with scarring is evident. The anatomical regions of the brain affected define the mechanism of injury. Distinction can be made between an insult that involved a relatively short period of total or near total hypoxia/ischemia (profound hypotension), or one occurring over a more prolonged period where HI was partial in degree (moderate hypotension).

In near total insults, the most metabolically active brain structures are damaged; the lentiform nuclei, especially the posterior putamina, the ventrolateral thalami, the Rolandic cortex and the hippocampi are predominantly injured, while there is little or no involvement of the remainder of the cerebral cortex.

In contrast, in partial and prolonged hypoxia, cortical white matter integrity is compromised, and there is relative preservation of the basal ganglia and thalami. In severe cases the whole cortex may be involved, while with milder injury, the principal areas damaged are the interfaces between the perfusion zones of the anterior, middle and posterior cerebral arteries. An excellent schematic derived from a medicolegal database of MR images of term neonates with partial-prolonged HI injury illustrates the geography of the inter-arterial watershed zone [89].

While these are the two distinctive and predominant patterns of HI brain injury seen, in reality, the type, pattern, duration and variability in severity of HI are a continuum, so there is a spectrum of MRI findings, and mixed patterns of damage are seen, with changes of varying degree in both the basal ganglia thalami and cortical regions [55, 57]. Very severe injury from moderate or profound hypotension can also cause global brain involvement, and extend to include the brainstem [66].

MRI detectable changes take time to evolve; the first abnormality seen is diffusion restriction which peaks at about 72 hours [57]; brain edema, identified as T2 hyperintensity, reflects the progression of energy failure that follows brain cell damage, and precedes cell death due to the apoptosis necrosis continuum. Where there is significant involvement of the cortex, abnormal T1 hyperintensity is evident from about 1 week following the HI event; this can persist for several weeks. T1 hyperintensity due to basal ganglia damage is visualized over a similar time frame. The end result of injury is permanent scaring (gliosis), and compensatory enlargement of the ventricles (ventriculomegaly) [7, 55, 57].

Destructive lesions characterized by periventricular hyperintensity, focal defects in the germinal matrix, and areas of abnormal signal intensity occur in developing white matter. In encephalopathic term newborns, non-cystic white matter injury is a distinct and common pattern. A helpful sign in those >37 weeks gestation is loss of normal signal intensity in the posterior limb of the internal capsule. Hemorrhage is associated with hypointense areas; signal intensity depends on degree of evolution.

Periventricular leukomalacia can develop during fetal life and in the newborn period. Imaging predominantly identifies PVL in preterm infants, but importantly, lesions also occur in term and late preterm infants (those born between 34 weeks and 0 days and 36 weeks plus 6 days gestation) [90].

Fetal MR imaging is a technique that complements prenatal sonography as it has higher contrast resolution and allows direct visualization of the fetal brain, and

hence more readily identifies both cerebral malformations and destructive lesions, including agenesis of the corpus callosum, cerebellar dysplasia, germinal matrix hemorrhage, IVH, multicystic encephalomalacia, periventricular leukomalacia, periventricular nodular heterotopias, porencephaly, and sulcation anomalies. For post-natal studies, diffusion-weighted MR imaging and proton MR spectroscopy are the most sensitive modalities for diagnosis in the early hours following injury.

Future advances in MRI hardware and software will likely enable neuroimaging technologies to contribute more by further delineating the site(s), progression and extent of injury; this will aid evaluation of causation and timing, and advance care strategies able to reverse or mitigate the long-term effects of perinatal brain injury.

Electroencephalogram (EEG): Patterns of brain waves obtained allow the location and relative severity of various brain pathologies to be identified. Seizure activity occurring in the brain but not visible clinically is detected. Patterns of depression of cortical brain activity on EEG have been defined that are associated with varying stages and severity of HIE [69]. Serial measurements document the evolution of, and recovery from, abnormal brain function and the effect of therapy.

Placental pathology: Examination of the placenta is an integral part of investigation of fetal brain injury and neonatal encephalopathy [67]. Pathology provides key information related to the fetus, and causal mechanisms underlying intrapartum events [91] e.g. fetal distress, chorioamnionitis and hemorrhage; and to maternal conditions that affect placental function and fetal oxygenation e.g. hypertension and diabetes. Evidence of placental insufficiency links to fetal growth retardation and increased risk of fetal distress. Any significant disturbance of placental gas exchange and fetal perfusion poses risks of brain injury; examples include pre-eclamptic toxemia, hemorrhage from placenta previa, uterine tachysystole, cord compression and placental abruption [92–94]; abruption is the commonest identifiable antecedent factor for injury in preterm infants with HIE. Examination can also identify causal pathology in the absence of a 'sentinel event' [67] and in circumstances where the umbilical cord is vulnerable e.g. abnormal insertion, tearing, true knots, prolapse, occlusion, and entrapment, each of which causes recognized adverse consequences for fetal oxygenation. Decreased placental maturation is associated with increased risk of white matter/watershed injury with or without basal ganglia/thalami involvement, and chronic villitis with basal ganglia/thalami injury irrespective of white matter injury [93].

6. Prevention of brain injury

Prevention of brain damage requires knowledge of the etiologies underlying injury, awareness of the availability of preventive measures, and timely employment of them to address the underlying cause. In addition, situations that may aggravate existing or evolving brain injury need to be anticipated, recognized, and appropriate evidence-based care provided that is capable of improving outcome.

Maternal and paternal medical history and lifestyle: Maternal nutrition and trace element status, the health and age of both parents at conception, and other factors related to current developmental origins of health and disease (DOHaD) concepts are all relevant to prevention [4, 95]. The risk of fetal brain injury is decreased where mothers maintain a good diet, add folic acid and iron plus required prenatal supplements (vit. D, calcium), avoid smoking and the detrimental effects of alcohol and drugs, and exposure to TORCH infections is prevented. There are benefits to becoming a mother earlier rather than later in life, and from both parents having lifestyles that promote physical health and mental wellness especially at conception.

Antenatal care is central to optimizing the fetal environment, monitoring maternal health, detection of entities that require intervention or forward planning, and enabling pregnancy to progress to term. Care should ensure that fetal growth progresses normally, all indicated US and lab studies are done, necessary referrals are made, and parents prepared appropriately. Prevention of brain injury centers on labor and delivery, but relies on attention to multiple factors throughout pregnancy. The fetal brain probably benefits most from prevention of avoidable preterm delivery, and therapy such as antenatal steroid use to mature the fetal lung when prematurity is inevitable. Post maturity with the inherent risks of placental failure and increased fetal morbidity must be avoided, especially where at risk situations exist such as gestational diabetes. Prior cesarean section requires special planning and supervision, to avoid uterine complications that can jeopardize fetal wellbeing.

Monitoring during pregnancy: Confirmation by US of gestational age reduces premature delivery; monitoring of fetal growth parameters anticipates intrauterine growth retardation, and can identify placental anomalies that increase morbidity. Genetic screening can detect anomalies linked to brain defects; termination of pregnancy is a care option when a fetus is known to have a major anomaly. Surveillance for a broad range of maternal illnesses is possible with investigative protocols and preventive entities available to optimize maternal care and fetal health, and select appropriate timing, mode and location of labor/delivery.

Advance consultation with obstetric and neonatal referral centers should occur where necessary to obtain advice regarding priorities for care and delivery.

Transport with the fetus in utero should occur if care at a higher level is required to optimize the logistics of delivery and provide for a good neonatal outcome [2].

Intrapartum care: Guidelines exist in most jurisdictions based on the evidence base for best practice in obstetric management where the health of the mother and/or fetus becomes at risk. Monitoring of maternal and fetal wellbeing requires entities that provide for anticipation, detection and management of complications, particularly those linked to maternal emergencies and/or generate fetal distress; e.g. placental insufficiency, failure or abruption, hemorrhage, hypo or hypertension, uterine tachysystole or rupture, obstructed labor, or cord compromise. Importantly, a non-reassuring electronic fetal heart rate pattern, or changes in FHR reflecting alteration in fetal cardiac function, usually occurs prior to brain metabolism being affected sufficiently for neurological damage to begin. Hence, recognition of a 'non-reassuring' tracing, a 'sentinel event' involving fetal heart function, or a pattern known to be associated with pathology (e.g. cord compression) [84], allows prompt assessment, and instigation of interventions required to relieve compromised fetal oxygenation, expedite instrumental delivery, or do an emergency cesarean section.

Staff with the required skills must be available to comprehensively resuscitate any sick newborn, and promptly address residual morbidity after delivery. Skill with assisted ventilation is important, as prevention of detrimental hyperoxia and hypocarbia reduces brain injury risk in premature infants, and improves outcome in any sick neonate where hypoxia and ischemia have occurred [67]. After appropriate resuscitation, all the care entities required to minimize the possibility of a brain injury being sustained, or an existing intrapartum injury compounded, must be provided. Priorities to do this include: support of respiration and the circulation; provision of a neutral thermal environment, appropriate hydration and nutrition; prophylactic antibiotics and management of proven infections; hematological and biochemical surveillance; and neuroradiological monitoring. Good communication and support of the physical and mental wellbeing of both parents must be ensured.

Controlled hypothermia is indicated where HIE develops; the concept of cooling being beneficial stems from animal studies and the neuroprotective effects of hypothermia in children following near-drowning and during cardiac surgery. Interventions to minimize the effects of hypoxia and HIE postnatally continue to evolve; early studies of short periods of cooling had limited, contradictory results. Later studies were more promising; where cerebral hypothermia was initiated after HI insult, and before onset of secondary energy failure, newborns with moderate encephalopathy had better neurodevelopmental outcome compared to normothermic controls [96]. Neuroprotective hypothermia for neonatal encephalopathy has been the subject of systematic review [97]; it is currently the standard of care for moderate and severe HIE; improves survival without CP or other disability by 40%; and current protocols are considered near optimal. Therapy within 6 hours of age at 33–34°C, continued for 72 hours, decreases death or disability at 18 to 24 months of age and increases the number of normal survivors [8, 67, 97]. Defined obstetric antecedents indicative for cooling include umbilical cord prolapse, uterine rupture and placental abruption [98]. In cooled encephalopathic newborns, time to recovery of amplitude integrated EEG is a good predictor of outcome [8]; early MRI scans (3-6 days of life) robustly predict the predominant pattern and extent of injury, and late scans (10-14 days) long-term outcome, and the predictive value of MRI is not affected by hypothermia [99, 100].

In future, earlier initiation of cooling after resuscitation may prove beneficial; ongoing research aims to identify other neuroprotective approaches that can be used in parallel, and evaluate potentially beneficial therapeutic agents; ways that may help reduce the incidence of IVH during rewarming are also being explored.

7. Conclusion

Many causes of fetal and neonatal brain injury are now preventable. The consequences of cerebral hypoxia and ischemia remain considerable. Evidence-based care strategies during pregnancy and for premature and sick newborns infants are improving outcome.

Author details

Andrew Macnab[1,2]

1 Department of Paediatrics, Faculty of Medicine, University of British Columbia, Vancouver, Canada

2 Stellenbosch Institute for Advanced Study, Wallenberg Research Institute at Stellenbosch University, South Africa

*Address all correspondence to: andrew.macnab @ubc.ca

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Chapter 5

Traumatic Brain Injury in Children

Dyah Kanya Wati

Abstract

Traumatic brain injury (TBI) in children occurs as a result of a sudden bump, roll, or jerk to the head or a penetrating injury to the head that interferes the normal brain function. Traumatic brain injury (TBI) is the leading cause of death and disability in children. More than half a million children present annually to the emergency department for TBI-related visits, and resulting in the death of >7,000 children annually in the United States, with highest incident rates seen in children aged 0–4 years and adolescents aged 15 to 19 years. In Indonesia, from Riskesdas data in 2013 shows the incidence of head trauma in children is about 0.5% of the population from other injury rates. Pediatric TBI is associated with an array of negative outcomes, including impaired cognitive and academic abilities, social impairments, and behavioral problems. The scalp is highly vascularized and a potential cause of lethal blood loss. Even a small loss of blood volume can lead to hemorrhagic shock in a newborn, infant, and toddler, which may occur without apparent external bleeding.

Keywords: TBI, injury, disability, children

1. Introduction

Advancement in knowledge regarding traumatic brain injury (TBI) is incessantly pursued, especially in terms of key terms definition establishment. The exertion of external force on the brain, whether directly or indirectly, which causes disturbance in its structural or functional aspect defines TBI [1–3]. While the former definition is generally accepted, significantly more heterogeneous definitions can be compiled for a term closely related to TBI named concussion.

Most definitions agreed to refer to the constellation of clinical symptoms measured by mainly neurologic and cognitive dysfunctions and not exclusively evident in mild TBI [4, 5]. However, other definitions associate concussion with sports [6, 7], and although there are fundamental overlapping parameters, several areas of multiplicity impede the development of a universally accepted definition. This issue may affect every aspect of TBI as it determines the case definition in any given research.

2. Epidemiology

The global incidence of TBI is estimated at 939 cases per 100,000 people – which translates to 69 million people sustain a TBI every year [8]. Decreasing incident (4.4%) and increasing prevalence (6.6%) of TBI in the United States during 1990 through 2017 are reported by the Global Burden of Disease Study, with the latest

prevalence and incidence reported are 2.104 and 0.961 million, respectively. TBI incidence is among the highest compared to other neurological disorders, even with age-adjustment at 285 cases per 100,000 people [9]. Pediatric TBI contributes to a global incident range of 47–280 per 100,000 children [10]. Changes in Coronavirus disease 19 (COVID-19) pandemic circumstances since 2020 seem to affect TBI epidemiology as implied by the significant decrease in mild TBI incident for children aged 0–5 years (44%) and 6–17 years (93%) in Canada [11].

The epidemiological characteristics are also invariably affected by geographical and sociodemographic features. Countries with the lowest and highest incidence are Sweden (12 cases per 100,000) and Australia (486 cases per 100,000). Higher incidence, severity, and mortality in pediatric TBI are observed in rural as opposed to urban areas [12]. Bimodal age distribution with peaks at 0–4 years and 14–18 years with male-gender preponderance in the pediatric population is observed [13]. Meanwhile, the role of race and socioeconomic status requires further confirmation [10].

The most common injury mechanisms are falls and motor vehicle accidents, although the relative proportions vary by age distribution. The majority of pediatric TBI cases are mild (70–90%), and severe TBI only accounts for 3–7% of all cases. Consistently, the hospitalization rate is 129 per 100,000 in pediatric population and over 90% recover [10, 13, 14]. Nevertheless, 88% of concussions are left undiagnosed and one-third of properly diagnosed cases may experience ongoing sequelae, which would remain undetected until the development reached frontal lobe maturity [1, 14].

3. Anatomical and physiological consideration

Before further consideration on injury mechanisms, it is important to appreciate the evolving anatomy and physiology in every stage of child development and its impact on injury biomechanics (**Table 1**). Note that this difference is also relevant to TBI diagnosis and management in children.

Children have a relatively higher head-body ratio and, consequently, greater relative head weight as opposed to adults. The large head size increases the possibility of experiencing head trauma, while the weight imposed results in distinct acceleration dynamics when exposed to external forces. Early-stage facial development is characterized by maximum craniofacial ratio, protruding forehead, and less developed paranasal sinuses. These unique properties subject increased likelihood of frontal trauma, especially with lesser capability of the sinuses to absorb the energy.

Younger children have thin calvarium rich in bone marrow with fontanels and sutures closing at different times. The pliable skull, along with open sutures and fontanels, allows for deformation and limited intracranial pressure (ICP) buffering. Hence, the existence of fracture should raise clinical suspicion for significant

Cranium	Head-body ratio, craniofacial ratio, fontanels and sutures patency, calvarium characteristics
Brain	Underdeveloped myelin sheaths, water content, pulsatility
Cervical	Relative position of the fulcrum of movement, underdeveloped neck muscles and ligaments, susceptible articulations

CSF, cerebrospinal fluid; ICP, intracranial pressure.

Table 1.
Age-dependent characteristics in TBI.

underlying parenchymal injury despite lacking evidence on imaging investigation. The downside of high skull plasticity with regards to cortical vessels and brain parenchyma is that it may cause stretching and shearing of these structures in response to the external force.

The craniocervical structures depend mainly on the ligaments and soft tissues for stabilization. Weaker neck muscles and ligaments, upper position of fulcrum of the vertebral body, and flexible articulations in younger children predispose to craniocervical instability particularly when combined with the disproportional head weight. Therefore, a high index of suspicion for concomitant spinal injury has to be maintained until proven otherwise.

Cerebral white matter is less myelinated and contains more water compared to that of adults. Although the nerve fibers are pliable and less likely to rupture, their pliability increases the risk of cerebral contusion and subdural hematoma. The unmyelinated areas are significantly more prone to injury. Cerebral compliance is also affected by other age-dependent factors, such as cerebral blood flow and volume and cerebrospinal fluid (CSF)-brain ratio [13, 15].

4. Biomechanics

The biomechanistic aspect of head trauma is composed of two forces: translation or linear (LA) and rotational (RA) accelerations. The former results from direct impact measured in gravitational force unit (g), whilst the latter results from indirect or whiplash impact and is measured as radians per second squared (rad/s^2). Upon sudden impact with a surface, the head experiences deformation and deceleration in the same direction as the initial force and result in LA. The bending of the skull produces a wave-like pattern which causes tension propagating from the outer to inner skull. Tension propagation magnitude and direction determine the ensuing fracture initiation.

Intracranial damage occurs as a consequence of either brain motion or pressure gradient established by the LA. Brain motion is proposed to potentiate focal hematoma directly. Other authors proposed that the focal site of an impact is exposed to positive gradient resulting in focal injury and the distal site is exposed to negative gradient resulting in shear stress and cavitation. Previous researches reported a strong correlation between LA and ICP, and ICP with subsequent neurologic dysfunction.

Holbourn was the pioneer researcher who stated that RA-mediated brain injury was caused by shear stress and strain. Impact duration should also be taken into account as different combinations of impact duration and magnitude result in different injury types. Longer duration at a lower magnitude of RA generates diffuse axonal injury, and the opposite generates subdural hematoma. Although LA and RA are often described separately, the inherent coupling of both forces is inevitable in reality [16, 17].

5. Pathophysiology

TBI pathogenesis involves primary and secondary injuries culminating in a temporary or permanent neurological deficit. Primary injury represents brain dysfunction as a direct result of brain deformation. Structural damage in focal, multifocal, or diffuse pattern in primary injury can only be prevented before the collision. Consequent molecular, chemical, and inflammatory cascades further extend the reversible secondary injury from minutes to days after the primary insult [18].

Theoretically, cerebral blood flow (CBF) and therefore, cerebral perfusion pressure (CPP) is determined by the difference between mean arterial pressure (MAP) and ICP. It is noteworthy that in TBI cases, studies demonstrated that the cerebral autoregulation mechanism impairment in the presence of normal CBF and CPP values. Decreased metabolic demand in coma or ischemic conditions may be the plausible explanation for cerebral hypoperfusion after TBI. Under such pathophysiologic conditions, CBF continues to decline to reach ischemic level thus exacerbating the impact of secondary injury [19]. CBF restoration may also cause reperfusion injury mediated by oxidative stress, leukocyte infiltration, and blood brain barrier dysfunction [20, 21].

Deterioration of CBF deprives the cells of their metabolic needs and forcing them to switch into anaerobic metabolism. Less energy and more lactate production in anaerobic metabolism give rise to failure in cellular functioning and generate an acidic milieu [20]. Moreover, the glial-neuronal uncoupling further enhances extracellular lactate production independent of ischemia, resulting in lactate storm in severe cases [22].

One of the main concern in the cerebral metabolic alteration is the failure of the sodium/potassium (Na/K) pumps. Massive sodium influx precipitates the cascades in secondary injury through neuron depolarization. Depolarized neurons release excitatory neurotransmitters, including glutamate and aspartate, which leads to intracellular calcium increase and enzymes and free radicals activation [20, 22, 23]. Neuronal cells degradation triggers neuroimmune responses and instigates BBB dysfunction, both of which add up to the cerebral edema progression [23, 24]. Vasogenic and cytotoxic edema in TBI is followed by raised ICP. According to the Monro-Kellie doctrine, the brain responds to the edema by displacing CSF and venous blood away. Failure of this compensation mechanism ultimately results in brain compression and death [20, 23].

6. Diagnosis and clinical manifestations

Amidst many classification systems and scales constructed for TBI diagnosis, this review focuses on definition generalizability since some recent studies focused solely on sports-related concussion. Disease severity is classified into mild, moderate, and severe based on GCS level and imaging findings.

6.1 Mild TBI

The mildest form of TBI, or concussion, conversely raises considerable concern because of its large proportion and rather unsettled recognition approach. This mild manifestation can coexist in more severe TBI cases. Despite vast heterogeneity in definitions provided, the common ground is that the patient is alert and experiencing any of the mild TBI clinical phenotypes after head injury. As observed in **Table 2**, no clear-cut definition for concussion and loss of consciousness alone is not a prerequisite in defining concussion. Some organizations focus on the clinical criteria, while others incorporate validated supplementary tools to objectify the assessment.

The most specific and systematic clinical criterias are provided by the Brain Trauma Foundation (BTF) [4] and Craton et al. [27] based on Concussion in Sport Group (CISG) guidelines. BTF clearly defined the clinical indicators and assigned specific time intervals for each in the first step of its guideline [4], whereas the second step of the guideline described clinical concussion subtypes and associated conditions [28]. Craton et al. on the other hand classified the symptoms into seven

	AAN [25]	**BTF** [4]	**CDC** [26]	**CISG** [7]	**NINDS** [2]
GCS	—	13–15	13–15 ≥ 30 minutes	—	—
Diagnostic criteria	Alteration in memory and orientation	Disorientation or confusion, impaired balance, slower reaction time, impaired verbal learning and memory	Confusion or disorientation, posttraumatic amnesia, focal signs, symptoms, or seizure	Symptoms, signs, balance impairment, behavioral changes, cognitive impairment, sleep/wake disturbance	LOC, headache, confusion, lightheadedness, dizziness, blurred vision, tinnitus, change in sleep patterns, behavioral or mood changes, and impaired memory, concentration, attention, or thinking
Supporting tool	PCSS, GSC, SAC		GSC, PCSS, HBI, PCSI	SCAT5, SAC	
Exclusion requirement	CT imaging in select cases		CT imaging in select cases (PECARN)	Clinical utility of advanced neuroimaging requires further validation	
Non-contributing factors	LOC		Hospitalization or neurosurgical intervention requirement	LOC	

AAN, American Academy of Neurology; BMI, body mass index; BTF, Brain Trauma Foundation; CDC, Centers for Disease Control and Prevention; CISG, Concussion in Sport Group; CT, computed tomography; GCS, Glasgow Coma Scale; GSC, Graded Symptom Checklist; HBI, Health and Behavior Inventory; LOC, loss of consciousness; NINDS, National Institute of Neurological Disorders and Stroke; PCSI, Post-Concussion Symptom Inventory; PCSS, Post-Concussion Symptom Scale; PECARN, Pediatric Emergency Care Applied Research Network; SAC, Standardized Assessment of Concussion; SCAT5, Sports Concussion Assessment Tool version 5.

Table 2.
Proposed definitions of concussion.

clinical phenotypes with *COACH CV* mnemonics and suggested specific testings in addition to supplementary tools for identifying each phenotype [27].

Supporting tools proposed by the guidelines are meant as a diagnostic adjunct to clinical indicators. The tools are validated and mentioned in the order of their priority as in the actual guideline. Each tool is age- and condition-specific, therefore careful consideration should be taken before administering and interpreting the results in decision making strategy. Computed tomography (CT) scan is indicated in select cases when more severe TBI or complication is suspected or as suggested by intermediate or high risk in Pediatric Emergency Care Applied Research Network (PECARN) decision rules.

6.2 Moderate and severe TBI

Detecting moderate and severe TBI cases are more straightforward with commonly accepted classification based on the level of consciousness measured in pediatric Glasgow Coma Scale (GCS) [29] and evidence of pathological imaging findings. GCS level lower than 9 is considered severe TBI, while GCS level within the range of 9–13 is considered moderate TBI. Based on anatomical structure

	Skull fracture	Intracranial bleeding	Cerebral contusion	Diffuse axonal injury	Abusive head trauma
Clinical findings	Subcutaneous swelling	Seizure (SAH)	—	Coma, decorticate or decerebrate posturing, neuropsychiatric impairment	Abnormal shaking behavior as mechanism of injury, seizure, retinal hemorrhage, rib fracture
Main radiological evidence	Linear, depressed, basal skull, or growing skull fracture	Hyperdense lesion in specific configurations	Mixed-density lesion surrounded by perilesional hypodense area	Foci of reduced diffusion and increased susceptibility	Coexistence of multiple hematomas with different onsets

SAH, subarachnoid hemorrhage

Table 3.
Diagnostic features of primary TBI manifestations [5, 13, 30].

involvement, primary TBI clinically manifests as skull fracture, extraparenchymal injury, intraparenchymal injury, and vascular injury, while secondary TBI manifests as diffuse cerebral swelling [13]. TBI manifestations are summarized in **Table 3**.

The appropriate imaging modality choice according to the American College of Radiology appropriateness criteria [31] depends on TBI onset and severity, risk assessment by PECARN criteria, and cognitive and neurologic signs. This guideline requires the exclusion of abusive head trauma in all cases and posttraumatic seizure in chronic cases. CT scan is recommended for acute and subacute cases, whilst magnetic resonance imaging (MRI) is recommended in subacute and chronic cases.

7. Management

Management strategy contingent on the severity of TBI. Management of mild cases highlights the importance of gradual rehabilitation while maintaining strict adherence to injury prevention. Indispensable emergency and intensive care in more severe cases warrant separate management planning.

The general strategy to manage mild TBI cases begins with complete rest. Once the child advance to a gradual return to regular activity, it is imperative to avoid any movement or activity that would provoke symptoms. Each of the next steps should be taken for at least 24 hours long, and any worsening of symptoms would render the child retreat to the previous step (**Table 4**). Similar gradual progression should also be applied to cognitive activities, especially in cases where mental activities exacerbate the symptoms. General preventive measures in commuting and playing sports should be exercised regularly [5].

Unconscious pediatric TBI patients need emergent tracheal intubation is recommended, along with the appropriate sedative or analgesic agent. Benzodiazepines are proven for their antiepileptic, anxiolytic, and amnestic properties. The dosage of benzodiazepine and opiate administrated is guided by proper preservation of mean arterial and cerebral perfusion pressure. The risk of respiratory depression as

Step	Activities	Time	Goal
Rest	No activity	24–48 hours	—
Nonaerobic activity	Normal daily activities	—	School or work activities
Light activity	Exercises at slow pace	5–10 minutes	Mild increase in heart rate
Moderate activity	Light resistance activities	Reduced than usual	Limited movement
Heavy noncontact activity	Noncontact exercises	Near usual	Intense activity
Full contact activity	Normal activities	Normal	Return to usual full-contact activities
Competitive activity	Full competitive activities	Normal	No restriction

Table 4.
Step-by-step to achieve the return to play [5].

the side effect of sedative agents could be prevented by securing airway and optimizing ventilation. Controlled mechanical ventilation for initial support by FiO_2 titration to achieve target SpO_2 of 92–99% or PaO_2 75–100 mmHg is recommended. The most recent proper ventilation goal involves preventing hyperventilation, hypocapnia, and hypoxia [32–34].

Optimal intravascular volume status encompasses central venous pressure (CVP) and urine output monitoring, blood urea nitrogen and serum creatinine assessment, fluid management, and nutrition therapy. Normovolemic status is achieved by administering normal saline as much as 75% of the maintenance requirement to maintain CVP between 4–10 mmHg and urine output >1 ml/kg/hour. Initial use of 5% dextrose in normal saline infusion may be necessary to avoid hypoglycemia in younger patients. Nutrition therapy should start as early as 72 hours. The core temperature should be maintained within >35 °C and < 38 °C [33].

The first tier after baseline care is maintaining ICP threshold below 20 mmHg. Levels above this threshold urge intervention by methods in the following order: CSF drainage, hyperosmolar therapy, analgesic and/or sedation escalation, or neuromuscular blocker initiation should be considered. Coupling nature of ICP and CPP means that the increase in ICP is often followed by CPP improvement. Permissive intracranial hypertension remains an option, although the second tier of maintaining the CPP threshold should be decided carefully due to precipitous herniation risk. Age-specific CPP threshold ranges between 40–50 mmHg in concordance with increasing pediatric age extremes. Refractory increase in ICP despite first tier treatment requires a repeat CT scan when surgical option is indicated. Surgical intervention to remove mass and/or decompressive craniectomy is indicated when new or expanding lesion is detected [33].

8. Future directions

Pediatric TBI poses a great challenge with wide-ranged prognosis. Both mild and severe extremes in the TBI severity spectrum necessitate thorough assessment and management strategies. Future endeavors should be directed to establish universal definition of concussion, more reliable biomechanical models, optimal treatment algorithm, and effective prevention strategies.

Author details

Dyah Kanya Wati
Department of Child Health, Faculty of Medicine, Universitas Udayana/Sanglah General Hospital, Denpasar, Bali, Indonesia

*Address all correspondence to: dyahpediatric@yahoo.com

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Chapter 6

Management of Patients with Brain Injury Using Noninvasive Methods

Gustavo Frigieri, Nicollas Nunes Rabelo, Ricardo de Carvalho Nogueira and Sérgio Brasil

Abstract

In the last decades, the development of new noninvasive technologies in critical care allowed physicians to continuously monitor clinical parameters, aggregating important information that has been previously inaccessible or restricted due to the invasiveness of the existing techniques. The aim of this chapter is to present noninvasive methods in use on intensive care units (ICU) for brain injured patients monitoring, collaborating to the diagnosis and follow-up, aiding medical teams to achieve better outcomes.

Keywords: noninvasive methods, brain injury, monitoring, ICP pulse waveform, ICPwf, US optic nerve sheath diameter, ONSD, CT scan optic nerve sheath diameter, MRI optic nerve sheath diameter, near-infrared spectroscopy, NIRS, transcranial Doppler, TCD

1. Introduction

The technological development achieved in recent decades has made possible to access previously unimaginable information. Sensors with greater sensitivity, more detailed imaging tools and accurate sound analyzers have brought to light patho-physiological parameters previously inaccessible. The new technologies also disclose a new trend to the medical area, the possibility of accessing patient information with noninvasive devices, minimizing risks, costs and opening new possibilities for better management.

This chapter addresses how the new tools can enlarge the therapeutic window, thereby bringing more patient safety and assertiveness to physicians. The following technologies will be presented in this chapter:

- Intracranial pressure pulse waveform monitoring
- Ultrasound optic nerve sheath diameter (ONSD)
- Computed tomography optic nerve sheath diameter
- Magnetic resonance imaging optic nerve sheath diameter

- Near-infrared spectroscopy - NIRS
- Transcranial Doppler - TCD

The objective of this chapter is to present these technologies and stimulate the search for more information to the application of these technologies in daily practice of health professionals.

2. ICP pulse waveform monitoring

Intracranial pressure (ICP) is an important clinical parameter, it is related to the volumes of the intracranial contents and the skull bone cavity. The ICP monitoring provides three distinct information:

- The average value of ICP
- The trend of ICP over time
- ICP pulse waveform (ICPwf)

The ICP mean value directly and punctually portrays the pressure value in the environment in which the sensor is inserted. Clinical experience has shown that as important as knowing ICP values, was to have information about the period of time in which the subject was submitted to hypertensive conditions, that is, the possibility of ICP trend following over time [1]. Studies initiated from the second half of the last century correlated the ICPwf with intracranial compliance, a new parameter introduced in medicine used to assist in the diagnosis and prognosis of patients [2].

The invasibility of methods that allowed obtaining ICP pulse morphology caused this parameter to be indicated only in high risk of herniation cases. Most ICP monitoring techniques do not present information on ICP pulse morphology. The absence of accurate ICP pulse morphological displaying and information on the waveform components relations in invasive methods make this analysis operator dependent.

The noninvasive detection of the morphology of ICP pulses became a reality in 2007, when Brazilian researchers began studies to monitor cranial elasticity over time. Cranial elasticity was initially analyzed by gluing strain-gauges to the cranial bone. This study was important to show that it is possible to capture pulses over the skull, and that these pulses are related to changes in intracranial volumes and pressure [3].

These results allowed the development of a noninvasive sensor (brain4care corp.), which touches the surface of the patient's scalp. This sensor mechanically captures the variations in the trend and morphology of the intracranial pressure pulse, without radiation, light or sound emissions for patients and operators [4].

ICP pulses are the result of blood pressure, breathing and cerebrospinal fluid (CSF) interaction. The cardiac-derived ICP pulse is formed by three components, P1 formed by the systolic wave, P2 originated by the scattering of fluids in this environment and p3, resulting from aortic valve closure [5] (**Figures 1** and **2**).

Subjects with ICP pulse morphology considered normal have the first component (P1), higher than the second (P2). When there is alteration of this order, ICPwf is considered abnormal [6].

This noninvasive sensor acquires beat by beat ICPwf spectrum and translates its peak relations to numbers. The algorithm calculates the amplitudes of pulses P1 and P2 and the ratio of these parameters (P2/P1 ratio = AmpP2/AmpP1). When the value of this ratio is greater than 1, morphology is considered abnormal as it indicates that peak P2 is greater than peak P1.

This method can be used to aid diagnosing and assisting patients with risk of intracranial hypertension (ICH), and consequently reduction of intracranial compliance (ICC) [4]. The latter is called with reference to the homeostasis among intracranial structures, such as the brain itself, vascular volume and CSF volume [7].

Figure 3 shows a monitoring sample with this technique, in a patient with neurological drawdown before and after the procedure to control ICH. The first waveform shows an altered morphology before the procedure, with 1.22 its P2/P1 ratio. Posterior to treatment, is presented his ICPwf pattern with a P2/P1 ratio of 0.87.

This technique is already in clinical use and has collaborated with the diagnosis and follow-up of patients who present suspicion, risk or confirmed conditions

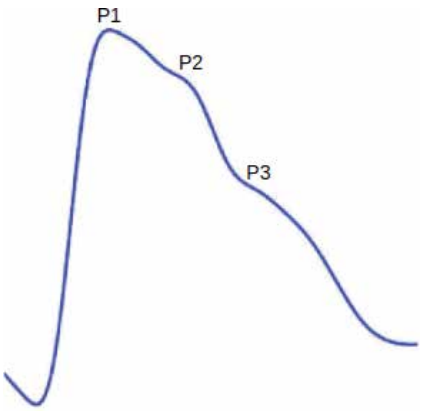

Figure 1.
Normal intracranial pressure pulse waveform.

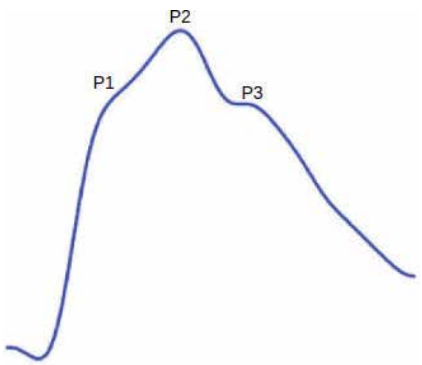

Figure 2.
Abnormal intracranial pressure pulse waveform.

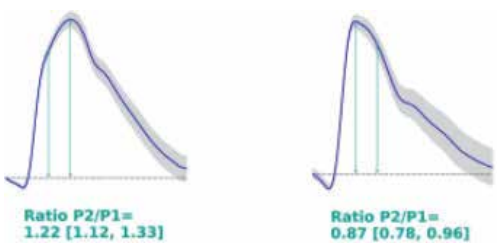

Figure 3.
Effect of a procedure to decrease the intracranial pressure monitored with the brain4care sensor.

of reduction of ICC, in situations as traumatic brain injury, stroke, intracranial tumors, hydrocephalus, central nervous system infections, reduction in cerebral flow, post cardiorespiratory arrest, liver diseases, kidney diseases and other conditions that may lead to ICH.

3. US optic nerve sheath diameter (ONSD)

The optic nerve can be anatomically subdivided into an intraocular, intraorbital, canalicular, and intracranial segment [8]. The optic nerve, as part of the central nervous system, is covered by a leptomeningeal sheath, which is expandable in the anterior segment, behind the globe.

Optic nerve sheath ultrasound is a simple, safe, inexpensive, bedside diagnostic test analogous to the measurement of BP and has the potential to replace invasive ICP monitoring in cases of raised ICH. Ophthalmic ultrasound typically uses a frequency between 5 and 10.5 MHz to evaluate the eye and orbit [9, 10].

Two measurements are made for optic nerve:

One in the transverse plane, with the probe in horizontal, and one in the sagittal plane, with the probe in the vertical.

The final ONSD is the average of these measurements. ONSD is measured 3 mm behind the optical disc [11, 12]. The optic nerve appears as a sagittal hypoechoic structure, 4.5 to 5 mm thick, with 25 mm in length that runs from the outer part of the eyeball to the apex of the orbit.

The optical disc is seen as a hyperechoic line at the posterior pole of the globe. With high interobserver agreement, with a median difference of 0.2–0.3 mm [11].

Ultrasonography of the optic nerve sheath is easy to perform. Despite this, in-depth knowledge of the anatomy of ultrasound and the scanning technique is mandatory for the proper use of the technique in the appropriate clinical setting [11, 12].

Most authors have suggested that the reasonable upper value of ONSD is 5 mm. However, further studies suggest that the cutoff value of the ONSD that provides the best precision for the prediction of intracranial hypertension (ICP = 20 mmHg) is 5.7–6.0 mm and that the ONSD values above this limit should alert the doctor for the presence of raised ICP [9–11].

According to Geeraerts et al., a strong relationship was found between the ONSD average and the ICP. When using 5.8 mm values as a cutoff point, a very low probability of having a high ICP was observed when the ONSD had smaller dilations [13–18].

Despite the advantages, ultrasound of the optic nerve sheath has some limitations. In patients with ocular trauma and other diseases of the optic nerve complex, the assessment of ONSD can be challenging. Traumatic optic neuropathy is seen in a significant number of patients with severe head trauma, and the effects of eye trauma on ONSD are unclear [3, 18–24].

4. CT scan optic nerve sheath diameter

Measurement of the optic nerve sheath by tomography is also a valid method. In a study with 41 patients, with a cut-off point of 6.35 mm, obtained a sensitivity of 0.93 (95% CI 0.84–1.00), specificity of 0.80 (95% CI 0.50–1.00), and AUC was 0.87 (95% CI 0.69–1.00). The values are different between several studies. Sekhon et al.

reported that ONSD measured 3 mm posterior to the retina by portable CT predict elevated ICP with a cutoff point of 6.0 mm, the sensitivity of 97% and specificity of 42% [15]. Vaiman et al. describe that ONSD could also predict elevated ICP when measured 10 mm posterior to the retina and with a cutoff point of 5.5 mm, the sensitivity of 83% and specificity of 94% [15, 16, 25–28].

Recently Liu et al. described that 4.99 mm was the ideal cutoff point to predict PIC>20 mmHg., with a sensitivity and specificity of 68.75% and 94.74%, respectively. Also, these authors developed a prognostic model with the admission GCS and Rotterdam tomographic scores. They observed that when the measurement of the optic nerve sheath was included, there was a higher discriminative power, sensitivity, and specificity for surgical indication. There are standard indications for surgical intervention described in the various guidelines (hematoma, compression of the cisterns at the base, deviation from the midline, and Glasgow coma scale). Complementary, the width of the sheath of the optic nerve, especially if higher than 5.09 mm (in this Liu et al. model) can be a predictor of surgical indication [15, 16, 22–30].

Despite this, we note that this analysis will help a lot in decision making. New studies with a more significant number of patients will be able to assess whether the sheath of the optic nerve will be included in flowcharts for surgical indication [16, 31, 32].

5. MRI optic nerve sheath diameter

The ONSD dimensions measured by MRI have been reliable in predicting ICP as reported by recent studies. Geeraerts et al. found that ONSD measured by conventional brain T2-weighted MRI correlates with invasive ICP [33]. They have demonstrated that an enlarged ONSD was a robust predictor of raised ICP with an area under Receiver Operating Statistic (ROC) curve equal to 0.94. An ONSD <5.30 mm was unlikely to be associated with raised ICP, whereas an ONSD above 5.82 mm was associated with a 90% probability of raised ICP.

The most significant limitation of its use in the acute phase of trauma is related to the examination duration and the need for care related to the magnetic field [30, 31].

6. Near-infrared spectroscopy - NIRS

Near infrared spectroscopy (NIRS) is an imaging technique used in both clinical and emergency medicine, as well as in research laboratories to quantify and measure the oxygenation status of human tissue non-invasively [34].

This is done by monitoring changes of the oxygen saturation of hemoglobin molecules in the body, based on the absorbance of near-infrared light by hemoglobin. The importance of such measures, especially in cerebral physiology, is that the human brain utilizes oxygen to continuously supply neurons with energy used for vital body functioning. In the absence of oxygen, as is the case during ischemic stroke or exsanguination, cognitive and functional impairment resulting in death often occurs.

Patients with raised ICP have alterations in the NIRS, mainly during the Lundberg B waves. Based on their observations in patients with TBI, spontaneous fluctuations in Hb and HbO2 changed their pattern with an increase in ICP [35–38].

The basis of NIRS relies upon two principles:

1. that tissue is relatively transparent to near-infrared light and

2. that there are compounds in tissue in which absorption of light is dependent on the oxygenation status of the tissue.

The propagation of light in tissue depends on the combination of absorption, scattering, and reflection properties of photons. Absorption and scatter in tissue is dependent on the wavelength. Scatter decreases with increasing wavelengths; thereby favoring the transmission of near-infrared light compared to visible light.

NIRS, like most technology, has various limitations. The most important of those limitations are as follows: interference from non-targeted chromophores; indefinite differential path-length; unknown scattering loss factor; and complicated signal interpretation.

Considering the pending technical challenges, the limited number of patients studied, and the conflicting results and opinions on this subject, we believe that this non-invasive method of predicting ICP should be restricted to research centers.

Cerebral injury due to hypoxic/ischemic and hyperperfusion are common issues associated with clinical and surgical practice. Monitoring of cerebral oxygenation during surgery, e.g.; cardiac and cerebral endarterectomy, has been shown to improve patient outcomes and reduce the risk of negative surgical outcomes. In addition to surgical monitoring, NIRS technology provides useful insight into cerebral hemodynamics when used in combination with other cerebral monitoring systems. NIRS monitoring and comparisons have been made with transcranial Doppler (TCD) and electroencephalography (EEG) in its ability to accurately predict cerebral ischemia and hyperperfusion. In addition to perioperative monitoring in clinical settings, many researchers utilize the various NIRS systems to reflect on the cerebral tissue oxygenation status during environmental and exercise interventions despite strong evidence and proper analytical techniques [36, 39].

7. Transcranial Doppler - TCD

Transcranial Doppler (TCD) was developed in Switzerland in 1982 by Aaslid et al. [28]. A low frequency transducer (≤2 MHz) emits and receives ultrasound waves able to pass through skull bone and allow hemodynamic brain evaluation noninvasively2, through the observation of arterial blood flow systolic and diastolic velocities (**Figure 4**). With the introduction of TCD in Neurology, Neurosurgery and Intensive Care, new frontiers were opened to the understanding of the physiopathology of the various diseases associated with the dynamics of brain blood flow. TCD is performed at the bedside, has low cost and can be repeated whenever necessary without the need for patient transport, allowing the diagnosis and evolutionary follow-up of cerebrovascular diseases.

The main applications of TCD for brain hemodynamic monitoring in adults and children are:

- functional evaluation of intracranial circulation by estimating cerebral perfusion pressure and reactivity tests at different stimuli (CO2, arterial pressure, etc.) [40, 41].

- subarachnoid hemorrhage (HSA)6, head trauma and other diseases that may occur with intracranial hypertension and segmental vessel stenosis [42]

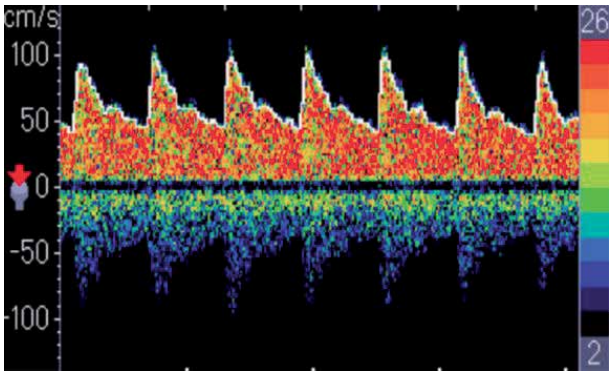

Figure 4.
Spectral wave graph that has a peak systolic velocity (A) and final diastolic velocity (B).

- evaluation in ischemic cerebrovascular disease with and without arterial diseases, of intra- and extracranial arteries [43, 44],
- ischemia mechanisms determination, whether arterial–arterial embolism, cardioembolic, arterial–venous shunting or hemodynamic [45, 46]
- measurement of hemodynamic repercussion in systemic diseases (sepsis and liver failure) [47, 48]
- risk of stroke evaluation and follow-up in sickle cell anemia16,
- complementary diagnosis of brain death [49, 50]

7.1 Hemodynamic indices of transcranial Doppler and functional evaluation

The indexes calculated from the spectra of blood flow velocities obtained by TCD allow the characterization of brain circulatory patterns (**Table 1**). Thus, the following variables are analyzed: mean velocity (Mv), systolic velocity (Sv), diastolic velocity (Dv), Gosling Pulsatility Index (PI), Pourcelot Resistance Index (RI), Lindegaard Index (LI), Soustiel Index (SI) and breath-holding index (BHI).

Mv is the central parameter of brain blood flow velocity spectrum analysis and is defined by the following formula: $Mv = Sv + (Dv \times 2)/3$ [51] .Mv is a variable influenced by different physiological factors and its interpretation cannot be performed in isolation. Changes in Mv are due to age, sex, temperature, partial CO_2 pressure ($PaCO_2$), mean arterial pressure (MAP), hematocrit, pregnancy, presence of hypermetabolic states, and administration of anesthetic/sedative drugs. In general, there is an increase of the Mv from 6 to 10 years of age, then, there is a lifetime reduction [52].

PI is the relationship between systole and diastole of the cerebral blood flow velocity spectrum. In situations where there are no cardiovascular pathologies and where there is no change in the diameter of the studied vessel, this index can be used to indirectly assess the integrity of the distal vascular bed and provide information on the microvascular brain resistance. It is calculated by the formula: Sv-Dv/Mv; its acceptable value ranges from 0.6 to 1.19 [53]. In stenosis or proximal occlusions, there may be a reduction in PI due to downstream arteriolar vasodilation. On the other hand, critical stenosis or distal occlusions, as well as microvascular vasoconstriction may be associated with PI elevation in proximal arterial segments. The PI below 0.5 may indicate the presence of intracranial arteriovenous malformation,

Index	Formula
Average speed (Mv)	Mv = Sv + (Dv × 2)/3
Pulsatility Index (PI)	IP = Sv - Dv / Mv
Resistance Index (RI)	IR = Sv – Dv / Sv
Lindegaard Index (LI)	IL = MCA Mv / extracranial ipsilateral ICA Mv
Soustiel Index (SI)	IS = BA Mv / VA Mv
Breath-holding index (BHI)	BHI = (Mv after apnea - Baseline Mv) / Baseline Mv) × 100/30

MCA - middle cerebral artery; BA - basilar artery; VA - vertebral artery; Mv – mean velocity; Sv - systolic velocity; Dv - diastolic velocity.

Table 1.
Brain hemodynamic indexes.

since the resistance in the proximal vessels is reduced due to the absence of brain tissue between arterioles and venules. PI can correlate positively with intracranial pressure (ICP); changes of 2.4% in PI may reflect a variation of 1 mmHg in PIC. The RI is calculated by the following formula: Sv-Dv/Sv. In practice, it has the same function of PI and values greater than 0.8 indicate an increase downstream of resistance to blood flow [54].

LI is defined as the relationship between the Mv of the middle cerebral artery and the Vm of the ipsilateral extracranial internal carotid artery. In the condition of significant increase of Mv in the middle cerebral arteries, this index allows the differentiation between hyperdynamic blood flow and vasospasm [55]. A LI lower than 3 may suggest hyperdynamic blood flow and an LI greater than 3 may suggest narrowing of an artery segment as occurs in vasospasm. SI consists of the relationship between the Mv of the basilar artery and the extracranial vertebral artery. This index is used for the diagnosis of vasospasm in the posterior brain circulation. These indices together with Mv in the studied arteries are also used to classify the degree/severity of vasospasm, as shown in **Table 2**.

7.1.1 Reactivity test

BHI or voluntary apnea Index evaluates CO2 reactivity and is given by the following formula: (Mv after apnea - baseline Mv) /baseline Mv) × 100/30, in which 30 represents time in seconds of voluntary apnea performed by the patient. This index evaluates brain circulatory reactivity to hypercapnia (CVR), that is, the vasodilator capacity of brain circulation during elevation of carbon dioxide induced by apnea. BHI > 0.6 indicates preserved CVR, between 0.21 and 0.60 indicates compromised reactivity, and ≤ 0.20 reserves significantly compromised. Impairment of CVR may be related to a higher risk of cerebral ischemia caused by hemodynamic mechanism [56].

7.1.2 Noninvasive estimation of cerebral perfusion pressure

Several studies have shown that the measurement of blood flow velocities in the middle cerebral arteries by TCD allows an alternative noninvasive method of estimating cerebral perfusion pressure (eCPP) with high positive predictive value and low negative predictive value. The estimation of eCPP by TCD uses a method that involves Fourier's analysis of the first harmonic of the waveforms of both systemic blood pressure and the velocity of blood flow in the middle cerebral artery [57].

Vasospasm severity (MCA)	**Mv (cm/s)**	**LI**
Take	120–130	3rd-3.9th
Moderate	131–180	4–6
Serious	>180	>6
Vasospasm Severity (AB)	**Mv (cm/s)**	**SI**
Take	70–85	2–2.49
Moderate	>85	2.5–2.99
Serious	>85	>3

MCA - middle cerebral artery; BA - basilar artery; Mv - mean velocity; LI - Lindegaard Index; SI - Soustiel Index.

Table 2.
Diagnostic criteria for vasospasm by CTD.

Several studies have demonstrated an adequate correlation between TCD to estimate eCPP and invasive measurement through the ICP catheter. Therefore, it has been proposed as a safe technique with the potential benefit of allowing intermittent or continuous analysis through monitoring. It can be used in situations where invasive measurement cannot be performed or when eCPP does not appear to be real or questionable. It is a robust, noninvasive method and allows qualitative analysis of CBF and tissue perfusion. Therefore, it can be used as an important guide for clinical management of patients who are victims of acute brain injury [58].

7.2 Subarachnoid hemorrhage (SAH)

Patients with SAH may experience cerebral blood flow and metabolic changes that may culminate in increased intracranial pressure and ischemia. Three hemodynamic stages can be identified in this context: hyperemia, oliguemia and vasospasm. With TCD recognition of hemodynamic stages, physicians can be guided for optimal patient treatment [59].

7.2.1 Oliguemia stage

In general, in the first 24 hours, there is an overall decrease in cerebral blood flow (CBF) which may be due to two mechanisms: increased intracranial pressure associated with reduced cerebral perfusion pressure and intense microvascular constriction associated with low concentrations of nitric oxide (NO). These phenomena can trigger tissue hypoperfusion, decreased supply of tissue O2 with consequent ischemia.

TCD in the hyper-acute phase of SAH may demonstrate cerebral oliguemia status. Thus, it helps decision-making in clinical conduct to be adopted, such as: 1) management of mean arterial pressure (MAP) more appropriate; 2) avoid hyperventilation, which in turn will cause hypocapnia and further reduction of CBF; and 3) avoid states that increase brain tissue metabolic demand (e.g. fever, seizure, etc.).

7.2.2 Hyperemia stage

Brain microcirculatory vasodilation causes overall elevation of CBF. States of brain hyperemia may signal neurovascular decoupling and autoregulation impairment due to brain or systemic tissue acidosis and, in general, occurs 24 hours after the state of oliguemia.

TCD is able to identify the state of cerebral circulatory hyperdynamia and, consequently, guide the management of the hemodynamic condition of patients in order to avoid brain swelling associated with this condition. At this stage, situations that worsen the condition of brain hyperemia, such as hypercapnia, systemic arterial hypertension, anemia, and hypermetabolic brain conditions (e.g., seizure) should be avoided. In the study of cerebral autoregulation (CAR) the ability of the brain to maintain constant blood flow dynamics regardless of variations in systemic blood pressure is evaluated. SAH is one of the pathologies in which ra is impaired, which requires adequate systemic blood pressure levels to prevent hyperemia or oliguemia. TCD can identify CAR impairment through the relationship between flow velocity oscillations in the face of MAP changes (spontaneous or provoked); and this analysis is performed through modeling used in signals analysis, requiring the use of specific software for this purpose. Thus, TCD can help identify the most appropriate blood pressure range in impaired states.

7.2.3 Vasospasm stage

Vasospasm in SAH is one of the main causes of late cerebral ischemia. Therefore, its early recognition is mandatory in the clinical management of neurocritical patients. Before symptoms arise, vasospasm can be detected by TCD. Thus, clinical treatment of vasospasm can be instituted early, before the installation of neurological deficits.

There are several reasons that determine late cerebral ischemia in SAH-related vasospasm: 1) vasospasm intensity; 2) occurrence in multiple arteries or sequential vasospasm in "Tanden"; 3) presence or absence of activated collateral circulation; 4) early onset of vasospasm; 5) fast vasospasm progress (elevation of >25 cm/s/day); 6) associated tissue hypermetabolism; 7) mitochondrial tissue dysfunction; 8) presence of intracranial hypertension; 9) associated circulatory oliguemia; 10) impaired brain microcirculatory reserve; 11) preexistence of intracranial stenosis [60].

TCD is capable of detecting vasospasm in the middle and basilar cerebral arteries with high sensitivity and specificity [60]. Classically, vasospasm can occur between 4 and 14 days after the day of bleeding, and in some cases (13% of patients) can be detected early in the first 48 hours or late after 17 days. The possibility of monitoring vasospasm intensity may allow the optimization of clinical management. In severe vasospasm, the conjunction of other hemodynamic factors also observed by TCD determines the indication of, in addition to clinical measures, such as the use of vasoactive drugs and/or endovascular interventional treatment. The opportunity for the evolutionary follow-up of the response obtained to the treatment adopted is also an important benefit of TCD at this stage. **Table 2** shows the diagnostic and classification criteria of vasospasm severity by TCD using Mv and LI.

7.3 Traumatic brain injury

Intracranial circulatory abnormalities occur frequently in patients with TBI. Ischemic brain lesions can be identified in about 90% of patients who die after severe TBI [61], suggesting that changes in systemic and/or brain blood flow dynamics are frequent causes of ischemia and unfavorable outcomes. Studies of blood flow and brain metabolism suggest that hyperemic brain phenomena are the most frequently found in comatose patients after severe TBI [62].

7.3.1 Brain hemodynamic phases after severe TBI

As in SAH, there is a definition of 3 hemodynamic stages after severe TBI. The oliguemia stage occurs on the day of TBI (day 0) and is characterized by a reduction

in CBF. The hyperemia stage usually occurs on days one through three and is characterized by increased CBF. The vasospasm stage usually occurs from days 2 to 6 after TBI and there may be a reduction in CBF.

7.3.1.1 Oliguemia stage

Cerebral changes in the acute stage of moderate or severe TBI, characterized by reduced blood flow velocity and increased PI in intracranial arteries, can be revealed by TCD, including during the first three hours after TBI occurrence. At this stage, TCD should be used early in order to guide therapeutic approaches. When oliguemia has been demonstrated, the possibilities of systemic blood pressure insufficiency of maintaining CBF dynamics (MAP below the autoregulation range), hyperventilation with reduction of partial arterial CO2 pressure, resulting in cerebral microvasculature vasoconstriction, posttraumatic thrombosis of the carotid arteries, and intracranial hypertension (especially if associated with increased PI) should be considered. The reduction in blood flow velocity in cerebral arteries may also be due to brain hypometabolism that may be associated with severe brain lesions. Presence of oliguemia may be associated with a higher risk of brain ischemia and an unfavorable prognosis [63].

7.3.1.2 Hyperemia phase

Cerebral hemodynamic patterns indicative of hyperemia can be detected by TCD in about 30% of patients during the first two weeks after severe TBI. The occurrence of this pattern is associated with worsening brain swelling and increased intracranial pressure. TCD can identify patients with posttraumatic brain hyperemia prior to the development of brain swelling, which allows the establishment of therapies aimed at minimizing neural tissue lesions secondary to ICH, such as the determination of the best mean arterial blood pressure range or the determination of the best PCO2 for a patient on mechanical ventilation. Persistence of hyperemia status may be associated with poor neurological prognosis [64].

7.3.1.3 Vasospasm phase

Studies with TCD in TBI estimate the occurrence of vasospasm in 50% of patients. There is an important association between vasospasm with severe hemodynamic repercussion and unfavorable neurological prognosis, although this repercussion is lower than in cases of spontaneous SAH. It is important to highlight that posttraumatic vasospasm of the basilar artery doubles the possibility of unfavorable prognosis, compared to patients without spasm of this artery. The duration of vasospasm in patients with TBI tends to be shorter due to the non-inflammatory nature as a cause, unlike subarachnoid hemorrhage. Possibly the origin of traumatic vasospasm is associated with stretching of the arteries during trauma and peak intensity, in many cases, occurs between the fifth and seventh day after trauma, although a duration similar to SAH is observed in some cases [65].

Among other applications of TCD in severe TBI, it is worth mentioning: 1) to detect brain circulatory changes resulting from ICH; 2) to evaluate the degree of autoregulation and cerebrovascular reactivity impairment, enabling the prediction of prognosis; 3) to provide evidence of posttraumatic dissection or thrombosis of the arteries that irrigate the brain, allowing early investigation and adoption of

measures to prevent brain infarctions; 4) to verify relative changes in the dynamics of brain blood flow in response to the treatments instituted.

7.4 Intracranial hypertension

TCD is important for assessing the effects of ICH on brain circulation. It is especially useful in patients where invasive ICP monitoring is absent because it allows the estimation of cerebral perfusion pressure (eCPP) (Section 1.1.2). In addition, changes in intracranial pressure may be associated with alterations in intracranial flow waveform. Thus, the increase in ICP can lead to PI elevation with progressive reduction of mean and diastolic blood flow velocities. In general, PI modifications occur when CPP is less than 70 mmHg2. At the moment when ICP is equal to diastolic systemic blood pressure, the blood velocity of diastolic flow reaches zero, characterizing the momentary absence of cerebral blood perfusion during the diastolic phase of the cardiac cycle [66].

In other situations, even with invasive ICP monitoring, TCD also plays a key role as a real-time evaluator of the efficacy of therapeutic measures used for the treatment of ICH; TCD can also be used as an alternative method to detect erroneous measurements of ICP monitors. Furthermore, TCD may reveal that increased ICP may be associated with hyperdynamic brain circulation due to impaired cerebrovascular autoregulation. In this condition, CPP formula cannot be used as a parameter to improve cerebral perfusion in the presence of ICH.

TCD also allows the evaluation of intracranial compliance by means of simultaneous compression maneuvers of the internal jugular veins and the increase of MAP. Under normal conditions, this maneuver causes a slight increase in brain blood volume and ICP augmentation. In patients with reduced intracranial compliance, venous compression would cause PI elevation and reduction of mean brain blood flow velocities [67] leptomeningeal arteries during acute arterial occlusion. Still in the acute phase, the detection of emboli by TCD in the region of the occluded artery may be indicative of recanalization of this arterial segment.

In the subacute stage of ischemic cerebrovascular disease, TCD assesses the hemodynamic repercussion of extracranial carotid disease through CO2 reactivity tests and the presence and hemodynamic repercussion of intracranial stenosis. Embolic activity in a single intracranial arterial system may suggest an embolic source that originates from the ipsilateral carotid artery (arterial embolism) and this finding is suggestive of an increased risk of recurrence of the ischemic event when embolic activity is detected in multiple intracranial arterial systems such as bilateral carotids and vertebrobasilar, it may be suspected that the emboli have cardiac, aorta and/or paradoxical origin. With the infusion of saline solution with microbubbles (small particles of gas) in peripheral vein, TCD can detect the passage of microbubbles in brain circulation, allowing diagnosis of communication between arterial and venous circulations, such as the oval foramen persistence or pulmonary fistula [68].

In summary, TCD in ischemic cerebrovascular disease allows: 1) to detect intracranial arterial stenosis and occlusions; 2) to study the hemodynamic brain effects resulting from extracranial occlusive carotid diseases; 3) to evaluate the pattern and effectiveness of brain collateral circulation; 4) quantify vascular reserve by means of reactivity tests to carbon dioxide; 5) detect the passage of microemboli, in real time, through intracranial circulation; 6) to monitor the reopening of obstructed intracranial arteries, either spontaneous or consequent to thrombolytic therapy, in the acute stage of the ischemic cerebrovascular event.

7.5 Transcranial Doppler in systemic conditions

7.5.1 Liver cirrhosis with encephalopathy and liver failure

Several studies show that CBF is compromised in patients with acute or chronic severe liver disease, especially in the presence of hepatic encephalopathy (HE). In this condition, there is impairment of brain autoregulation and, consequently, the variation of MAP may be associated with changes in CBF. Although hyperammonemia is the main cause of HE, recent evidence suggests that abnormalities in CBF may also have some relationship in its pathophysiology. There is a hypothesis that cirrhotic patients with encephalopathy present cerebral vasoconstriction more pronounced and, consequently, progressive PI elevation and BHI reduction as the disease progresses (score CTP $\geq$ 7 or MELD $\geq$14). The more severe encephalopathy, the more changes are observed in cerebral hemodynamics [69].

In mild HE, there is also an increase in brain microcirculatory resistance and, consequently, an increase in PI and RI, with a significant correlation with the increase in Child-Pugh score. Therefore, TCD may be an aid in the diagnosis of HE in cirrhotic patients. An important complication of severe HE is intracranial hypertension. This is due to three main mechanisms: 1) brain swelling secondary to the cytotoxic effect of hyperammonemia; 2) breakage of the blood brain barrier and 3) hyperemia secondary to CAR impairment. TCD can provide information regarding the dynamics of brain blood flow in patients with ICH and assess CAR [70].

7.5.2 Sepsis and sepsis-associated encephalopathy

Hemodynamic impairment is a fundamental feature of sepsis. Brain microcirculation can be gradually compromised and, consequently, cause significant changes in CBF. These factors play an important role in the etiology of sepsis-associated encephalopathy (SAE) [71]. SAE is a frequent brain dysfunction that occurs in 50% of patients admitted to intensive care units, being one of the most common causes of delirium in this population. In addition, SAE is associated with an increase in mortality.

In the early phase of sepsis, there are progressive increases in Mv and PI over time, which are evident 24 hours after onset; at this stage, CAR may remain unchanged. In contrast, in the posterior stage of sepsis (patients with severe sepsis or septic shock), there are progressive reductions in Mv and PI, as well as impairment of CAR. The increase in PI associated with increased cerebrovascular resistance has been correlated with a higher prevalence of delirium and coma. Many of the factors that lead to changes in CBF (such as changes in CVR and CAR) are often the result of a dysfunction of brain tissue microcirculation due to the release of inflammatory mediators.

The use of TCD to assess brain hemodynamic patterns has some clinical advantages: 1) TCD can be used to identify cerebral hemodynamic patterns in sepsis that may precede systemic hemodynamic signs; 2) increased PI in confused patients may be an early sign of sepsis and help decrease time to diagnosis [71]; and 3) the identification of real-time CBF changes with TCD, correlating with systemic hemodynamic changes, may improve the management of blood pressure and blood volume in septic patients.

7.6 Brain death

Brain death is defined as total and definitive cessation of all brain functions. TCD is valued in the medical literature as an examination of choice for this purpose

due to the advantages of being noninvasive, of being performed at the bedside and of allowing repetition, if necessary38. TCD sensitivity for brain death diagnosis reaches values greater than 95% and specificity of 100% [50].

TCD should show no bilateral blood flow in the arteries of the intracranial carotid system and the vertebro-basilar system under normal body temperature conditions for at least 30 minutes. The criteria are: 1) presence of oscillatory flow (systolic velocity equal to reverse diastolic velocity – final flow zero) or 2) systolic spikes or 3) disappearance of intracranial flow with typical signs observed in the extracranial circulation [72].

8. Conclusion

Cerebral circulatory changes are often found in ICU daily practice and can lead to secondary tissue damage. Hypoxia, ischemia, intracranial hypertension, traumatic brain injury, stroke, kidney or liver failure, and sepsis can impair CAR. Since CAR mechanisms have been impaired, CBF passively follows MAP changes, which in turn compromise CPP.

A number of factors can influence the CBF and its regulation, so the monitoring and control of these factors by TCD can help adjust CBF to brain metabolic demands.

TCD has the advantage of allowing bedside access to brain hemodynamic modifications, whether intermittent or serial and continuous monitoring. The disadvantage of the method is given by operator dependence and intensive training requirement, so that it can be applied in practice by physicians with clinical expertise in various primary or systemic diseases that affect the CNS.

9. Last words

Noninvasive methods represent an advance in patient management, and will be increasingly present in hospitals. Understanding and proper use of these methods are essential to ensure that the best results will be achieved.

Author details

Gustavo Frigieri[1*], Nicollas Nunes Rabelo[2], Ricardo de Carvalho Nogueira[3] and Sérgio Brasil[2]

1 Brain4care - Scientific Department, São Paulo, Brazil

2 Department of Neurology, University of São Paulo, São Paulo, Brazil

3 Laboratory of Neurosonology and Cerebral Hemodynamics - Division of Neurosurgery, Department of Neurology, School of Medicine, University of São Paulo, Brazil

*Address all correspondence to: gustavo.frigieri@brain4.care

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Chapter 7

Hyperbaric Oxygenation in the Treatment of Traumatic Brain Injury

Robert Louis Beckman

Abstract

Hyperbaric Oxygen Therapy can help heal brain wounds: TBI/PTSD/Concussion. Peer-reviewed positive scientific and clinical evidence in over 7500 cases demonstrates that HBOT helps heal wounded brains and returns patients to a life denied them by DOD/VA/Army that will not talk about, or even use or pay for HBOT treatment for TBI/PTSD/PCS/Concussion. Successful treatment with HBOT [40 one-hour sessions] virtually eliminates suicidal ideation, an effective "suicide prevention" method. Patients also reduce their drug intake to nearly zero and experience 50% reduction in pain and time to withdrawal. The history of HBOT for TBI is littered with bad science, but evidence-based and clinical medicine data show the safety, efficacy and cost effectiveness of HBOT as a standard of care that should be put on-label and insured.

Keywords: hyperbaric oxygen, TBI, PTSD, concussion

> *"The truth goes through three stages: first, it is ridiculed, then it is violently opposed, and then, it is accepted as self-evident."*
>
> **Arthur Schopenhauer**

> *"First they ignore you, then they laugh at you, then they fight you, then you win."*
>
> **Mahatma Gandhi**

1. Introduction

Though neither of these quotes is quite true, they lead this introduction because those who are working to heal broken brains and stop the suicide epidemic are closer to winning than when they started. There are no guarantees that collective successes will overcome medical resistance to accepting the obvious: what "they" are doing does not work to heal brain wounds, and "they" ignore and denigrate a safe and effective treatment that does. Yet those trying to get urgent help to suicidal brain wounded service members see victory on the near horizon for the varieties of truths told in the research and worldwide clinical medicine. As with many advances, an anecdote helps elucidate the main point: changing minds and medicine, even with science, data and facts, is not easy work.

Two renegade Australian MDs, Barry Marshall and J. Robin Warren, in **1981** knew there was a simple treatment for gastritis and peptic ulcers: an antibiotic to kill Heliobacter pylori bacteria. Now, Helicobacter pylori may be the most successful pathogen in human history. While not as deadly as the bacteria that cause tuberculosis,

cholera, and the plague, it infects more people than all the others combined. Yet conventional medicine already knew that ulcers were caused by stress. An entire set of industries grew up around "healing" stress and its aftermath: antacids, stomach surgery for bleeding ulcers, gastritis, stomach cancer, depression. "To gastroenterologists, the concept of a germ causing ulcers was like saying that the Earth is flat." [1] To them, the cause of all the illness and death was psychosomatic, "all in the head." Marshall went so far to prove his point that he gave himself ulcers by drinking a broth of H.pylori and curing himself. And still not recognition. Cut to the chase: For their relentless persistence and science on H.pylori, in **2005** Marshall and Warren won the Nobel Prize. Treatment with an antibiotic is standard medicine for stomach cancer [2]. Twenty-four years to go from goats to Nobel laureates. Along the way, the men were ridiculed and denounced by learned councils around the world. And then the "truth."

As you read these pages, we expect that you will be whipsawed by the truths exposed as authors and readers wonder about the answer to the Obvious Question: *Since this works, why are they opposed to it?* As you will see, there are no complete answers, but the data and the peer-reviewed research do provide compelling and overwhelming evidence of the safety, efficacy, and cost-effectiveness of this treatment. Over 7500 successes cannot be entirely wrong.

2. Background

On August 30, 2002, Medicare announced its intention to issue a national coverage determination (NCD) for Hyperbaric Oxygen Therapy (HBOT) in the treatment of diabetic wounds of the lower extremities. The arguments that led to that determination [3] established that oxygen under pressure was safe and effective for this fourteenth indication, or disease state.

The evolution in thinking and the subsequent research was enabled by the 1999 refinement and restatement of the drug definition of HBOT as the use of greater than atmospheric pressure oxygen as a drug to treat basic pathophysiologic processes and their diseases [4]. The UHMS defines hyperbaric oxygen (HBO2) as an intervention in which an individual breathes near 100% oxygen intermittently while inside a hyperbaric chamber that is pressurized to greater than sea level pressure (1 atmosphere absolute, or ATA) [5]. With that definition the totality of on-label indications could be understood as cohesive sets of diagnoses connected by HBOT effects on the acute and/or chronic underlying pathophysiology common to the diseases.

Doctors noticed that the definition necessarily could be applied to the use of HBOT for additional diseases that shared this pathology. Of the 14/15 indications accepted by the FDA/CMS, at least five are non-healing wounds and therefore closely related to brain wounding from blast, falls, impact, stroke, Improvised explosive devices, and concussion. Those indications are: Crush injury, compartment syndrome, and other acute traumatic ischemias; Arterial Insufficiency, entailing enhancement of healing in selected problem wounds (includes uses like Diabetic Foot Wounds, Hypoxic Wounds); Radiation tissue damage (soft tissue and bony necrosis); Skin grafts and flaps (compromised); and Air or gas embolism (resulting from rapid decompression and blast injury [6].)

The accurate drug definition of HBOT, and its implications for the findings and data in research into traumatic brain injury, is used in this paper to argue for HBOT safety and effectiveness in the treatment of Traumatic Brain Injury. The argument is constructed by identifying the underlying pathophysiology in traumatic brain injury. Evidence for the beneficial effects of HBOT on TBI is presented. Benefits to patients with TBI is discussed. Evidence for HBOT for TBI risk/benefit and cost/are discussed. The conclusion is simple: coverage of HBOT for TBI.

3. Traumatic brain injury basics

Research over the last two decades has revealed the complex microcosms of multiple pathophysiological processes resulting from insults to the brain, including traumatic brain injury [7]. The three essential components determining the outcome of head injuries are brain blood flow; the pressure in the skull leading to swelling; and hypoxia, the lack of oxygen [8].

According to the Centers for Disease Control and Prevention (CDC), "traumatic brain injury (TBI) is caused by a bump, blow or jolt to the head or a penetrating head injury that disrupts the normal function of the brain." TBI severity ranges from "mild," i.e., a brief change in mental status or consciousness to "severe," i.e., an extended period of unconsciousness or amnesia after the injury [9]. The CDC keeps current statistics on TBI death and disability.

Traumatic brain injury (TBI) is a major cause of death and disability in the United States. Those who survive a TBI can face effects that last a few days, or the rest of their lives. Among TBI-related ED visits and hospitalizations in 2014, statistics notable for the CDC include:

- Hospitalization rates were highest among persons 75 years of age and older
- The highest rates of ED visits included persons 75 years of age and older
- For adults 55 years of age and older, falls were the leading cause of hospitalizations and ED visits
- Among TBI-related deaths in 2014, rates were highest for persons 75 years of age and older
- In 2014, an average of 155 people in the United States died each day from injuries that include a TBI
- Between 2001 and 2010, the estimated average annual numbers of TBI in the US equaled: TBI contributed to the deaths of 56,800 people; 282,000 hospitalizations; and 2.5 M ER visits.
- Accidental traumatic brain injuries contributed to more deaths than suicides and homicides together [10].
- Approximately 5.3 M people in the US live with a permanent TBI [11]
- The lifetime economic cost of TBI, including direct and indirect medical costs, was estimated to be approximately $76.5 billion (in 2010 dollars) [12].
- Current estimates put the yearly costs of TBI among veterans at $48 billion [13].

UCLA researchers, citing animal and human studies, speak of "a neurometabolic cascade of events that involves bioenergetic challenges, cytoskeletal and axonal alterations, impairments in neurotransmission and vulnerability to delayed cell death and chronic dysfunction.. .. linking the neurometabolic cascade to clinical characteristics as well as on new connections being made between acute post-concussion pathophysiology, long-term biological changes and chronic sequelae." [14] Further: "The etiology of postconcussive syndrome is debated, but may be caused by diffuse axonal injury or persistent metabolic alterations resulting in neuronal dysfunction and develops in 38–80% of patients with TBI...." [15].

Advanced neuroimaging reveals the basic neurobiology of concussion/mild TBI in animal models, which is increasingly corroborated in human studies. These images of the brain with such techniques as diffusion tensor imaging (DTI) validate the wounding from the brain injury.

Since HBOT has been studied as a science for over 84 years [16], a wealth of evidence exists - with or without brain imaging or functional imaging such as SPECT scans - that points to the wounding of the brain as an underlying cause of TBI and, in many cases, the cooccurrence of Post-traumatic stress disorder (PTSD). Controversy continues to wage over proper diagnoses of TBI and PTSD. The author is aware for over a decade of clinical medicine and the accumulation of "anecdotal evidence" in over 7500 successful uses of HBOT to help treat and heal TBI, that those combat veterans presenting with "PTSD only" diagnoses from the VA are overwhelmingly afflicted with undiagnosed TBI. Researchers have not yet fully understood how TBI commonly affects the neurological and clinical presentation of PTSD [17]. Despite this high prevalence, the pathogenesis of TBI, PTSD and TBI/PTSD remains largely unknown, hindering prevention and treatment efforts [18].

No matter how acquired, TBI in a veteran or a civilian, is an injury to the brain tissue. Damage is physiological, behavioral, and emotional. Symptoms can include altered consciousness; headaches; structural damage to brain matter and blood vessels and nerves; loss of neurological function that can lead to loss of motor, sensory, coordination, balance, vision, hearing and other abilities; inability to multi-task, slowed reaction time, decreased attention and concentration, inability to think fast; and frequent incapacity to work, sleep, relax, think or discern what is normal. When wounded, the brain, like all body organs, responds with the inflammatory process which proceeds to form scars, scar tissue, and chronic wounds. When the brain injury is compounded by post traumatic stress disorder (PTSD) the victim is subjected to hyperarousal, avoidance behaviors, trauma re-experiencing, increased mental vigilance, difficulty falling asleep, nightmares, constant anxiety resulting from progressive sleep deprivation and elevation of injurious stress hormones. Behaviors and emotions are magnified, intensifying the patient's negative responses: relationship problems, domestic violence, substance abuse, depression, criminal activity, unemployment, incarceration, homelessness, and too frequently suicide. Where the degenerative cycle can be arrested with drugs or psychological interventions, the result may be a lifetime of degraded quality of life on welfare – not only for the patient but typically for the caregiver as well.

In 2016, researchers at the Uniformed Services University of the Health Sciences in Bethesda, Md., found evidence of tissue damage caused by blasts alone, not by concussions or other injuries [19]. According to the New York Times, this could be the medical explanation for shell shock and the sequalae of psychological problems called PTSD [20]. The implications are clear: IEDs, breeching, enemy and/or friendly fire from personal weapons can lead directly to physical brain damage and the accompanying effects, many of which are diagnosed as "only PTSD."

Not to be overlooked are the complex interactions among brain injury, trauma, and physical/emotional/behavior/mental health. Psychiatrist Bessel van der Kolk, in The *Body Keeps the Score* [21], explains how trauma and its resulting stress harms us through physiological changes to body and brain, and that those harms can persist throughout life. Stress, trauma, depression, mental and physical health are so intertwined that it is hard to know the seat of the disease. The author argues that trauma is one of the West's most urgent public health issues. The list of its effects is long: on mental and physical health, employment, education, crime, relationships, domestic or family abuse, alcoholism, drug addiction. As with PTSD and TBI, whether a brain insult precedes mental health problems, it is certain that the brain and the body will suffer in time.

Several studies have looked at this downward cycle in untreated brain injuries [22] and noted a correspondence between the symptoms resulting from that brain injury and the HBOT Mechanisms of Action that work to arrest and heal the traumatic brain injury.

4. Hyperbaric oxygenation mechanisms of action

Medical studies have shown that Hyperbaric Oxygen Therapy is medicine's best way to provide oxygen to all parts of the body in the shortest period of time. Among many effects, HBOT has been shown to be effective in:

- Reducing local swelling (edema) and reperfusion injury
- Promoting wound healing
- Improving and repairing injury, by increasing oxygen delivery to damaged tissues
- Improving infection control
- Releasing nitric oxide with migration to point of injury
- Increasing the production of collagen
- Releasing stem cells with migration to area of injury
- Improving blood flow to the affected area of the brain
- Restarting stunned cellular metabolism and stunned mitochondria
- Generating blood vessel growth (angiogenesis)
- Activating stem cells 8x normal to repair neural pathways (neurogenesis)
- Decreasing markers of inflammation in the body and brain [23]

While it is uncommon to hear HBOT talked about in terms of healing wounds to the brain, the facts are now obvious: a major organ of the body is damaged. "Treatments" in the DoD and Veterans Administration for a brain-wounded population of at least 414,000 post-9/11 veterans typically resolve to rest and "a mix of cognitive, physical, speech, and occupational therapy, along with medication to control specific symptoms such as headaches or anxiety." [24] Virtually the last time TBI is referred to as a wound is when speaking of "the Invisible Wounds of War."

Brain wound healing demands that the body grow new tissue: blood vessels, connective tissue, new brain tissue. Cells have to grow and divide to form new tissue, necessitating stimulation of cells to divide and multiply. DNA must be stimulated [25]. By 2008 DNA analysts found that a single hyperbaric treatment turns on as many as 8101 genes in the 24 hours following HBOT treatment [26]. In short, "the turned-on genes are those genes that code for growth and repair hormones and the anti-inflammatory genes." [27] As already noted, HBOT is already approved for several on-label indications collectively similar as wound healing. It is worth noting that HBOT chambers are present in 1158 of a total of 3342 hospitals in the US [28].

Those chambers are primarily used for Wound Healing. For a variety of reasons, those chambers are not put to use on off-label uses of HBOT. Nevertheless, the bulk of science on animal and human patients with TBI has been collected in both hospital-based and private clinics.

Dr. Paul Harch prepared voluminous evidence on HBOT for wound healing in his arguments for recognition of DFW in 2002 [29]. More specific to TBI, Dr. Philip James, in "Head Injuries – the Curse of Life in the Fast Lane," [30] traces the development of HBOT-for-TBI research as far back as 1972 [31]. The study found that tissue oxygen levels that fight hypoxia rise with the increase in either the oxygen concentration or pressure: hyperbaric oxygenation. James writes that "*this one study* answers all the questions and objections raised about using hyperbaric oxygen treatment for patients with head injury." [32] Oddo in 2011 identified hypoxia as a culprit. Brain hypoxia is associated with poor short-term outcome after severe traumatic brain injury independently of elevated ICP, low CPP, and injury severity. Reduced brain oxygen (Pbto [2]) may be an important therapeutic target after severe traumatic brain injury [33]. Dr. Daphne Denham, the nation's premier expert on HBOT treatment of acute concussion, reported that 98% of her patients in her Fargo ND clinic [348 out of 350] treated within ten days of suffering a concussion, completely resolved their symptoms in five treatments or less [average of 2.4 treatments] [34]. The only difference in her patients and the thousands of concussed athletes in North Dakota who linger with symptoms for weeks and months using standard of care medicine [AKA "the tincture of time"] was HBOT. [NOTE: Maroon and Bost in 2011 write that nonpharmaceutical alternatives, dietary supplements and hyperbaric oxygen "may be a better first-line choice for the treatment of PCS, which has generally been underreported by both athletes and the military." [35] Of note for the CMS population is the work of Dr. Anne McKee on the connections between concussion and Chronic Traumatic Encephalopathy (CTE) [36]. "CTE is a progressive neurodegeneration clinically associated with memory disturbances, behavioral and personality change, Parkinsonism, and speech and gait abnormalities.... traumatic injury may interact additively with [Alzheimer's Disease] to produce a mixed pathology with greater clinical impact or synergistically by promoting pathological cascades that result in either AD or CTE."

Of no small importance is groundbreaking research from Washington State University. Researchers found that HBOT can halve the pain and symptoms of opiate withdrawal/detox [37].

And in current investigations of the use of HBOT to arrest and reverse the effects of COVID-19, preliminary evidence from China [38] (five cases) strongly suggests that based on the immutable science of HBOT and recent clinical application to deteriorating severely hypoxemic COVID-19 pneumonia patients, HBOT has significant potential to impact the COVID-19 pandemic. Fifty-eight patients as of this writing have been positively affected. Further, clinicians in at least five independent studies in the US using HBOT are raising the PO2 levels in patients in ICUs to the point where they avoid being put on ventilators and, in many cases, are being sent home after as few as five treatments [39].

5. Decades of science: studying HBOT to treat TBI

A review of the scientific evidence produced in both animal and human HBOT trials over the past twenty years demonstrates conclusively that Hyperbaric Oxygenation of TBI is safe and effective [40]. As early as 1977, Holbach and Wasserman demonstrated that HBOT at 1.5ata puts the most oxygen into the brains

of chronic stroke patients [41]. The overriding principle of wound healing, of course, is that the wound must have energy and oxygen to heal. Hypoxia is the most pervasive result of brain insults of all kinds, occasioned by inflammation that leads to reduced oxygen delivery to all body organs.

Following a Consensus Conference in 2008, at which it was declared that HBOT was safe [42], DoD/Army/VA researchers commenced a series of studies to discern whether HBOT was effective in treating TBI. Those studies over nearly eight years consumed over $126Million. Other studies in the private sector costing orders of magnitude fewer dollars were also conducted. To date, there have been at least seventeen peer-reviewed studies that have produced data and findings [43].

U.S. and Israelis clinical trials have provided well-structured, controlled studies demonstrating HBOT medicinal properties in mild TBI and persistent post-concussive symptoms [44]. Positive symptom scores for TBI and PTSD symptom scores for the two government-sponsored studies [45], the Army-sponsored study of Miller et al. [46], a civilian-sponsored study of Harch et al. [47], and an Israeli civilian study [48] show statistically significant improvements over baseline after HBOT treatments.

The studies involved patients with TBI who also suffered from Persistent Post-Concussive Syndrome (PPCS) for at least two years. It was highly unlikely that spontaneous recovery would occur. Five studies provide useful cross-study comparable measures. The U.S. studies used the Immediate Post-Concussion Assessment, Cognitive Testing, Rivermead Post-Concussion Questionnaire, and PTSD Checklist–Military (PCL-M) as the primary and secondary endpoint measures. Even though the Army/VA/DoD sponsored studies claim to be "sham-controlled," they are really dosing and-pressure-varying trials.

Clinical improvements in the studies were significant and consistent. Looking at dose response profiles shows that lower oxygen levels (100% O2) and lower pressures (2.0 ATA) are probably better for PTST/mTBI and PPCS symptom recovery.

Government-sponsored study authors assumed incorrectly that their control groups received inactive treatment. Yet they write; "We recognize that a sham is not inert, and we cannot completely discount the physiological effects of minimal increases in nitrogen or oxygen from pressurized room air. However, we believe it is biologically implausible that air at 1.2 ATA (equivalent to 2 m of seawater pressure) has a beneficial effect on healing the damaged brain remotely after mTBI [49]. (It is worth noting that the comment bears on relationship to the established science about the medicinal effects of low levels of either oxygen or pressure.) [50] Positive improvements from pretreatment (baseline) measures are observed in all the DoD/VA/Army and civilian studies. The measured responses to both HBO and HBA treatment groups are therapeutic, but a minimal effective dose of O2 at 1ata pressure has not been established in the hyperbaric medical literature. Thus, the use of a sham is problematic and confounding for study interpretation.

Deng and his team in a metanalysis evaluated nine studies comparing the efficacy between hyperbaric oxygen treatment and controls in traumatic brain injury patients [51]. "Brain metabolism, cognitive function, and outcome were taken into consideration. Results showed that HBO treatment significantly improved the Glasgow outcome scale (GOS) score and reduced overall mortality in patients with severe TBI compared with controls. In patients with mild TBI, HBO showed function alleviating the cognitive disorder after trauma, including memory, executive function, attention, and information processing speed." In patients with TBI, HBO showed significant improvement of Glasgow outcome scale score and reduction of overall mortality while NBO may play a favorable role in improving brain metabolism.

6. Implications of the science

For over four years, clinical and "evidence-based" medicine continue to show that HBOT is safe and effective in treating brain injuries. Objective analysis of the data from all the pivotal RCTs and crossover studies show in over 700 patients that positive improvements result from HBOT treatment protocols. And objective analyses of the studies and data reinforce the findings and the clinical evidence [52].

Dr. Wolf is a principle co-author of the first Army study. This recent USAF paper reanalyzing the data in the cornerstone DOD/VA/Army study concludes: "This pilot study demonstrated no obvious harm [and] both groups showed improvement in scores and thus a benefit. Subgroup analysis of cognitive changes and PCL-M results regarding PTSD demonstrated a relative risk of improvement.... There is a potential gain and no potential loss. The VA/Clinical Practice Guidelines define a "B evidence rating" as "a recommendation that clinicians provide (the service) to eligible patients. At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm .... Hyperbaric oxygen therapy for mild traumatic brain injury and PTSD should be considered a legitimate adjunct therapy if future studies demonstrate similar findings or show comparable improvement to standard-of-care or research-related treatment modalities." [53] Subsequent studies meet those criteria.

The Journal of Hyperbaric Medicine is the most prestigious journal on Hyperbaric Medicine in the world. In 2012 its editor wrote: " While we applaud good science, there comes a point.. .. of stagnation as the standard of evidence required for the blessing of organized medicine exceeds reality (where most of us live.... I feel, as do many of my colleagues, that there is sufficient clinical and research evidence to justify the use of [HBOT] as a standard-of-care treatment for [TBI] that should be reimbursed by CMS and Tricare.... I have no doubt that, over the next several years, [HBOT] will be proven beyond a reasonable doubt to be one of the most effective treatments for [TBI].... There is a preponderance of evidence now to justify the use and funding for the treatment...." [54] Wang et al. concur: "Compelling evidence suggests the advantage of hyperbaric oxygen therapy (HBOT) in traumatic brain injury. ...Patients undergoing hyperbaric therapy achieved significant improvement. ... with a lower overall mortality, suggesting its utility as a standard intensive care regimen in traumatic brain injury." [55].

The Samueli Institute wrote of DoD studies: "Results showed that both the HBO and sham procedures were associated with significant improvements in post-concussion symptoms and secondary outcomes, including PTSD (which most participants had), depression, sleep quality, satisfaction with life, and physical, cognitive, and mental health functioning.. .. these results are consistent with 2 other sham-controlled clinical trials among service members and veterans involving a range of HBOT doses. ... The most remarkable lesson of this study was the difference in clinical outcomes between the 2 chamber procedures (HBO 1.5 ATA and 'sham' air 1.3 ATA) and routine post-concussion care. ... These findings reinforce the argument that effective interventions [i.e., the current standard of care practiced by military medicine] do not yet exist within the present structure of care or that routine post-concussion interventions within the [DOD or VHA] may even have iatrogenic effects that contribute to symptom persistence, the equivalent of a negative placebo (nocebo) effect." [56].

While this research has been going on, the VA has been quietly conducting a controlled "demonstration project" to monitor the effects of HBOT for "PTSD-only" veterans. For nearly three years, first two and now five sites around the US are using HBOT to treat PTSD and TBI patients: Tulsa OK, Travis AFB, Joint Base Sam Houston, Tampa, and Fargo ND. While the numbers are small, the results are

extremely positive. 30 out of 30 patients have all shown positive medical improvement [57]. Significantly, numerous of the participants are diagnosed with TBI by the VA or have been found to have undiagnosed TBI. Either way, the overwhelming number of patients have improved significantly. These results are significant for reasons related to previous attempts to treat PTSD. The National Academies, writing in 2014 stated: "DoD and VA are spending substantial time, money, and effort on the management of PTSD in service members and veterans [$9.3Billion+ through 2014] [yet] neither department knows with certainty whether those many programs and services are actually successful in reducing the prevalence of PTSD in service members or veterans and in improving their lives." [58].

A Summary of the positive findings in the studies sponsored by DoD/VA/Army is instructive. They find that HBOT "offered statistical and in some measures clinically significant improvement over local routine TBI care." They even note the improvements in all groups when measured against the no-treatment group. Even their "expert" consultants wrote that HBOT heals brain injuries. The Army's premier researcher, Dr. Scott Miller, despite seeming to be looking for "the final nail in the coffin" of HBOT, says on the Veterans Affairs web site: "People did get better and we can't ignore those results." [59].

7. NOTE BENE: the sham and placebo controversies in HBOT

Expert commentary on the issues surrounding the HBOT "sham" revealed the fundamental flaws in the DoD/VA/Army research [60]. In a sham treatment, the researcher goes through the motions without actually performing the treatment. The intent is to have an inert or medically inactive procedure or substance used to compare results with active substances. A placebo is often used with half the people in a drug trial to help show whether the drug being studied is more effective than an inactive "sugar pill." The results of each group are compared. [NOTE: Debate continues on whether it is possible, under the circumstances of HBOT treatment, to construct a true sham-controlled study.]

The placebo effect is very difficult, if not impossible, to prove in HBOT studies on patients suffering from PPCS that accompanies TBI. Further studies cannot ignore a placebo, but the overwhelmingly positive effects in so many, and so widely different studies, make the likelihood of a placebo unusual. [NOTE: when physiologic changes, such as both structural and functional increases in brain mass and activity are noted – as they were not in DoD/VA/Army studies, since they refuse to perform such objective science – it is impossible to ascribe the changes to the placebo effect. In numerous of the non-government published peer-reviewed studies on the use of HBOT for TBI, however, such positive transformations have been noted in the treated patients. Objective evidence of changes are shown in peer-reviewed research using such methods as SPECT scans, RightEye, qEEG, etc. Those changes can only be the effect of exposure to HBOT [61].]

A worldwide surge of challenges arose when the DoD/Army/VA studies purported to use a sham in their studies and reported that HBOT "does not work." [62] International researchers and authorities could read that both the data and the discussion in all the purported randomized controlled studies said virtually the same thing: "Both intervention groups [sham and treated] demonstrated improved outcomes compared with PCS care alone" [63] Dr. Pierre Marois spoke for many: "By definition "sham" is "something false or empty". Hyperbaric treatments at 1.2 ATA substantially increase the amount of dissolved oxygen in the blood and simultaneously induce cascades of metabolic changes and genes activation. Therefore, the supposedly sham treatment of Miller's study is not close to being a placebo." [64].

The clearest example to date that demonstrates that these gas/pressure combinations have a therapeutic effect on brain injury models is the article by Malek et al. [65] They demonstrated that HBO (100% O2) and HBA (21% O2/79% N2) were equivalent in protecting neurons after transient forebrain ischemia in the gerbil using 2.5 ATA. The role of a potential placebo effect was ruled out in this study and demonstrates the activity of HBO and HBA in a neurologic injury model.

The certainty that hyperbaric medicine begins with any increase in oxygen concentration and/or pressure is further substantiated by on-going work at the University of Wisconsin [66]. Animal studies already show a significant increase in mobilized stem progenitor cells and decrease in Inflammatory cytokines when HBOT and HBAT (room-air) are applied at pressures as low as 1.2ata. Together these findings support the likelihood of biologic activity, consubstantial with HBOT, being activated at much lower dose of hyperoxia than previously postulated. Those results, coupled with decades of experiments by the US Navy and US Air Force [67], demonstrate that the Army's and UHMS's claims that hyperbaric medicine only occurs at pressures higher than 1.4ata are fallacious. Any increase in oxygen concentration and/or pressure is a medical intervention.

The USAF TBI study used the Agency for Healthcare Quality and Research recommendations for future HBOT research for TBI. One pertinent comment was the following: "Whether placebo-controlled trials are necessary to evaluate HBOT has received a great deal of attention in discussions about HBOT. Participants on all sides of this debate make the assumption that an "evidence-based" approach implies devotion to double-blind, placebo-controlled trials without regard to practical or ethical considerations. This assumption is false. Double-blind, placebo-controlled trials are the "gold standard" for government regulators overseeing the approval of new pharmaceuticals, but not for clinical decision-making or insurance coverage decisions. Evidence-based clinical decisions rely more heavily on comparisons of one treatment to other potentially effective therapies, not to placebos." [68].

8. The economic argument in favor of coverage

In what will be a ground-breaking analysis released on Veterans' Day, November 11, 2020, The TreatNOW Coalition, building on the seminal work done in 2011 [69], will update and expand the "true cost of ownership" to the American taxpayer of untreated brain injuries. Most studies attempting to estimate costs typically pay attention to the obvious cost categories – drugs, yearly health care costs, ER visits, hospitalizations, psychiatric care, home health care, long term care, lost wages, and sometimes even the impact on the family. TreatNOW has gone much further in examining the "ripple effect" through the family and into society.

The Study looks at impact on the family in categories such as physical and mental damage to immediate family members, including children and care-givers; social services for children affected by turmoil; and spousal suicides occasioned by violence and abuse. Divorce, homelessness, drug abuse, incarceration, death-by-cop, and the estimated 135 people seemingly affected with every suicide [70].

A major "cost" to society beyond the medical expenditures are the tax implications of taking a brain-wounded citizen out of the work force. In too many cases, that actually equates to two lost incomes and taxes because a care-giver is typically a full-time aide to the wounded.

Brain Injury Facts about veterans are hard to pin down accurately since there are so much missing data. For example, the VA estimates that 70% of veterans are not part of the VA system. The VA also estimates TBIs alone for the period of 2000–2017 is over 414,000. RAND estimates that about one-third of all returning vets reported

symptoms of some mental health or cognitive condition. More recent estimates range up to 800,000+ for post-9/11, and an equal number of living veterans from service in the 20th century. Civilian casualties are estimated by the CDC as 2.5 million per year, with more than 5 million American effectively unemployable and unable to perform activities of daily living.

To summarize a much more robust analytical picture: untreated brain injuries cost billions of dollars each year when many of them could be reversed by application of HBOT to help heal the underlying and frequently ignored or misdiagnosed brain injury. It costs somewhere between $40,000 and $60,000 per year for each brain injured patient. HBOT treatment has shown an 85% probability of making a significant contribution to the health and welfare of treated patients, at a cost of approximately $20,000. Thus, for less than 2% of the costs of sustaining the brain wounded on welfare, those brain injuries could be treated. The possibility of returning Quality of life and independence to a significant fraction of those wounded is high.

9. Coverage with evidence

Should further research be required before HBOT for TBI receives an indication, the Center for Medicare and Medicaid (CMS) issued Guidance for the Public, Industry, and CMS Staff, Coverage with Evidence Development, November 20, 2014 [71]. CMS and AHRQ declared that the principal purpose of the study would be to test whether the item or service (HBOT for TBI) meaningfully improves health outcomes of affected beneficiaries who are represented by the enrolled subjects. Unsurprisingly, the data and the demographics support immediate use of HBOT.

10. Conclusion

It has been the experience of independent scientists over the last decade that peer-reviewed evidence from around the world attests to the safety and efficacy of HBOT in treating and helping to heal TBI and other neurological disorders. Yet the bulk of research on brain diseases and injury focuses on description and causes rather than treatments. Research into "treatments" is by design focused on treating symptoms. Clinical Practice Guidelines from the VA/DoD, for example, specifically focus on the "management" of concussion/mild traumatic brain injury [72]. Their CPG is a compendium of best practices for dealing with symptoms, not with healing or curing. No mention is made in the document of the wound to the brain, nor to healing that wound. And none of the treatments listed as standard of practice are approved by the FDA for treating TBI [73].

Unsurprisingly, huge sums are being poured into worldwide research, some coordinated, most in a competitive surge to devise better ways to understand the structure, function, aberrations and diseases, and treatments for the brain. The US (the Brain Initiative), Europe (Human Brain Project), Japan (Brain/MINDS Project), China (Brain Project), Israel, Australia and Canada have funded major projects [74]. Groups like One Mind and Paul Allen's Brain Institute are exploring how the brain works and what causes neurological disorders. While the projects vary slightly in their aims, the thrust is on knowledge rather than clinical medicine and healing. Longer-term goals of course include medicine to the patient. Yet precious little in all the efforts is being done to find immediate-use methods to intervene in areas of wide and profound importance to human mental health.

On a more mundane basis, federal, state, local, public and private efforts continue year-after-year to address in conferences and papers and legislation the perennial, interrelated issues of suicide, mental health, brain injury, addiction, and neurocognitive and neurological decline. It is hardly surprising that the expenditures promise phenomenal rewards for breakthroughs. Meanwhile, billions are expended treating symptoms of underlying brain damage that the science demonstrates is both treatable and potentially reversible, not later, but now.

Wright and Figueroa summarize for the majority of researchers on the use of HBOT to treat and help heal TBI: "There is sufficient evidence for the safety and preliminary efficacy data from clinical studies to support the use of HBOT in mild traumatic brain injury/persistent post concussive syndrome (mTBI/PPCS). The reported positive outcomes and the durability of those outcomes has been demonstrated at 6 months post HBOT treatment. Given the current policy by Tricare and the VA to allow physicians to prescribe drugs or therapies in an off-label manner for mTBI/PPCS management and reimburse for the treatment, it is past time that HBOT be given the same opportunity. This is now an issue of policy modification and reimbursement, not an issue of scientific proof or preliminary clinical efficacy." [75].

It is time to recognize the worldwide body of data, reduce healthcare costs, improve the lives of millions of brain-wounded and their families, and avoid lifetimes of lost earnings and the social impact of avoidable suffering. HBOT should be endorsed for the treatment of Traumatic Brain Injury. This can be achieved by extending CMS coverage to this diagnosis.

Author details

Robert Louis Beckman
Foundation for the Study of Inflammatory Disease, TreatNow.org, North Bethesda, USA

*Address all correspondence to: heal@treatnow.org

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traditionally misunderstood in terms of respiratory metabolite effects with a transient hyperoxemia that dissipates once the patient leaves the chamber. However, for 358 years, and especially in the modern era (1960 to present), permanent and later trophic effects of HBOT have been documented with both single and repetitive HBOT. [3] One of the mechanisms of action was recently elucidated as epigenetic modulation through direct effects of hydrostatic pressure and hyperoxia of gene expression/suppression of over 40% of the protein-coding genes in the human genome. The largest clusters of upregulated genes are the growth, repair, cell signaling, and anti-inflammatory genes, and the largest clusters of down-regulated genes are the pro-inflammatory genes and those that control programmed cell death. A single HBOT has been shown in multiple studies to have dramatic persisting effects on disease pathophysiology, especially inflammation, its ubiquitous acute form, reperfusion injury (e.g., carbon monoxide poisoning, necrotizing infection, resuscitation, and others), and extreme forms of acute respiratory distress syndrome (ARDS) and on reversing the lethal oxygen debt from cardiac arrest. In the Chinese COVID-19 patients HBOT was likely treating pulmonary and systemic hypoxia, inflammation, other pulmonary pathophysiologic targets, reversing oxygen debt, and modulating gene expression both acutely and durably as evidenced by the patient's sustained improvement with each daily HBOT." These are similar processes experienced in use of HBOT to treat TBI, yet another substantiation of HBOT Mechanisms of Action. Ironically, the "Chinese physicians replicated an historical experience with HBOT in a near identical pulmonary viral pandemic, the Spanish flu pandemic of 1918. Dr. Orval Cunningham of Kansas City, USA applied hyperbaric oxygen therapy (pressure and oxygen) to a moribund cyanotic Spanish flu patient with agonal breathing who experienced the same dramatic reversal of his disease that the Chinese physicians witnessed. "See: Zhong X, Tao X, Tang Y, Chen R. The outcomes of hyperbaric oxygen therapy to retrieve hypoxemia of severe novel coronavirus pneumonia: first case report. Zhonghua Hanghai Yixue yu Gaoqiya Yixue Zazhi. 2020. doi: 10.3760/cma.j.issn.1009-6906.2020.0001; Zhong XL, Niu XQ, Tao XL, Chen RY, Liang Y, Tang YC. The first case of HBOT in critically ill endotracheal intubation patient with COVID-19. Beijing, China: Novel Coronavirus Pneumonia Research Network Sharing Platform of China Association for Science and Technology. 2020; Jain KK. Textbook of Hyperbaric Medicine. 6th ed. Cham, Switzerland: Springer. 2017; Rogatsky GG, Shifrin EG, Mayevsky A. Acute respiratory distress syndrome in patients after blunt thoracic trauma: the influence of hyperbaric oxygen therapy. Adv Exp Med Biol. 2003;540:77-85; Sellers LM. The fallibility of the forrestian principle. "semper primus pervenio maxima cum VI". Laryngoscope. 1964;74:613-633.

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Chapter 8

Head Impact Injury Mitigation to Vehicle Occupants: An Investigation of Interior Padding and Head Form Modeling Options against Vehicle Crash

Ermias G. Koricho and Elizabeth Dimsdale

Abstract

Traumatic Brain Injuries (TBI) occur approximately 1.7 million times each year in the U.S., with motor vehicle crashes as the second leading cause of TBI-related hospitalizations, and the first leading cause of TBI-related deaths among specific age groups. Several studies have been conducted to better understand the impact on the brain in vehicle crash scenarios. However, the complexity of the head is challenging to replicate numerically the head response during vehicle crash and the resulting traumatic Brain Injury. Hence, this study aims to investigate the effect of vehicle structural padding and head form modeling representation on the head response and the resulting causation and Traumatic Brain Injury (TBI). In this study, a simplified and complex head forms with various geometries and materials including the skull, cerebrospinal fluid (CSF), neck, and muscle were considered to better understand and predict the behavior of each part and their effect on the response of the brain during an impact scenario. The effect of padding thickness was also considered to further analyze the interaction of vehicle structure and the head response. The numeral results revealed that the responses of the head skull and the brain under impact load were highly influenced by the padding thickness, head skull material modeling and assumptions, and neck compliance. Generally, the current work could be considered an alternative insight to understand the correlation between vehicle structural padding, head forms, and materials modeling techniques, and TBI resulted from a vehicle crash.

Keywords: vehicle interior padding, traumatic brain injury (TBI), head model, vehicle occupants safety, finite element model (FEM)

1. Introduction

Traumatic Brain Injury (TBI) can occur when the head is suddenly impacted by an object and the reaction forces cause internal tissue damages and alter the normal brain function. Traumatic Brain Injury (TBI) is a major contributing factor to a third (30.5%) of all injury-related deaths in the United States. About 75% of TBIs that occur each year involve concussions or other forms of mild injuries [1].

Recently, worldwide the number of people affected with war related TBI has increased due to terrorism, civil and military conflicts [2, 3]. To minimize the severe illness and mortality resulting from blasts, vehicle crashes, and projectiles, several types of head protective equipment with different material options have been proposed since the end of the 19th century. Starting from the 1960s, multi-layers composite materials became a preferred option for personal armor applications, resulting in improved body armor with lightweight, good protection, flexibility, and improved comfort [4]. On the other hand, padding has been used for improving energy absorption in protective structures, packaging systems, sports equipment, handheld devices, as well as comfort and support systems. Particularly, the interior of motor vehicles has been identified as an area where severe head and neck/spinal injuries can occur in frontal, side, rear, roll over, or oblique impacts. Hence, there is a critical need to reduce occupant injuries, including potential head injury. Several researchers have investigated head impacts with the roof, pillars (A-Pillar, B-Pillar), and support structures [5–9]. For instance, Friedman and Nash [8] have proposed preventing head contact with the vehicle interior through interior padding and increased headroom to prevent serious injury during rollover crashes. Lim [9] investigated the energy absorption characteristic of foam and plastic paddings used for vehicle interior and the head injury performance. Results showed that depending on the type of materials and countermeasure space, the energy absorption and the resulting head injury varied.

However, despite evidence of correlations among impact energy, materials, and head acceleration, all of the above research did not present the influence of padding material and geometry variations on the skull-brain relative motion and the resulting strain and stress values.

In this study, simplified and complex head models with various geometries and materials including the skull, cerebrospinal fluid (CSF), muscle, and neck were considered to better understand and predict the behavior of each part and their effect on the brain response during the impact scenario. The effect of padding thickness was also considered to further analyze the interaction of the vehicle structure and the head. Particularly, the response of the head was evaluated based on the peak and rate of acceleration, strain, and stress at various locations in the brain.

2. Numerical model

2.1 3D head model

The head form was developed using Blender v. 2.79 3D computer graphics software toolset. Multiple digital pictures of a human head form were taken from different directions (top, front, rear, left, and right views) using a digital camera and imported into Blender to create the desired computer aided design (CAD) models, as shown in **Figure 1**.

As can be found in the open literature, the human head consists of a scalp, bone, and a series of three fibrous tissue layers namely Dura mater, Arachnoid, and Pia mater, known as the meninges [10], as shown in **Figure 2**. In this work, the head form was symmetrical to reduce the computation time. The brain and various skull parts were developed in SolidWorks by taking several cross-sections of the MRI sagittal, lateral, and transverse head images and corresponding dimensions [10]. Additional features such as neck bone and muscle were also incorporated in the model, as shown in **Figure 2**.

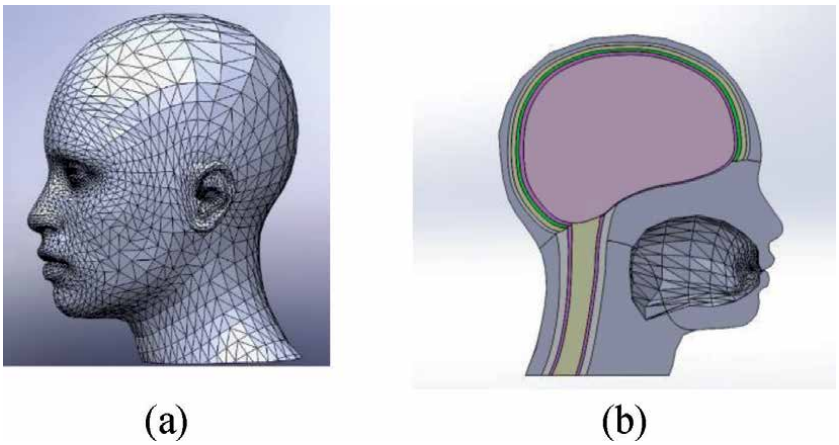

Figure 1.
3D head model: (a) Exterior section, (b) detailed modified interion section.

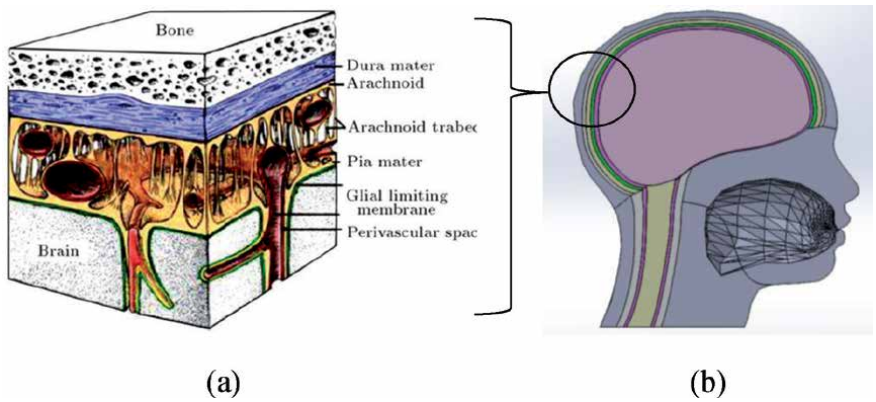

Figure 2.
(a) Schematic diagram of the subarachnoid space (SAS) space, trabeculae, pia, and arachnoid. [10]; (b) detailed 3D head model.

2.2 Materials model

2.2.1 Materials model for head

The mechanical properties of different sections of the head are the most critical and challenging parts to develop in order to construct a reliable finite element method (FEM) based head model. The material models chosen for the brain were isotropic and elastic linear viscoelastic with shear and bulk relaxation behaviors described by

$$G(t) = G_0\left[1 - \sum_{k=1}^{N} \underline{g}_k^P \left(1 - e^{-t/\tau_k}\right)\right] \tag{1}$$

$$K(t) = K_0\left[1 - \sum_{k=1}^{N} \underline{k}_k^P \left(1 - e^{-t/\tau_k}\right)\right] \tag{2}$$

The characteristic parameters of the Prony law used in Abaqus, g_k and k_k, are the weight factors, defined as.

$$g_k = \frac{G_k}{G_0}, k_k = \frac{K_k}{K_0} \tag{3}$$

Where G_k and K_k are the bulk moduli associated with the relaxation time τ_k, and G_0 and K_0 represent the instantaneous glassy shear and bulk modulus, respectively,

where N, $\underline{g}_i^P$, and τ_i^G, $i = 1, 2, \ldots, N$ are material constants. Substitution in the small-strain expression for the shear stress yields

$$\tau(t) = G_0\left(\gamma - \sum_{i=1}^{N}\gamma_i\right) \tag{4}$$

$$\text{Where } \gamma_i = \frac{\underline{g}_i^P}{\tau_i^G}\int_0^t e^{-s/\tau_i^G}\gamma(t-s)ds$$

Different authors [10–14] have proposed the short-time shear modulus G_0 from G_0 = 528 kPa to G_0 = 10 kPa and the long-time (infinite) shear modulus G_∞ from G_∞ =168 kPa to G_∞ =2 kPa. In this work, values of τ, G_∞, G_0, K, chosen for the FEM model are shown in **Table 1**.

In this work, the mechanical properties of the bone were considered as isotropic and elastic with the Young's modulus, E = 15GPa, the Poisson's ratio $\upsilon = 0.21$, and the materials' density $\rho = 1800\frac{kg}{m^3}$, [11]. The CSF had an average thickness of 2 mm and was considered as an elastic, incompressible medium with Young's modulus, E1 = E2 = 15 kPa, Poisson's ratio, v = 0.499, and shear modulus, G12 = 0.01 kPa [15]. The material properties for the neck bone, inner and outer tables, dipole, and neck muscles used in this work are summarized in **Table 2**.

The mechanical properties of the steel were found from the experimental tests performed in our lab, E = 210 GPa, $\upsilon = 0.3$, and $\rho = 7890\frac{kg}{m^3}$, yield strength, $S_y = 330\,MPa$, and ultimate strength $S_{utt} = 523\,MPa$. Also, the characteristic of polypropylene foam, which was utilized as an energy absorber for the vehicle structural padding, was taken from the previous work [19]. The material model

Shear modulus, G_0, **at** $t = 0$	$328\,kPa$
Shear modulus, G_∞, at $t = \infty$	$168\,kPa$
Bulk modulus, K	$307\,kPa$
Density, ρ	1040 kg/m^3
Relaxation time, (τ)	τ_1 = 0.02 sec, $\tau_2 = 10^{-4}$ sec

Table 1.
The mechanical properties of brain tissue for a linear viscoelastic material model.

Parts	Young's modulus, [GPa]	Density [kg/m^3]	Poisson's ratio
Neck bone [16]	1	1300	0.24
Inner Tables [17]	12.2	2120	0.22
Outer Tables [17]	12.2	2120	0.22
Dipole [18]	1.3	900	0.22
Neck muscles [10]	0.01	1010	0.38

Table 2.
Material properties for the head model.

used for the foam was isotropic, elastoplastic, crushable foam with hardening and rate dependency.

2.3 Modeling and meshing

In this work, the numerical model was carried out using ABAQUS® version 2017–1. In the FEM model, three main parts were involved in the impact scenario: a steel pole, padding made of polypropylene foam, and the head, as shown in **Figure 3**. Three FEM head models were considered to evaluate the effect of modeling assumptions on the response of the head skull and the brain during an impact scenario, as shown in **Figure 3**: a) the simplified form, Skull-Brain (SB), b) Skull-CSF-Brain (SCB), and c) Composite Skull-CSF-Brain (SCCB). For the head models, 8-node solid elements with a size of 5 mm were used. For the steel pole and the padding, 4-node shell and hexahedral solid elements were used, respectively. To reduce computational resources, the head model was reduced to a symmetrical model, as shown in **Figure 3**. Depending on the padding thickness and the head skull models, the entire model consisted of a various number of elements and nodes.

The contact between the head and the pole was defined with penalty contact (for tangential behavior) and hard contact for normal behavior. The "hard contact" option allows automatic adjustment for the stiffness generated by the "penalty contact" algorithm to minimize penetration without detrimentally affecting the time increment. The coefficient of friction between the pole and the head was assumed to be $\mu = 0.3$. The padding was constrained with the steel pole using the

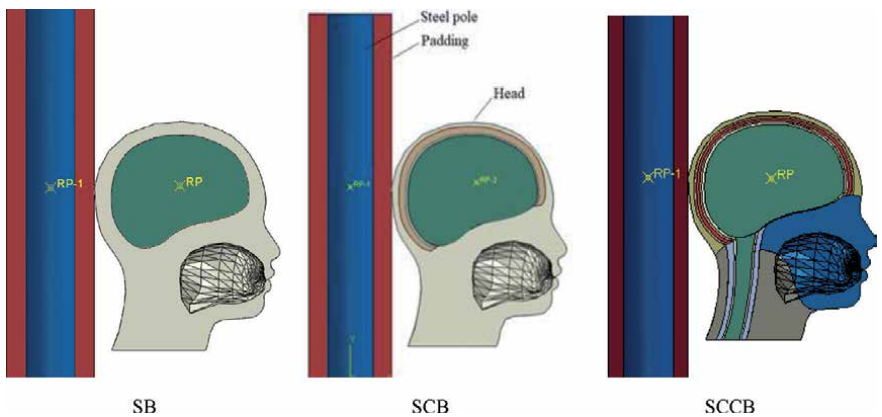

Figure 3.
FEM head models.

"Tie option" interaction available in ABAQUS®. Similarly, at the interface between the skull and the CSF, the CSF and the brain, as well as the skull and the scalp, a tie option was also implemented. In this work the pole was constrained with a fixed boundary condition at the two ends. The initial condition was imposed on the head with a predefined velocity of 4 km/hr. towards the pole.

3. Result and discussion

As shown in **Figure 4**, in all head form models, the head peak accelerations were delayed when the pole was laminated with various padding thicknesses as compared with the head when it impacted against the steel pole (SB_0, SCB_0, SCCB_0). For the simplified head form model, SB, increasing of the padding thickness exhibited an insignificant peak acceleration reduction, however, the rate of acceleration reduced as the padding thickness increased From a point of vehicle crashworthiness, delaying the peak acceleration can significantly reduce the head/brain injury. Recent studies have indicated that a high rate of onset acceleration, i.e. high jerk, during a low-speed vehicle collision increases the risk of whiplash injury by triggering inappropriate muscle responses [20, 21].

It is also worth mentioning that the development of a representative head form model plays a crucial role to obtain the actual acceleration/deceleration and predict the injury level resulting from the vehicle crash. As shown in **Figure 4(c)**, the head form, SCCB, that consisted of the scalp, composite skull, CSF, neck, and muscle exhibited the highest acceleration and became more responsive to padding thickness and (a reduction of acceleration) when it impacted the steel pole: at 25 mm padding thickness, the lowest acceleration was obtained by the SCCB. On the other hand, the more rigid and simplified model, SB, exhibited the lowest acceleration at zero padding thickness and was less responsive to the change in padding thickness;

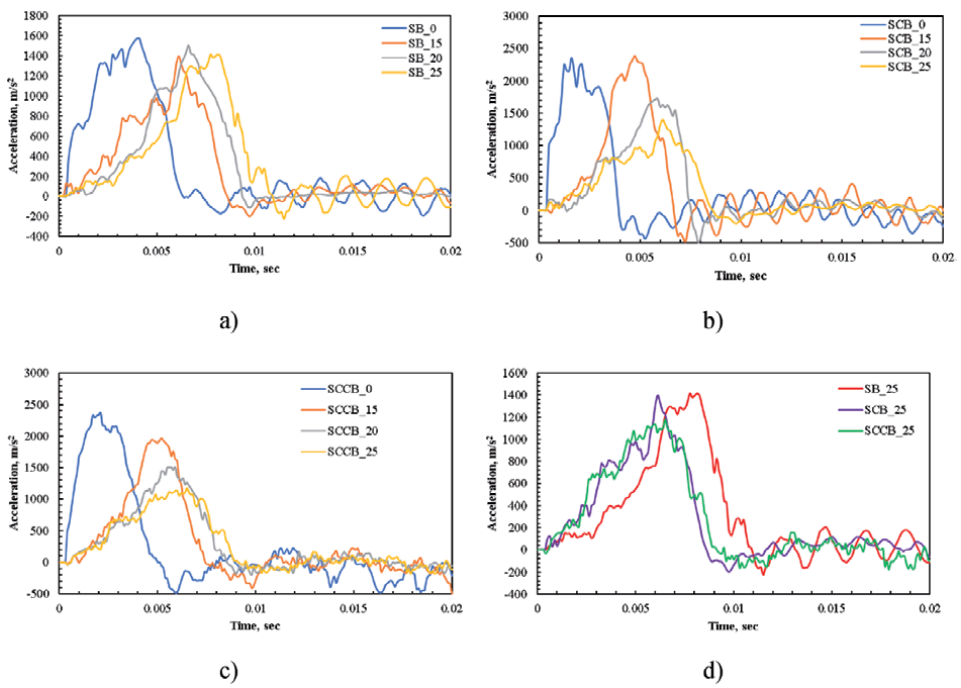

Figure 4.
Comparison of acceleration-time graph: (a) SB, (b) SCB, (c) SCCB, (d) 25 mm padding thickness.

at 25 mm padding thickness, the highest acceleration was obtained by the SB, as shown **Figure 5(d)**. This phenomenon can be explained by the fact that in the SB model, the skull, CSF, neck, and muscle were represented by a single material type, the bone, that increased the stiffness of the model and reduced the energy absorption resulting from the interactions among the head form parts and the pole. Generally, padding of the interior part of a vehicle structure with energy absorbing materials, regardless of the type of head model (simplified or detailed model), significantly reduced the peak and the rate of acceleration.

Figures 5 and **6** show the results for the strain time-histories in three regions of the brain (coup (back), contrecoup (front), and middle (reference point (RP), **Figure 3**)). **Figure 5** displays the strain versus time-history of the coup for a duration of 20 milliseconds for various padding thicknesses for each head model. **Figure 6** shows the strain for the contrecoup and middle regions of the brain as well, for a similar time history for the three head models at a padding thickness of 25 mm. As expected, the simulation results for each case concluded with a general decrease in the peak strain present within all regions of the brain as the thickness of the padding increased. By analyzing the various models, it was concluded that the presence of the CSF resulted in a quicker strain response, as well as a damping effect on the peak strain present within the brain. The most simplified model, SB, resulted in a delay of the peak strain on the contrecoup compared to the more detailed models, SCB and SCCB, due to the rigidity of the system corresponding with the absence of the CSF, shown in **Figure 6(b)**. The stress delay on the contrecoup also corresponds with the absence of materials, including the skull and the CSF within the system, resulting in a larger time duration before the strain from the impact transfers to the contrecoup. Due to the fluid material properties of the CSF, a damping effect of the strain present within the brain upon impact was also applied to the models where CSF was implemented, SCB and SCCB, resulting in a

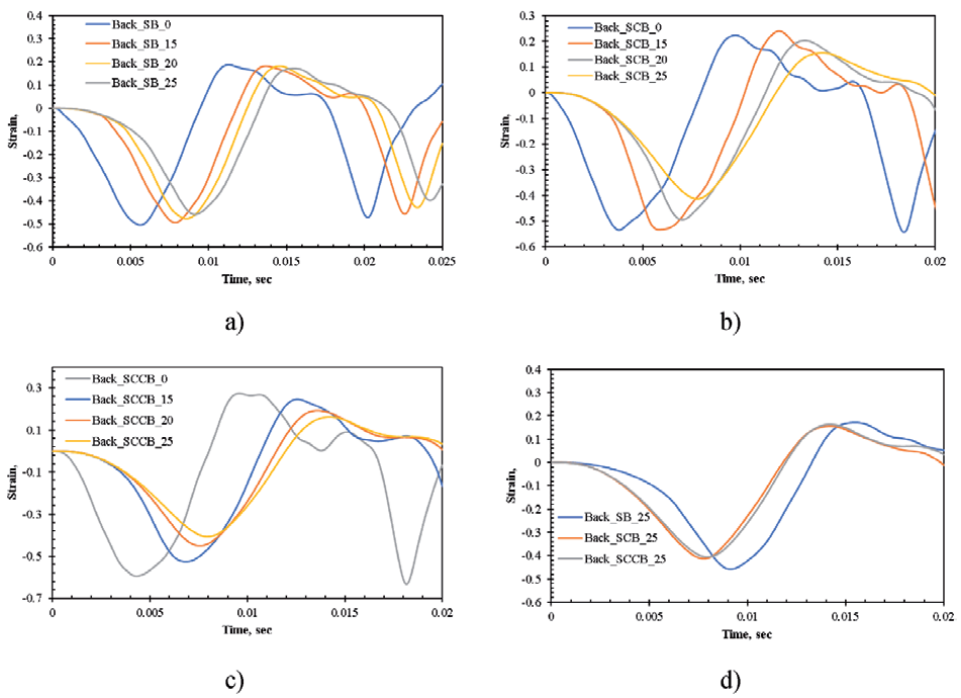

Figure 5.
Comparison of strain-time graphs for three head form models: (a) SB, (b) SCB, (c) SCCB, (d) at 25 mm padding thickness.

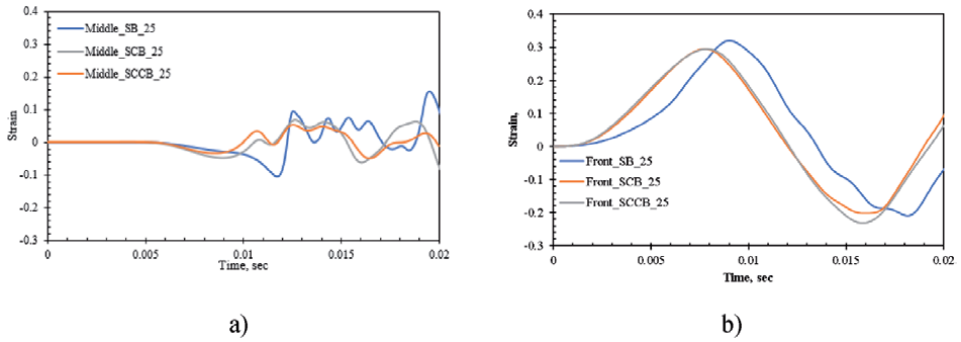

Figure 6.
Strain-time graph: (a) middle, (b) front.

significant decrease of the peak strain values. However, when analyzing the middle region of the brain, the peak stresses resulted in a much lower value, overall. The stress wave fluctuations in this region, shown in **Figure 6(a)**, also resulted in a decrease of peak strain values with the presence of the CSF. However, for the most simplified model, SB, the drastic change in strain value due to the stiffness of the system, as well as the stress fluctuations between the coup and contrecoup could potentially cause a significant shear tear-out behavior of the brain tissue. Such behavior could lead to a diffuse injury, or shear injury, which is an important aspect involved in the causes of long-term TBI [22].

Figure 7 illustrates the pressure being transmitted through the brain due to the impact with a padding thickness of 25 mm at various time histories. The pressure

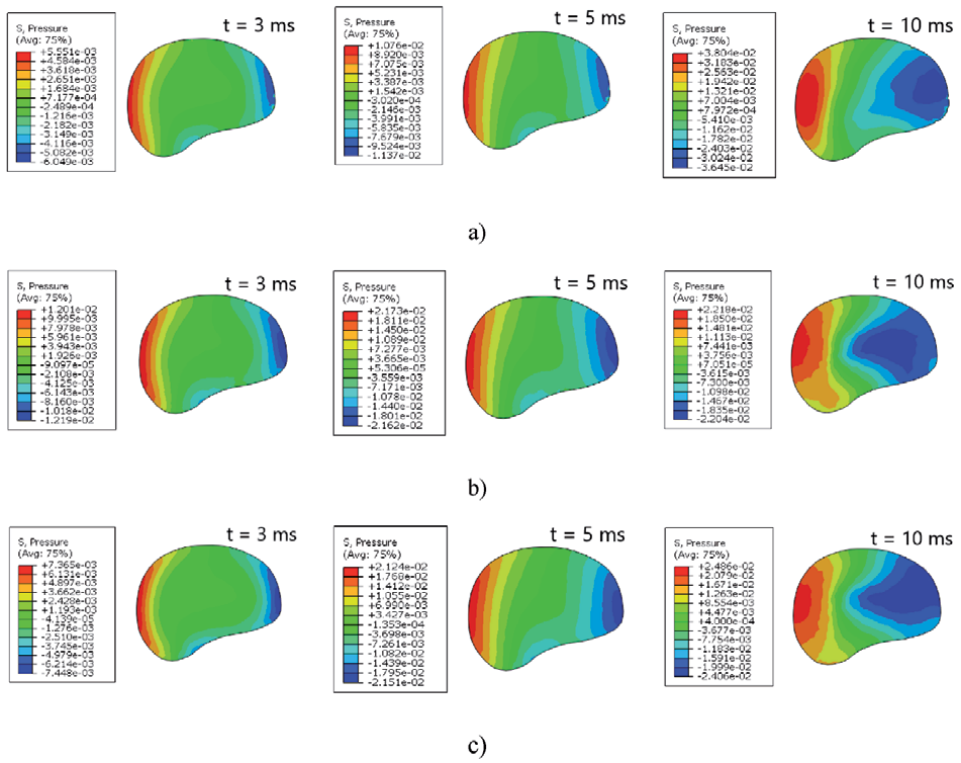

Figure 7.
Pressure response: (a) SB, (b) SCB, (c) SCCB.

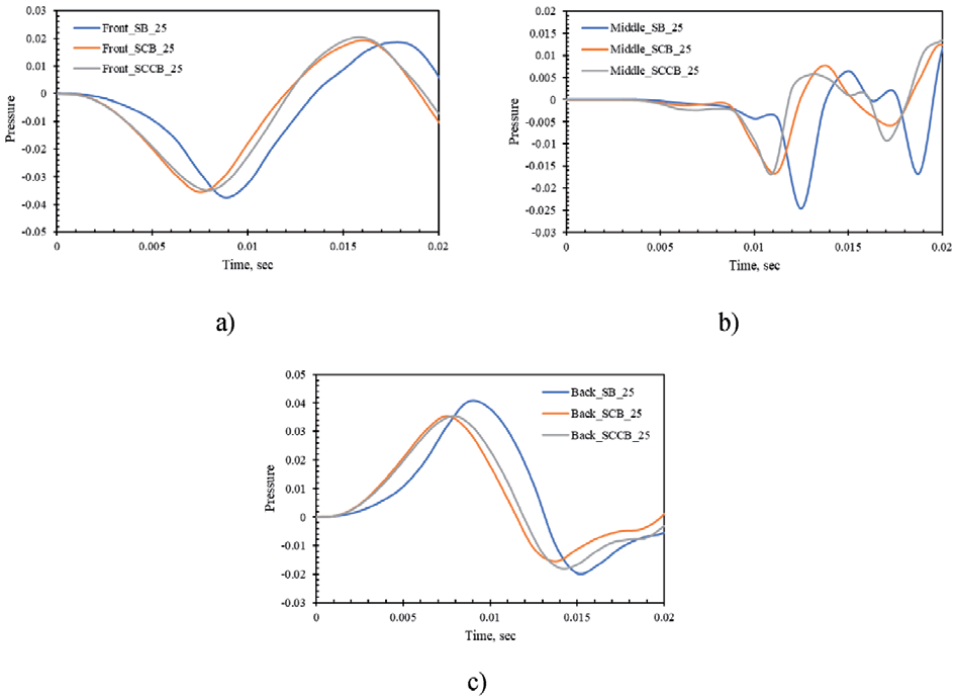

Figure 8.
Pressure–time graph: (a) front, (b) middle, (c) Back.

in the brain for each head model, SB, SCB, and SCCB, is illustrated for t = 3 ms, t = 5 ms, and t = 10 ms. **Figure 7** displays specific parameters, including the pressure versus time-history for the coup, middle, and contrecoup of the brain in order to visualize the quantitative tensile and compressive behaviors of the brain upon impact. Comparable to the strain versus time-history results in **Figures 5** and **6**, the initial peak pressure values of the more detailed models, including the CSF, significantly decreased compared to the simplified model, SB, shown in **Figure 7**, along with the corresponding graphical results in **Figure 8(a)-(c)**. These outcomes similarly correspond with the results provided from previous studies [23] that displayed the reduction of pressure oscillation due to the damping factor provided by elastic materials, such as CSF. The buoyancy of the CSF, as well as the effect of mass due to the presence of the skull and CSF layers, results in a reduction in the peak pressure values for the coup, middle, and contrecoup, corresponding with the reduction in the peak strain values as well. However, when analyzing the simplified model, the decreased acceleration, illustrated in **Figure 4(d)**, corresponds with an increase in pressure, **Figure 8(c)**, within the brain due to the inflexibility of the model. On the other hand, when comparing the similar pressure behaviors of SCB and SCCB, it is seen from **Figure 8(a)** that the peak pressure of the contrecoup increases for SCCB while the acceleration increases as well, shown in **Figure 4(d)**, due to the flexibility of the neck from the alteration of the modulus of elasticity in the most detailed model.

4. Conclusion

This current work has studied the effect of vehicle interior padding thickness on the response of three head form FEM models subjected to an impact loading. The

numeral results revealed that the responses of the head and the brain under impact load were highly influenced by the padding thickness, the head skull material modeling and assumptions, and neck compliance. The results from this study are summarized as follows:

- Padding of the interior part of a vehicle structure, regardless of the type of head model (simplified or detailed model), significantly reduced the peak and the rate of acceleration.

- The buoyancy of the CSF, as well as the effect of mass due to the presence of the skull and CSF layers, results in a reduction in the peak pressure values for the coup, middle, and contrecoup, corresponding with the reduction in the peak strain values as well.

- Simplified model, SB, exhibited a drastic change in strain value and the stress fluctuations between the coup and contrecoup that could potentially be interpreted as an indication of a significant shear tear-out behavior of the brain tissue. Such behavior could lead to a diffuse injury, or shear injury, which is an important aspect involved in the causes of long-term TBI [22]. However, the buoyancy of the CSF in SCB and SCCB models had significantly reduced the strain and the pressure fluctuation. This implies that a detailed head form model, such as the SCCB, is essential to predict the head injury, particularly the TBI, resulting from vehicle crash. Hence, unrealistic or over-simplified FEM model (e.g. SB) could mislead not only the interpretation of the results by overestimating/underestimating key parameter such as strain, pressure, and rate of acceleration but also the effect design modification on vehicle crashworthiness.

Overall, the numerical simulations have provided qualitative and quantitative information about the response of the head against impact loading. The current work could be considered an alternative insight to understand the correlation between the vehicle interior padding, various types of head form models, materials modeling, and output parameters such as acceleration, strain, and pressure that can be correlated to TBI resulting from a vehicle crash.

Author details

Ermias G. Koricho* and Elizabeth Dimsdale
Department of Mechanical Engineering, Georgia Southern University, Statesboro, GA, USA

*Address all correspondence to: ekoricho@georgiasouthern.edu

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Chapter 9

Benefits of Early Tracheostomy in TBI Patients

Sabrina Araujo de França, Wagner M. Tavares, Wellingson S. Paiva and Manoel J. Teixeira

Abstract

Severe traumatic brain injury (TBI) patients are constantly submitted to interventions to cope secondary injury and insults. Oxygen therapy is mostly initiated by endotracheal intubation at the scene of the accident. Due to the severity of the trauma, prolonged mechanical ventilation is expected and tracheostomy (TQT) is often indicated. TQT became one of the most common bedside surgical procedure performed in an Intensive Care Unit (ICU). However, discussion regarding the optimal time for TQT placement to improve outcomes of severe TBI patients remains under discussion. This chapter aims to review TBI's physiopathology and enlighten early tracheostomy's role in severe TBI management.

Keywords: benefits, early medical intervention, outcome, severe brain injury, tracheostomy, traumatic brain injury

1. Introduction

The major focus on traumatic brain injury (TBI) management is to avoid and restrain ongoing brain damage and to increase brain recovery chances by reducing brain edema and intracranial pressure (ICP). Optimizing oxygenation, perfusion, nutrition, glycaemia and temperature homeostasis are paramount [1]. In this chapter, we will discuss the role of oxygenation in TBI management with a special focus on early indication of tracheostomy (TQT) as a support to oxygen therapy.

2. Incidence and prevalence of TBI

TBI is a critical public health concern with large socioeconomic repercussions. The main causes of TBI include violence, falls and road traffic accidents [2]. In 2010, the global burden of disease (GBD) reported 89% of trauma-related deaths occurring in low- and middle-income countries (LMICs) [3]. In 2030, the worldwide estimated incidence of TBI places this type of trauma as a 4th leading cause of lost disability adjusted life years (DAYLS) and 7th cause of death [4].

The Centers for Disease Control and Prevention (CDC) estimated 2.53 million emergency department (ED) visits, 288.000 hospitalizations and 56.800 deaths related to TBI, in 2014 [5]. The TBI's lifetime economic costs (direct and indirect medical costs) was estimated at $76.5 billion (2010) and fatal TBIs can account for up to 90% of total medical costs. Since TBI is a growing health burden, it is an utmost importance the optimization of hospital resources and staff [2, 6].

TBI can be classified following its severity: Mild, Moderate and Severe [7]. This classification is based on the Glasgow Coma Scale (GCS), with Mild - GCS Score 13–15; Moderate - GCS Score 9–12; and Severe - GCS Score 8–3. Subsequent TBI management will rely on the first evaluation and the prevention of secondary injuries.

3. TBI physiopathology and oxygen importance

TBI presents two main classifications for intracranial lesions: focal or diffused [7–9]. Focal brain damage is the consequence of cortical lacerations, compression, or concussion forces, compromising blood supply and culminating in neuronal and glial necrosis. The structural injury is resulted from the brain collision to rigid structures, depressed skull fractures, vascular injuries or penetrating trauma [8–11].

Diffuse brain damage is caused by acceleration/deceleration forces, that shears and stretches brain tissue, causing functional disturbance, culminating in brain swelling or diffuse axonal injury [8–11]. The co-existence of both types of injuries are frequently present, as a result from the mechanical distortion of the head that leads to a combination of neural and vascular events [10–13].

Additionally, the TBI process can be breakdown in two successive, intertwined, pathophysiological moments, labeled as primary and secondary injury.

3.1 Primary injury

The primary injury arises from the mechanical damage occurring at the time of the impact, being exclusively responsive to preventive measures [8, 14]. On the macroscopic level, damage can be recognized by shearing of white-matter tracts, diffuse swelling, focal contusions, and intracerebral and extracerebral hematomas [15–17].

On the cellular level, mechanoporation of axolemma (caused by the traumatic axonal injury) results in sodium channelopaty [18] and unregulated influx of Ca^{2+}, which initiates calpain activation and mitochondrial swelling [19–22]. Calpain activation and cytochrome *c* accumulation increases axonal injury, detachment and apoptosis [23]. This cascade of events occurs 24 to 72 hours after the trauma and is denominated as secondary axotomy [11]. Injured axons are also susceptible to demyelination [17].

The microvasculature suffers from injury changes, such as swelling of perivascular astrocytic end-feet, increased adherence of intravascular leukocyte, perivascular hemorrhage, transvascular erythrocytes diapedesis, and increased activity of endothelial microvacuolation and micropseudopodia [24, 25].

3.2 Secondary injury

The second injury emerges from a complex series of molecular and cellular interrelated events, resulted from the biochemical cascades triggered by the trauma [9, 11]. An essential goal in the critical care is to establish recognition and treatment for secondary injury, and prevent secondary insults, which worsen patient's outcomes [26, 27].

Post-traumatic edema likely occurs by the dysfunction of sodium-potassium pump, due to pH-induced conformational change or cellular energy failure, resulting in water and sodium accumulation within the cell [11, 25]. Other factors that contributes to intracranial edema are excitotoxicity (induces intracellular sodium accumulation) [28], and membrane disruption [29] and depolarization (induced by influx of chloride, due to sodium influx) [30].

Excitotoxicity is the result of the excess of excitatory amino acids (EAA) that are released in the extracellular space, such as glutamate and aspartate, which raises intracellular sodium, calcium, chloride and water [10, 15]. This accumulation results in organelle and plasma membrane swelling [31], apoptosis, activation of destructive enzymes (such as calpain, nitric oxide synthase) [32], positive feedback loop by voltage-gated calcium channels [33], and necrosis [34].

Besides other secondary brain injuries, such as calcium dysregulation (which leads to cytoskeletal degradation), patients experience superimposed secondary insults (with intracranial or systemic repercussions) [10, 14, 15, 27]. Systemic repercussions are hypotension, hypoxia, hyperthermia, and hypoxemia. **Figure 1** recapitulate TBI's sequence of events. **Figure 2** recapitulate TBI's neurometabolic cascade.

Intracranial insults include cerebral ischemia, elevated ICP (or intracranial hypertension), and cerebral fluid-mediated swelling. The Monro Kellie doctrine (**Figure 3**) demonstrates the constancy relationship in the sum of volumes of brain, intracranial blood and cerebrospinal fluid (CSF) [7, 36, 37]. Once the brain suffers from the intracranial insults and equal volumes of CSF and intracranial blood are compressed, ICP remains normal (compensated state). When the brain enters in a decompensate state (after exhaustion of compensate state), the balance is interrupted and the ICP raises exponentially [7, 16].

It is important to mention that secondary injury does not have the same meaning as a secondary insult [11, 14]. Secondary insult occurs at the organ system level, being considered as a second hit event, exacerbating the damage from the primary

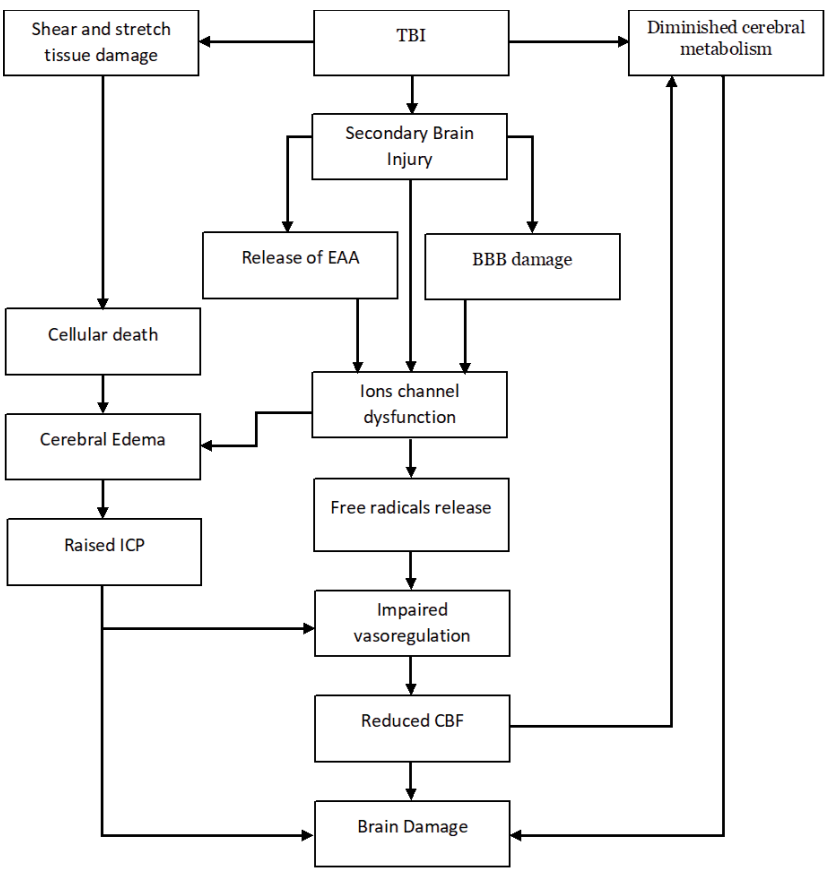

Figure 1.
TBI's sequence of events.

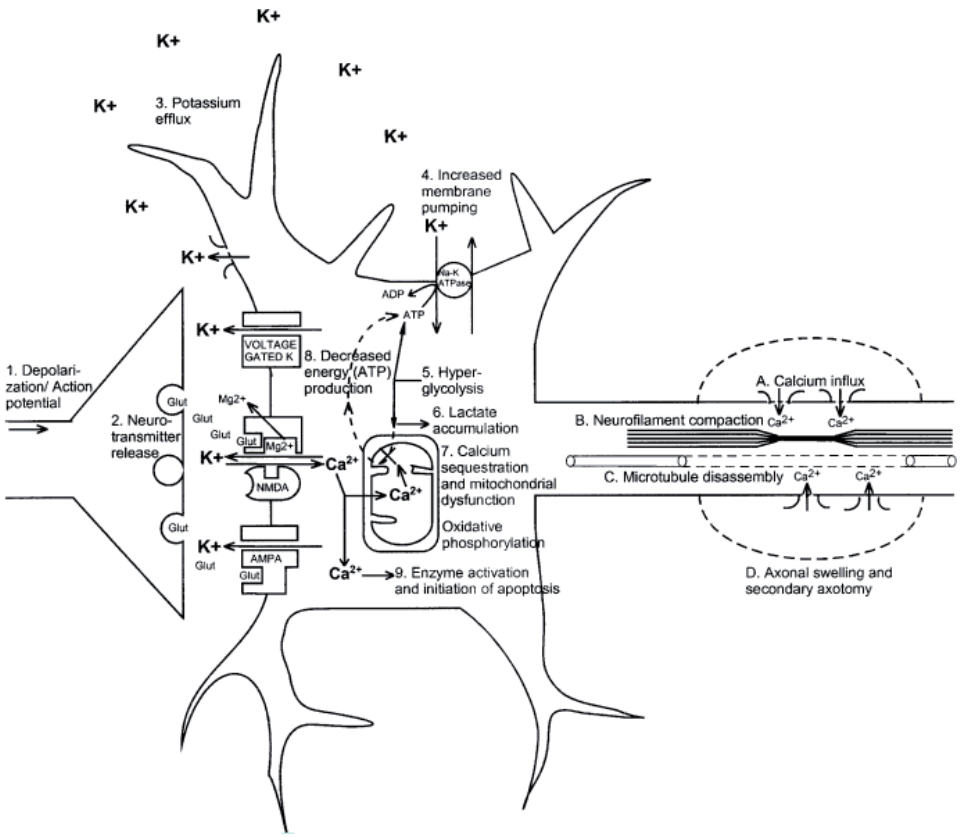

Figure 2.
[35] TBI's neurometabolic cascade. (1) nonspecific depolarization; (2) neurotransmitter release - excitatory neurotransmitters (EAAs); (3) increase potassium efflux; (4) increased membrane pumping to restore homeostasis; (5) Hyperglycolysis to increase adenosine triphosphate (ATP) availability; (6) lactate accumulation; (7) calcium sequestration and mitochondria dysfunction resulting in oxidative metabolism; (8) decreased ATP production; (9) Calpain activation and apoptosis initiation. A - Axolemma and calcium influx. B - Neurofilament compaction. C - microtubule disassembly. D - axonal swelling and secondary axotomy. K^+: potassium; Na^+: sodium; Glut: glutamate; Mg^{2+}: magnesium; Ca^{2+}: calcium; NMDA: N-methyl-D-aspartate; AMPA: d-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid.

TBI. The same reasoning is applied to the primary insult, which alters the cerebral metabolism and blood flow, resulting in cellular dysfunction and predisposition to cognitive impairment, seizures, hypotension and hypoxia [8].

3.3 Oxygen and TBI

The brain requires an uninterrupted supply of glucose and oxygen to maintain cellular viability and metabolism, consuming up to 20% of individual's total oxygen, with an average of cerebral metabolic rate of oxygen ($CMRO_2$) between 3 and 3.8 ml/100 g/min [38–41]. Brain metabolism represents the largest source of energy consumption in the human body, since neuronal activity is supported through the production of adenosine triphosphate (ATP), which consumes nearly 60% of oxygen [42, 43]. When cerebral oxygenation is maintained, minimization of secondary insult can be achieved [44].

Brain's energy consumption fluctuates following neuronal activity on localized regions, and in order to provide adequate energy supply, neurovascular and neurometabolic coupling mechanisms are involved [42]. However, within hypoxia or low oxygen conditions, prolyl hydroxylase domain-containing enzymes (PHDs) are

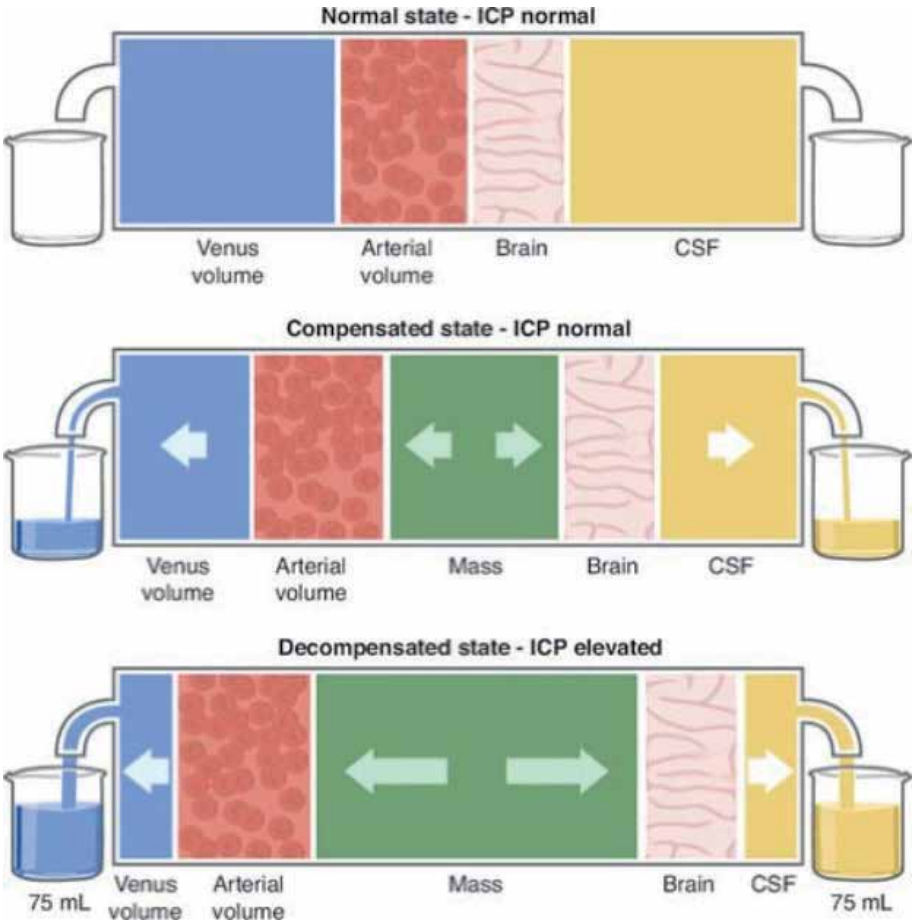

Figure 3.
The Monro Kellie doctrine.

inhibited, reducing inproline hydroxylation, and altering availability of hypoxia-inducible factor-1α (HIF-1α), which assist the metabolism adaptation and function during hypoxic conditions [42, 45–47]. Then, nuclear accumulation of HIF-1α enhance transcriptional activity within HIF-β, promoting gene expression that contains a hypoxia response element (HRE) [42, 46, 48]. Remarkably, HIF-2α is also induced in hypoxic brain, being expressed in astrocytes and endothelial cells [49]. This dysfunction is associated with poor neurological outcomes [50].

In order to cope hypoxia stress, this adaptive response converts cellular metabolism to anaerobic metabolism and inducts erythropoiesis, glycolysis, angiogenesis (by vascular endothelial growth factor), among other events [46, 48, 51]. Nevertheless, anaerobic glycolysis is unable to apport sufficient energy to sustain brain demands, depleting ATP stores, which results in failure of ATP dependent membrane ionic pumps [52]. Likewise, under chronic hypoxic conditions, there is an increase in oxidative stress, cell death, inflammation and the interruption of cerebral blood flow (CBF), directly affecting brain structure and function, leading to neuronal damage and death [51, 53, 54]. A normal average of CBF in adults is 44–45 ml/100 g/min. However, the CBF threshold for irreversible tissue damage (in TBI) occurs with the decrease to 15 ml/100 g/min [27, 41, 55] and cellular function is disrupted under 10 ml/100 g/min [56]. Neurons in the hippocampus, striatum and cortical regions die after 5, 10, and 15–20 min of ischemia [57, 58], respectively.

Considering that the brain is susceptible to ischemic injury, cerebral perfusion and oxygenation are vital to be maintained. In TBI setting, cerebral ischemia occurs due to different mechanisms: damage to blood vessels, hypotension, mechanical compression, and reduced perfusion (impaired autoregulation, which leads to greater propensity to hypoperfusion) [16, 59]. Hypoxemia can represent a relative risk of mortality of 75%, when associated with hypotension [7].

According to the Brain Trauma Foundation [60], patients with severe TBI present pulmonary aspiration risks or compromised airway function, and initial treatment goals include early airway protection, adequate supplemental oxygen, and circulation support, ensuring that adequate oxygen and blood flow are delivered to the brain [61].

4. Prehospital care and oxygenation

TBI management begins at the prehospital care, assuring that the patient has no signs of upper airway obstruction, maintaining Oxygen saturation (spO_2) > 90% and considering intubation in patients that presents Glasgow Coma Scale (GCS) < 9, altered swallowing reflex or contributing to hypoventilation [60, 62–64]. However, it is of substantial value that the prehospital team is technically qualified (within technical skills, medical devices/medication, and protocols) to perform airway management and control possible detrimental effects of therapeutic interventions (such as worsening of cervical spine injury during endotracheal intubation [65]).

Studies examining the impact of prehospital intubation have conspicuously conflicting results. A Finnish [66] comparison between physician-staffed prehospital team and paramedics team (PM) demonstrated that the physician team performed 98% of advanced airway management against 16% in paramedics patient's group. Hypoxia was higher in the PM group at the emergency department arrival. Furthermore, one-year mortality rate was higher in the PM group. Singularly, anesthetics were available for physician teams only, while PM were limited to the sedatives. Patients that were submitted to emergence intubation during prehospital care presented an increased risk of morbidity and mortality (poor neurologic outcome [67, 68] and decreased survival rate [68–71]).

The French Society of Anesthesia and Intensive Care Medicine strongly recommends a prehospital medicalized team to assess patients, claiming higher survival rates [72]. Divergently, an Australian study [73] indicated that rapid sequence intubation performed by paramedics increased the 6 months rate of favorable neurologic outcome. The Trauma Research and Education Foundation of San Diego [74] also demonstrated improved survival in patients intubated in the field. Meanwhile, any benefit or harm of pre-hospital intubation could be stated [63].

Marehbian et al. [75] inferred that these inconsistencies may be attributed to multiple factors: GCS applied as a single scale to identify intubation candidates (can be misinterpreted by illegal substances or sedative effects), variability of protocols, and inadequate intubation or ventilation approaches, that can lead to hypo or hyperventilation.

Hyperventilation is commonly revealed as a higher incidence among prehospital intubated patients. Hemodynamically, hyperventilation rises the intrathoracic pressure, leading to a decrease in cardiac output [76–78]. Regarding the cerebral perfusion, hypocapnia decrease the cerebral blood volume (CBV), which directly decrease the cerebral blood flow (CBF), and lower ICP [79–82]. Studies had shown regional and local ischemia with tissue lactic acidosis immediately after hyperventilation, suggesting harmful effects in cerebral tissue due to cerebral vasoconstriction [7, 81, 82]. Currently, hyperventilation should be reserved to

refractory cases immediately before surgical intervention. It should not be used in ICU management of refractory ICP because of its detrimental hypoperfusion properties [7, 83–85].

The use of supplemental oxygen is required to correct hypoxemia and attempt to avoid secondary injury. Therefore, initial management for severe traumatic brain injury involves intubation and ventilation for airway management [7, 72]. However, the decision to perform invasive procedures on the trauma stage should be evaluated in a case to case basis since the experience of the team involved together with the conditions of the patient/surroundings (patient inside a car wreckage or in a war site) of the trauma can have a great influence in the decision making.

5. Tracheostomy and oxygenation

To prevent or reverse hypoxemia and provide oxygen to the tissues during acute respiratory failure, airway access is often provided by translaryngeal endotracheal tube. When mechanical ventilation is expected to be prolonged, TQT tube is frequently chosen as part of the airway management care plan [86–88].

Earlier TQT records were found in the Edwin Smith Papyrus (1600 BC), whereas an emergency airway was performed after a trauma [89]. The first surgical description of successful case of TQT was performed by Antonio Musa Brasavola (1546) [90] and a full book dedicated to this procedure, previously known as bronchotomy, was published in 1620 [91] by Nicolas Habicot, who pictured it as demonstrated in **Figure 4**.

Figure 4.
[92] Patient's tracheostomy by Nicolas Habitot. A: the patient; B: the larynx; C: bronchotomy insertion; D: bronchotomy's instrument; E: the cannula; F: cannula's strap; G: a band to apply over the cannula to control the air leakage; H: the needle to suture the wound when needed.

During the Second World War, TQT grown relevance in chest trauma patients [93] and since then, it is expanding its role in airway management, as well improvement of the surgical techniques, instruments and cannulas.

Prolonged/impractical intubation, ventilation support for weaning, pulmonary hygiene management and airway protection are main indications for TQT placement [86–88, 94]. Patients can benefit from tracheostomy that is performed by open surgical (OST) or percutaneous dilatory (PDT) techniques.

Patient's individual aspects assist the medical team to decide whether to use PDT or OST. PDT is recommended for patients who can hyperextend the neck, tolerate hypercarbia and hypoxemia, and present at least 1-cm distance between the inferior cricoid cartilage and the suprasternal notch (in case of needed re-intubated after accidental extubation) [86–88]. PDT relative contraindications are emergency airway access, anatomical incompatibility, coagulopathies, higher levels for support oxygenation (e.g. positive end-expiratory pressure ≥ 10 mm Hg or fraction of inspired oxygen ≥0.7), and infection at insertion site surroundings [86–88].

Studies were carried out to establish advantages and preferences between techniques. A Cochrane review did not find statistical difference for mortality and serious life-threatening adverse events between techniques [95]. However, PDT presented significantly reduced rate for wound infections/stomatitis and unfavorable scaring. Other systematic reviews and meta-analysis confirmed the same result trend: no difference in mortality and life-threatening complications [96–100]. Significant positive outcomes for PDT was cited as less infection rate [97–100] and less procedure time [96, 100–102]. Besides these results, OST could also impact hospital expenditures, since the procedure can require an operatory room and staff [88, 103, 104].

6. The benefits of tracheostomy on TBI

A multidisciplinary team collaborates in patient's care for adequate communication, ventilation and oxygenation [104]. The presence of a TQT may promote greater airway security, assisting in patient's mobilization and engagement to physical therapies [88]. Likewise, TQT allows sedation reduction or cessation, reduction of laryngeal lesions, assist in weaning protocol and improve oral nutrition and communication [105–107]. Mentioned risks are tracheal stenosis, tracheomalacia and hemorrhage [108]. However, TQT benefits overcome procedures risks [94, 109, 110].

Over the past decade, extensive research has been done concerning TQT timing for optimal results in patient's care, and an oscillation of a cut out day to consider TQT as an early procedure (ET) is perceived. Literature reveals authors acceptation of TQT as an early procedure, as those ones performed between 2 and 12 days after admission [111–116].

A systematic review and meta-analysis [115] revealed that ET, in severe TBI patients, is associated with shorter length of mechanical ventilation and intensive care unit (ICU) and hospital stay. Likewise, decreased risk of ventilator associated pneumonia was found. Complementary literature comparing early and late tracheostomy (LT) populations demonstrated lower ICU stay [113, 117–120], lower hospital stay [117, 120], lower rates for pneumonia [113, 117, 119, 120] and lower costs [113, 117].

Healthcare cost management has increasing its role as part of patient's care plan. Given an aging population and rising medical comorbidities, expertise in resource allocation is crucial. Herrit and colleagues [121] demonstrated the average weighted cost of ET (≤4 days) patients in ICU is $4316 less when compared with

LT (≥11 days). A continous demand/imporance of resources was produced and exposed by the latest worldwide heath care crisis caused by Corona Virus 19 (Covid-19). Mattioli et al. [122] briefly exposed that ET (≥7 days <14 days) could promote expedited ICU beds availability. Nonetheless, studies are needed to assure TQT role for COVID-19 management [123].

Mostly of the presented mortality rates between LT and ET analysis do not demonstrate statistically significance [113, 114, 117, 119, 120, 124–128], which could be a response of ET placement in critical state patients [86]. Hence, no definitive conclusion could be drawn by the absence of mortality significance, as well, patients functional state at discharge could not be assured.

The variation of tracheostomy protocols can contribute to misleading results. A retrospective study [129] across 19 countries and 54 TBI centers in Europe demonstrated that the incidence of ET (≤7 days after admission) ranged from 0 to 17.6% and LT from 7.9 to 32%. A delayed procedure was more likely to happen than an earlier one. LT patients presented higher reintubation, VAP and respiratory failure rates than ET.

7. Conclusion

Overall, ET could contribute to lower exposure to secondary insults and nosocomial adverse events, rising patient's early rehabilitation and discharge rates, and improve hospital/staff resources management. Establishment of guidelines for further homogenous approaches to better assist severe TBI patients and improve second injury control is concerned.

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Conflict of interest

The authors declare no conflict of interest.

Author details

Sabrina Araujo de França[1*], Wagner M. Tavares[2,3], Wellingson S. Paiva[3] and Manoel J. Teixeira[3]

1 Department of Research of IPSPAC – Paulista de Saúde para Alta Complexidade (Paulista Institute of Health to High Complexity Instituto), 199 Padre Anchieta Avenue - Room 2, Jardim, Santo Andre, SP, 09090-710, Brazil

2 Department of Research of IPSPAC – Instituto Paulista de Saúde para Alta Complexidade (Paulista Institute of Health to High Complexity Instituto), 199 Padre Anchieta Avenue - Room 2, Jardim, Santo Andre, SP, 09090-710, Brazil

3 Institute of Neurology, University of São Paulo, 255 Dr. Enéas de Carvalho Aguiar avenue, Cerqueira César, São Paulo, SP, 05403-900, Brazil

*Address all correspondence to: pesquisacientifica@ipspac.org.br

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Chapter 10

Demographic, Clinical, and Radiographic Characteristics of Cerebral Aneurysms in Tuberous Sclerosis Complex

Mehdi Chihi, Ulrich Sure and Ramazan Jabbarli

Abstract

To date, little is known on the prevalence, incidence, and characteristics of intracranial aneurysms (IA) in patients with tuberous sclerosis complex (TSC). Based on our recent systematic review and two cases treated in our institute, we summarize the current evidence concerning the distinct characteristics of these aneurysms. In contrast to saccular IA in healthy adults, IA in TSC present commonly with large or even giant sac size and fusiform configuration, location predilection on the internal carotid artery remote from the branching zones, remarkable higher prevalence of pediatric cases, inverted sex-ratio, and suspected rapid growth. Although the pathogenesis of IA in TSC is still unclear, all these features might point to the crucial role a congenital defect in the development of IA rather than extrinsic or environmental factors. Furthermore, we discuss the enhancement of the regular magnetic resonance (MR) imaging screening suggested by the last recommendations of the 2012 International TSC Consensus Conference with cranial time-of-flight MR angiography in order to enable timely identification and treatment of frequently complex IA in TSC.

Keywords: tuberous sclerosis complex, intracranial aneurysms, subarachnoid hemorrhage, vascular disorders

1. Introduction

Tuberous sclerosis complex (TSC) is a rare multiorgan neuroendocrine disease and belongs to the group of phacomatoses. As a multisystemic genetic disorder with an autosomal dominant inheritance, it can affect any organ in the body [1]. In fact, the damage of one of two genes, TSC1 on chromosome 9 or TSC2 on chromosome 16, that produce the tumor suppressors "hamartin" and "tuberin" [2, 3] results in the formation of benign tumors so-called hamartomas, such as subependymal giant cell tumors (SGCT) in the brain. Interestingly, more than 70% of TSC cases are new mutations, and among them, 75% are caused by TSC2 mutations [4].

The Vogt triad, a combination of epilepsy, mental retardation and adenoma sebaceum, is only present in 29% of the cases [5]. Epilepsy and mental retardation are respectively in 25 and 45% of the cases absent [5]. Because of the relatively mild disease manifestations, TSC was underdiagnosed until the 1980s [6].

Cerebral aneurysms, also known as intracranial aneurysms (IA), are usually pouch-like (saccular) or spindle-shaped (fusiform) focal dilations in the wall of major arteries in the circle of Willis [7] that grow and present a certain risk of rupture. To date, arterial wall anomalies in TSC, particularly in aneurysms, were only described in the extracranial vasculature, such as aortic aneurysms or kidney aneurysms that were considered as the result of a congenital defect [8]. The distinct features of IA in these patients have not previously been addressed in the literature. Indeed, there are sporadic cases or small case series that reported the coexistence of IA and suggested their congenital origin.

First cases of TSC and IA were reported in 1974. The first patient was a 24-year old man who died after a subarachnoid hemorrhage (SAH), and the ruptured aneurysm of the right middle cerebral artery was diagnosed at autopsy [9]. The second patient was a 12-year old girl that presented in 1965 with a sudden blurry vision, and bilateral aneurysms of both internal carotid arteries (ICAs) involving the region of the carotid siphon were diagnosed [10].

Heritable connective tissue disorders such as Marfan syndrome, Ehlers-Danlos Syndrome, Loeys-Dietz syndrome and autosomal dominant polycystic kidney disease (ADPKD) are commonly associated with small saccular aneurysms [10]. Our recent systematic review of the English literature [11] is the first to describe the characteristics of IA in TSC in comparison to the features of IA in healthy adults. Despite the eventuality of a congenital origin in TSC, there are some distinct features that characterize IA in TSC and differentiate them from common nonsyndromal IA. The purpose of this book chapter is to give an overview on the particular demographic, clinical, and radiologic features through a case illustration and discuss the possible natural history of IA in TSC patients. Patient informed consent was obtained.

2. Epidemiology

TSC is a rare condition. It has a birth incidence of 1 per 5800 and an incidence of 1 per 30,000 in the general population [6]. From all cases between 1900 and 2018 that were published in the English literature, only 33 patients with 42 IA were found [11]. But the incidence of IA in TSC might be higher as reported, as no screening trial has been performed yet. Furthermore, according to the recommendations of the 2012 TSC Consensus Conference [12], the MRI at diagnosis and every 1–3 years until the age of 25 years does not involve a special sequence for the vascular system, so-called time-of-flight MR angiography (TOF-MRA). This circumstance increases the risk of overlooking small aneurysms.

3. Characteristics of cerebral aneurysms in TSC

3.1 Case illustration

A 2.5-year-old child presented with new-onset focal seizures characterized by rightward head deviation and rhythmic movements of the right arm. Seizures were treated with Vigabatrin and were controlled. The child was born at term of 37 weeks gestation to a healthy mother who had an uncomplicated pregnancy. Further evaluation revealed multiple rhabdomyomas on echocardiography, subependymal tubers on cranial MRI leading to the diagnosis of TSC. Additionally, a left cavernous lesion was detected on MRI. A TOF-MRA showed an 8-mm-diameter left cavernous ICA aneurysm. A year later, a control MRI revealed a rapid growth of the aneurysm whose diameter reached 15.5 mm (**Figure 1**). At the age of 14 months, the child

presented with his mother to our neurosurgical department. Because of the aneurysmal rapid growth, the decision to treat the aneurysm was made and a digital subtraction angiography (DSA) was performed (**Figure 2**). The aneurysm was treated by embolization and parent vessel occlusion. After treatment, the patient tolerated the total occlusion of the ICA and no neurological deficits were noticed.

3.2 Demographic characteristics

The collected series [11] showed a specific demographic pattern. In particular, the male/female ratio was 1.9:1 and 66.7% of the patients were under the age of 18, among them 36.4% were 2 years of age or younger.

3.3 Clinical characteristics

Most IA in patients with TSC were diagnosed incidentally (36.4%) or due to a new onset of a neurological deficit (21.2%). IA were ruptured in only 7.1% of the cases [11].

3.4 Radiological characteristics

The most frequent location of IA was the anterior circulation (85.7%) in favor of the ICA (61.9%), where aneurysms originated remote from branching zones. Of the 42 IA, 57.1% were large (size: 10–24 mm) or giant (size: ≥25 mm) and 45.2% had a fusiform configuration. Multiple aneurysms were seen only in 21.2% of the cases and a rapid growth was described and documented only in 2 patients (6%) [11, 13].

3.5 Summary and comparison with other series

Cerebral aneurysms in TSC have distinct demographic, clinical and radiological features. Indeed, comparing TSC patients with those of the unruptured cerebral aneurysm Study of Japan (UCAS Japan) [14], significant differences are found between both series in the location on the ICA (61.9 vs. 34.1%, respectively), large/giant size (57.1 vs. 10.4%, respectively) and proportion of multiple

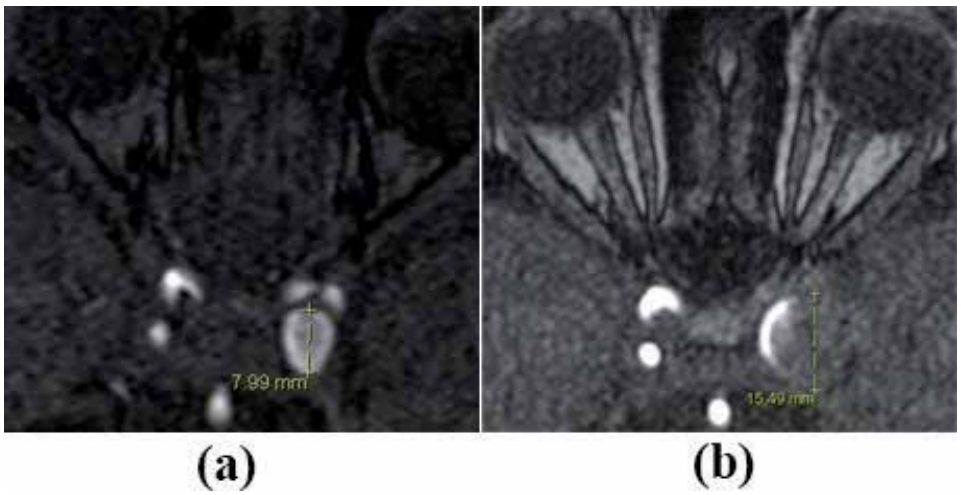

Figure 1.
TOF-MRA showing an incidental fusiform left cavernous ICA aneurysm (8 mm) of a 2.5-year-old child (a) with a rapid aneurysmal growth (+7.5 mm diameter within 12 months of period). (b) ICA: internal carotid artery, TOF-MRA: time-of-flight-magnetic resonance angiography.

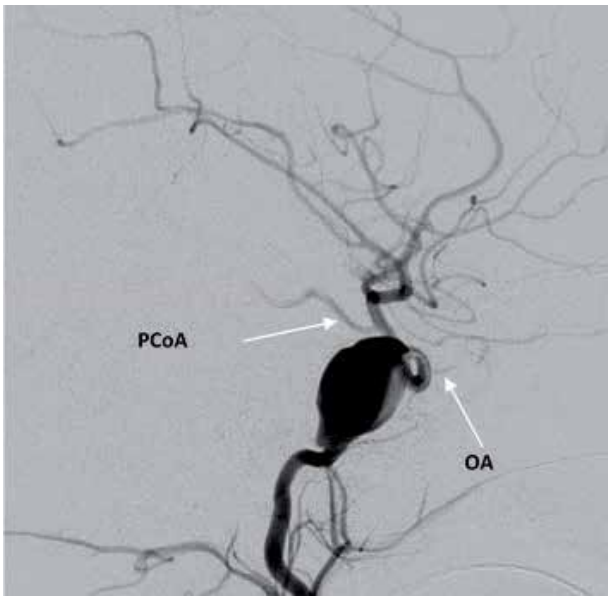

Figure 2.
DSA showing a lateral view of the fusiform left cavernous ICA aneurysm, obtained when the child was 14 months old. DSA: digital subtraction angiography, ICA: internal carotid artery, OA: ophthalmic artery, PCoA: posterior communicating artery.

IA (21.2 vs. 13.9%, respectively). Comparing TSC patients with individuals suffering from giant aneurysms, [15] a difference in the location of the IA (anterior vs. posterior circulation, respectively) and in patients' demographics are noticed, as giant IAs frequently manifest in women and during the fifth and sixth decades. Comparing TSC patients with pediatric series [16], several similarities are noticed, including the male predominance and high frequency of large/giant and fusiform aneurysms. However, the location on the ICA remote from branching zones remains the distinct characteristic of TSC.

A further comparison of IA in TSC patients with those with ADPKD [7] shows notable differences in the location on the ICA (61.9 vs. 16.8%, respectively), rupture status (7.1 vs. 37.9%, respectively), large/giant size (57.1 vs. 11.6%, respectively), fusiform configuration (57.1 vs. 2.1%, respectively), proportion of multiple IA (21.2 vs. 45.3%, respectively) and patient's median age (10.5 vs. 48.5 years, respectively).

The prevalence of IA in patients with TSC was retrospectively estimated to be 0.74% during a 10-year period in a cohort of 404 patients [17]. This is definitely lower than the prevalence of IA in the general population (3.2%) [18], but slightly higher than that of the incidental findings of IA on brain MRI after screening of "asymptomatic individuals" in the general population (0.35%) [19]. In a large series of patients with heritable connective disorders, the prevalence of IA during a 10-year period was estimated to be 14% by Marfan syndrome, 12% by Ehlers-Danlos syndrome and 28% by Loeys-Dietz syndrome [20]. Patients were adult individuals (mean age: 49.4 vs. 41.7 vs. 36.5, respectively) with a male/female equidistribution or female predominance (49 vs. 82 vs. 52%). IA were small (mean size: 4.4 vs. 6.9 vs. 4.8 mm), mostly saccular (75 vs. 64.3 vs. 87.5%), located on the ICA (75 vs. 85.7 vs. 62.5%) and unruptured (0 vs. 14.3 vs. 12.5%) [20].

In contrast, TSC patients are mostly young male individuals that present with asymptomatic, unruptured, large/giant, fusiform aneurysms that are located on the ICA, remote from the branching zones, with an eventual rapid growth. These

characteristics may support the idea that IA in patients with TSC are characteristically different from other syndromal and nonsyndromal aneurysms.

4. Diagnostic modalities, treatment strategies, and outcome

4.1 Diagnostic modalities

In our systematic review [11], digital subtraction angiography (DSA) was the most common diagnostic modality (57.6%) for the identification of IA followed by MRI (30.3%). DSA remains the gold-standard in the diagnosis of IA. However, because of the crucial technological advances, MR angiography at 3 Tesla was found to have a high positive predictive value (mean: 93.4%) and high sensitivity for the detection of unruptured IA (74.1% for aneurysms <3 mm and 100% for aneurysms ≥3 mm) [21]. Furthermore, contrast-free 3D-TOF-MRA at 3 Tesla accurately identifies the presence of IA and may replace DSA as a contrast-free, noninvasive, and nonradiation-based modality for the diagnosis and screening of IA [22].

4.2 Treatment strategies

Several treatment strategies were performed including aneurysm clipping and endovascular coiling. However, because of the complex morphology of IA with oftentimes fusiform and/or giant aneurysm sac, many other techniques as surgical ICA occlusion after superficial temporal artery-MCA bypass or stent-assisted coiling or endovascular ICA occlusion were also performed [11]. In the last two decades, an increase in endovascular treatment of IA was noticed. Nevertheless, the proportion of microsurgical vs. endovascular treatment was almost the same in the pooled TSC cohort. This circumstance might be related to high prevalence of above-mentioned complex IA, which are less eligible for conventional endovascular treatment. However, recent improvements in neuro-interventional radiology such as flow-diverters might enhance the indications to endovascular treatment.

4.3 Outcome

Among 16 patients that were operated, neurological outcome was reported in only 12 patients. Six patients had postoperatively no neurological deficits, three patients met an improvement of their focal neurological deficits (Oculomotor paresis/palsy, visual loss) and four patients experienced focal deficits (Oculomotor paresis, facial palsy and hemiparesis) [11].

5. Pathogenesis

The natural history of saccular aneurysms is to date well established, as higher hemodynamic shear stress and consequently stronger flow acceleration frequently promote aneurysm formation in cerebral vessel bifurcations [23]. In contrast, natural history of cerebral aneurysms remote from the branching zones as fusiform aneurysms still remains unclear. Some authors found a correlation between fusiform aneurysms and larger aortic root dimension, suggesting a shared pathophysiological mechanism with aortopathy [24, 25]. However, the lack of histological findings of IA in TSC patients represents a considerable drawback in understanding aneurysm pathogenesis in this disease. The sole histological analysis was performed in 1980 at autopsy on the cerebral aneurysm wall of a 26-year-old woman.

It revealed a "relatively hypocellular hyaline fibrous tissue." There were neither elastic fibers nor evidence of inflammation or necrosis [26].

The question of aneurysm formation always focused on their acquired vs. congenital nature. Many arguments plead in favor of a congenital defect of the arterial wall. First, the higher frequency of pediatric cases (66.7%) and the distinct location of IA unrelated to branching zones [11] might indicate the inferiority of extrinsic/environmental factors, which are considered to play a crucial role in the genesis of nonsyndromal IA in healthy adults [27]. Furthermore, the suspected rapid growth [11, 13] of these aneurysms could also support the presence of a genetic predisposition to IA development. Moreover, there is evidence of the pathogenesis of extracranial aneurysms in TSC that are likely caused by disorders of the connective tissue [28–31]. In fact, the postoperative pathologic examination of a large thoracoabdominal aneurysm wall of a 3-year-old child with a TSC2 mutation revealed a subintimal proliferation of smooth muscle cells (SMC) [32]. Further, it was demonstrated that the de-differentiation of aortic SMC through the activation of mammalian target of rapamycin complex 1 (mTORC1) signaling, characterized by increased proliferation of SMC and decreased expression of contractile proteins, contributed to the formation of the aneurysm [32]. Indeed, in vitro and in vivo evidence that the effect of TSC2 deficiency on vascular SMC is primarily driven by increased mTORC1 signaling was provided [32]. And these findings plead in favor of a coexistence of both diseases rather than a coincidence.

Therefore, genetic and histopathological studies must further investigate the anomalies of the vascular connective tissue in TSC, especially in the wall of intracranial aneurysms to better understand IA formation.

6. Recommendations

Morbidity and quality of life during adulthood in patients with TSC are determined by the neurological manifestations [33]. Life expectancy can be reduced by uncontrolled seizures and tuber burden that significantly affect the cognitive impairment of patients [34]. Indeed, 13 cases of "unclear death circumstances" preceded by seizures were retrospectively reported among 639 patients with TSC in two different investigations at the Mayo Clinic [35] and the Bath TSC Clinic [36]. Status epilepticus was listed in 9 cases and sudden unexplained death in epilepsy in 4 cases. Because of advances in diagnostic procedures and medical management, life expectancy of patients with TSC has drastically improved during the last 2 decades and the number of patients who survive to middle age and beyond is increasing [37].

The relatively young age of the individuals with TSC, the disproportionally high number of large/giant IA and the well-described rapid aneurysm growth in two children are sufficient arguments to prompt aneurysm treatment. Additionally, three cases of SAH were described. As long as the real incidence of IA in TSC remains unknown, the risk of aneurysm rupture in this population cannot be estimated. Therefore, the enhancement of the 2012 International TSC Consensus Conference with a cranial TOF-MRA at diagnosis and at the control examinations every 1–3 years might be reasonable for young individuals [11]. Prospective IA screening studies on a national and even international scale are urgently needed.

7. Conclusion

The epidemiology and pathogenesis of intracranial aneurysm formation in patients with TSC remains unclear. IA in TSC seem to have distinct characteristics

that differentiate them from other individuals with IA. Several demographic, clinical and radiological arguments plead in favor of a coexistence of both entities rather than a coincidence, due to a congenital defect of the arterial wall. Therefore, large population-based patient registers, prospective screening studies as well as genetic and histopathological studies are required to improve the understanding of IA formation in TSC. In this way, regular MRI screening with TOF-MRA seems to be appropriate in TSC young individuals.

8. Conclusions

Aneurysms were well described in the extracranial vasculature of patients with tuberous sclerosis complex (TSC) such as aortic and kidney aneurysms, where anomalies of the vascular connective tissue have been histopathologically and genetically investigated. In contrast, cerebral aneurysms remain uncommon and their incidence totally unknown. A recent systematic review of the literature found 33 patients with 42 intracranial aneurysms (IA) that seem to have distinct characteristics compared to other syndromal and nonsyndromal IA. Indeed, TSC patients with cerebral aneurysms were found to be young male individuals that present with large/giant, fusiform, mostly asymptomatic, and unruptured aneurysms, located on the internal carotid artery unrelated to branching zones, with an eventual rapid growth. Although the pathogenesis of IA in TSC is still unclear, several demographic, clinical, and radiological arguments plead in favor of the coexistence of both entities, due to a congenital defect of the cerebral arterial wall. As long as the real incidence of IA in TSC remains unknown, the risk of aneurysm rupture in this population cannot be estimated, especially that three cases of subarachnoid hemorrhage were reported. Therefore, prospective screening, genetic and histopathological studies are urgently needed to improve the understanding of the pathogenesis and epidemiology of IA formation in TSC. This cannot be achieved without enhancing the recommendations of the 2012 International TSC Consensus Conference with a cranial TOF-MRA at diagnosis and all regular screening consultations.

Conflict of interest

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this chapter.

Author details

Mehdi Chihi*, Ulrich Sure and Ramazan Jabbarli
Department of Neurosurgery and Spine Surgery, University Hospital Essen, University Duisburg-Essen, Essen, Germany

*Address all correspondence to: mehdi.chihi@uk-essen,de

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Chapter 11

Neurobehavioral, Cognitive, and Paroxysmal Disorders in the Long-Term Period of Pediatric Traumatic Brain Injury

Nikolay Zavadenko, Yuriy Nesterovskiy, Alexey Kholin and Irina Vorobyeva

Abstract

The consequences of the traumatic brain injury (TBI) in children and adolescents represent a major medical and social problem, as TBI interferes in the normal processes of neuroontogenesis. Brain damage in TBI in children and adolescents occurs during the ongoing processes of its growth and maturation, and therefore the clinical course and outcomes may differ significantly from those in adults. Poor outcomes of TBI sustained in early childhood may be explained considerably by the timing of injury in a period of rapid brain and behavioral development. Thus, TBI has a negative impact on the cognitive function development, behavior, school education, and social skills acquisition. Cognitive and behavioral disorders in children and adolescents in the long-term period of TBI become more prominent in co-occurrence with paroxysmal disorders, including posttraumatic headaches, posttraumatic epilepsy, and subclinical epileptiform activity on the EEG. In general, a favorable outcome is possible in children more often than adults even after severe TBI, due to the high neuroplasticity of the developing brain. Therapeutic and rehabilitation measures in the long-term period of TBI in children and adolescents should be intensively carried out both in the first 12 months after TBI, when the most significant results from their use are expected, and in the long-term period, considering the ongoing processes of morpho-functional maturation and neuroplasticity mechanisms.

Keywords: traumatic brain injury, consequences, children, adolescents, cognitive disorders, behavior disorders, posttraumatic headaches, posttraumatic epilepsy, treatment, neuroplasticity

1. Introduction

Traumatic brain injury (TBI) is the most common and potentially the most deleterious type of injuries in pediatric population [1]. The consequences of TBI in children and adolescents represent a serious medical and social problem.

TBI clinical course and outcomes in children have peculiarities as the damage impacts brain, which growth and maturations are continuing and not yet completed. The complexity of pediatric TBI is due to the heterogeneity of its pathophysiology

and depends on the age of impact, influencing different stages of brain development. TBI interferes with the normal course of neuroontogenesis, disturbing the development of cognitive functions, school education, behavior, and social skills formation. Cognitive and behavioral disorders in children and adolescents in the long-term period of TBI are significantly increased in the presence of paroxysmal disorders: post-traumatic headache, post-traumatic epilepsy, subclinical epileptiform activity on the EEG. Therapeutic and rehabilitation measures in the long-term period of TBI in children and adolescents should be intensively carried out both in the first 12 months after TBI, when the most significant results from their use are expected, and in the long-term period, considering the ongoing processes of morpho-functional maturation and high neuroplasticity of the developing brain.

Despite the importance of the problem, there is no specific treatment for the long-term consequences of childhood TBI, and the available recommendations are mostly extrapolated from studies conducted on adult patients, and thus do not take into account the features of the child's neurodevelopment and brain plasticity [2, 3].

2. Pathophysiology of pediatric TBI

Brain damage in TBI may arise by two mechanisms, including (1) primary (immediate) injury, directly caused by mechanical forces during the initial insult, and (2) secondary (delayed) injury, accompanied by further tissue and cellular damages following primary insult. Primary injury occurs at the time of impact and is mostly irreversible. The immediate impact of different mechanical insults to the brain can cause two types of primary injuries: focal (brain contusions) and diffuse (diffuse axonal injury, diffuse vascular injury, edema). However, the common co-existence of focal and diffuse injuries in patients suffered from moderate to severe TBI was demonstrated [4, 5].

Secondary damages to the brain occur after the initial impact. This is initial injury progression in delayed and prolonged manner, lasting from hours to many years. There are number of factors contributing to secondary injuries, which include hypoperfusion of the penumbral region surrounding the primary injury, excitotoxicity, mitochondrial dysfunction, oxidative stress, lipid peroxidation, edema, neuroinflammation, axonal degeneration and apoptotic cell death [6, 7]. Depending on the age when the TBI happens, the effects of secondary injuries will vary, altering a variety of biological processes of brain development, including myelination, neurotransmitter and neurotrophin development, synaptogenesis and synaptic reorganization, gliogenesis, programmed cell death, blood-brain barrier function and cerebrospinal fluid dynamics. The secondary injury is believed to be an important determinant of outcomes and it may be preventable and more responsive to appropriate and timely medical intervention.

Defining the severity of TBI in the acute period is important as it is predictive of the outcome. The periodization of TBI clinical course could be delineated as follows [8], depending on its initial severity:

1. The acute period lasting 2–10 weeks.

2. The intermediate (subacute) period, from 10 weeks to 6 months post-injury.

3. The long-term (chronic) period, from 6 months to up to 2 years or more.

The factors, defining the long-term impact of TBI on the individual functioning include:

a. the severity of the initial injury in the acute period

b. localization of damage

c. the rate and completeness of physiological recovery

d. the functions affected

e. the meaning of the dysfunction to the individual

f. functions which are not affected by TBI

g. the resources available to aid recovery.

The localization of damage for particular types of TBI is rather typical [9]. For instance, the areas predominantly affected by contusions are the frontal and temporal lobes as well as the brain stem—regions located near bony prominences. Brain regions particularly involved in diffuse axonal (or shearing) injury are the corpus callosum, subcortical white matter and the mid-brain.

However, not only the severity of TBI, but also the age at which it occurred, has a significant impact on the clinical manifestations of the consequences of TBI. Research on the response of children's brains to TBI has led to important results on the impact of age on recovery from injury and its functional consequences, and various opinions have been formulated.

Early studies of childhood TBI were largely directed at determining whether there were any long-term sequelae from such injuries. The prevailing view was that as children's brains are more plastic and better able to accommodate the effects of brain insults, children would experience fewer deficits than adults. The developing brain is capable of more significant reorganization and recovery after TBI. In addition, after damage to immature brain, progressive cognitive decline is less likely to develop, and ongoing neurodevelopment may contribute to recovery [10]. Most skills formed by the time of injury are preserved, even if they were temporarily lost or compromised [9]. As a result, children are more likely than adults to have a favorable outcome, even after severe TBI, due to the high neuroplasticity of the developing brain.

On the other hand, studies of Klonoff et al. [11, 12] and Rutter et al. [13] and some others have shown that TBI in childhood does have measurable consequences in terms of functional impairment. Another concept was formulated considering the developing brain as more vulnerable to TBI if it is affected during critical periods of significant growth, formation of brain circuits and functions, which may lead to more serious and persistent physiological changes after a TBI. Brain structures and functions that continue to mature at the time of TBI may be affected to a greater extent than those formed before the injury [14]. Thus, the age of TBI is an important factor influencing its consequences.

Many children who suffered TBI make a good physical recovery and appear outwardly normal. However, even after mild TBI, children may continue to experience problems when faced with the complexities of everyday life, particularly learning, skill acquisition, cognitive and psychosocial functioning [15, 16]. Thus, even a mild TBI suffered in childhood does not always pass without a trace, and its consequences can manifest years after the injury.

Educational and behavioral developments as well as social adaptation are dependent upon the intact capacities of learning, attention, and executive functioning (EF). Many of these skills are impaired as a result of TBI, even while intellectual functioning, as measured by traditional psychometric tests, may appear intact [17].

In general, a favorable outcome is possible in children more often than adults even after severe TBI. Nevertheless, neurological, cognitive, behavioral, emotional, and socio-psychological consequences can be observed in the long-term period of TBI in children and adolescents. The complexity of pediatric TBI is due to the heterogeneity of its pathophysiology and depends on the age of impact, influencing different stages of brain development.

3. Neurobehavioral consequences of moderate and severe closed pediatric TBI

Patients who have suffered moderate or severe TBI exhibit a broad range of possible outcomes, and it is generally not possible to predict the extent of recovery in the initial weeks after the trauma. Traditionally, children have been reported to have better outcomes than adults after TBI. But, unlike in adults, in children the effects of the brain injury on brain function interact with the maturation or development of the child. Skills that are emerging or developing may be affected differently by brain injury from skills that are already established.

However, while fewer focal deficits may be apparent, children appear to develop deficiencies across virtually all areas of higher cognitive functioning. These deficits may not become apparent until later in the child's development. Children with TBI face difficulties because of impaired new learning, inability to take on social cues, and behavioral, educational and schooling problems. Determining the combination of cognitive, behavioral and physical deficits is an important first step in setting goals for rehabilitation.

In our studies of the long-term sequelae of TBI the neurological and neuropsychological assessment of 283 patients aged from 5 to 14 years (201 boys and 82 girls) suffered moderate or severe closed TBI (contusion or diffuse axonal injury) was performed in the period from 6 months to 4 years after TBI [18, 19]. The diagnosis was confirmed during hospitalization in the acute period of head injury. The principal criteria for the severity of the TBI were the Glasgow Coma Scale score and the loss of consciousness duration. Moderate closed head injury was diagnosed in 150 patients (53%) and severe injury in 133 (47%).

During the long-term period of TBI all patients were referred with various complaints, the most common being:

1. frequent headaches (95% of cases)
2. chronic fatigability and decrease in endurance (88%)
3. memory problems (82%)
4. attention deficit and distractibility (74%)
5. learning difficulties at school with academic underachievement (73%)
6. behavioral problems (62%)
7. motor restlessness (60%)
8. sleep disorders (61%).

Secondary nocturnal enuresis developed in 16% of patients post-injury and speech and language disorders in 14%.

There is a direct relationship between general measures of intelligence (IQ) and the severity of TBI, with IQ being depressed for the more severe end of the severe TBI spectrum. In the milder end of severe TBI, and in moderate TBI, measures of IQ usually return to the normal range and may return to pre-trauma levels [20–22]. Despite this, many children who have suffered severe or moderate closed TBI have significant specific neuropsychological deficits that interfere with optimal cognitive functioning, adaptive behavior and academic achievement (**Table 1**).

In moderate or severe cases of TBI, the cognitive functions that are most vulnerable are memory, attention, speed of information processing, visuospatial and perceptual abilities, language skills, EF in particular. **Table 2** outlines the peculiarities of the TBI effects on the cognitive functioning and development of children (**Table 2**).

Some of the cognitive disorders are attributable to the specific focus of damage. But residual problems are commonly the consequence of diffuse damage or involvement of axial brain structures that modulate cortical functions. This combination of specific cortical damage and diffuse damage to axial and subcortical structures is responsible for deficits in different higher cerebral functions. Neuropsychological assessments can help to delineate the extent and type of cognitive disability that a child may experience.

Memory is easily damaged by TBI because several brain structures are involved in information-processing, storage, and retrieval. Short-term memory loss is the most common and most troublesome type of memory problem. This can manifest itself as forgetting new information, difficulties in scholastic learning and mastering new skills, repeating the same question over and over, getting details mixed up, forgetting a change in routine and forgetting where things have been placed.

Speed of information-processing. Slowing down the speed at which the brain performs information-processing is often due to diffuse axonal damage of the brain pathways. This results in problems such as not understanding fast speech, being unable to absorb instructions first time around, and not being able to quickly formulate a reply to a question.

Attention and concentration. A reduced concentration span after TBI is very common, as is a reduced ability to pay attention to more than one task at the same time. These problems are usually caused by damage to the frontal lobe. Attentional problems tend to get worse when the person is tired, stressed, or worried. When there are problems with concentration, it is difficult to follow instructions, plan ahead, or be organized.

EF: planning, organizing and problem-solving. EF is associated with the frontal lobes, which are especially fragile in TBI. EF includes goal-orientated behavior, initiation, attention control, flexibility, social learning, and self-control.

In general, executive skills are required in novel and complex situations, where routine responses do not exist. Damage to the frontal lobe can affect these skills, resulting in a subtle set of deficits which have been called "dysexecutive syndrome." This covers problems in making long-term plans, goal setting, and initiating steps to achieve objectives. The ability to stand back and take an objective view of a situation may be lacking, as may the ability to see anything from another person's point of view.

A number of studies have shown persistent cognitive and behavioral deficits following pediatric TBI [17, 23, 24]. A 2-year follow-up suggested that children sustaining severe TBI are particularly vulnerable to impairments in EF. While some recovery took place with time since injury, deficits remained 2 years post-injury and were suggested to have an impact on ongoing development [24].

In our clinical sample, the majority of patients who had suffered traumatic frontal lobe lesions demonstrated various manifestations of dysexecutive syndrome,

Behavior	School education	Social contacts and relations with peers
a. Irritability, temper tantrums, episodes of aggressive behavior	a. Academic underachievement, accumulated knowledge is dissimilar and fragmentary	a. Difficulties in co-operating with others and in understanding the rules of social interactions
b. Impulsivity, disinhibition, physical restlessness	b. Difficulties in entering schoolwork, poor performance with inconsistency and inflexibility	b. Poor judgment and deficient self-control leading to mistakes in contacts with others
c. Fluctuations of mood	c. Slowed thinking, difficulties in remembering new information and sustaining attention on tasks, distractibility	c. Limited social activity due to becoming easily tired, lack of energy, residual neurological deficit, ongoing treatment
d. Impaired goal-directed behavior, decreased interest in the achievement of good results in different tasks and activities	d. Inaccurate, makes a lot of careless mistakes, fails to finish assignments	d. Social activities (such as hobbies, games, sports, trips etc.) are limited or avoided due to behavioral and cognitive difficulties
e. Indecision, restraint, feelings of inferiority and failure	e. Unable to use other people's help to complete schoolwork or other assignments	e. Is behind peers in the acquisition of independent behaviors and skills socially valued for age
f. Dependent on others, unable to stick up for self	f. Difficulties with use of acquired information and skills, drawing conclusions and generalizations	f. Loss of friends, increased risk of social isolation
g. Does not perceive entirely the results of his/her behavior, does not modify his/her reactions		

Table 1.
Impairments in behavioral adjustment, school education, and social competence in the long-term following traumatic brain injury.

including poor planning and organizational skills, problems with initiation/inhibition, impaired problem-solving skills, inability to shift mental sets (inflexibility, perseverations), attention disturbances and impulsivity, impaired working memory, impaired temporal organization of behavior, impaired social behavior and affective changes, and disturbances of motor control.

Children with moderate to severe TBI have displayed poorer outcomes compared to children with orthopedic injuries in all neuropsychological domains at an extended follow-up (mean 4 years). Some recovery occurred during the first year post injury, but recovery reached a plateau after that time. Further recovery was uncommon after the first year [25]. Deficits in EF, pragmatic language skills and social problem-solving were the long-term social outcomes [26].

Speech and language disorders. Motor speech disorders are common in the acute period of TBI but tend to show considerable improvement with time. They include oral-motor apraxia, dysarthria, and difficulties with breath control resulting in short length of utterance, whispering, or a monotonous voice [27].

Language function may be impaired secondary to cognitive dysfunction or specific language deficits. Disorganized language secondary to impaired cognition is most common following TBI in its acute period. Although classic aphasias are rarely seen in pediatric TBI, aphasic symptoms are. These include the inability to name objects or remember names, word-retrieval problems, and auditory and reading comprehension deficits [28].

Processing speed	a. Decrement in processing speed which can be mistakenly attributed to lack of concentration.
	b. This impairment will have a pervasive effect on education as the pace of learning required in school increases.
Attention	a. Deficits in the focus, division, and ability to sustain attention may mean distractibility from play, study, or road safety.
	b. Child may have difficulty developing attentional control.
Memory	a. Young children are unlikely to report a difficulty spontaneously.
	b. The younger child has acquired less knowledge previously.
	c. New learning deficits can have a cumulative effect as the child fails to keep up—a minor problem can develop into a major difficulty.
	d. The task is to acquire skills.
Language	a. Language is central to the child's sociocultural and intellectual development.
	b. Children losing language due to left hemisphere damage before the age of 5–6 years are likely to regain these skills due to plasticity.
	c. Complete recovery is less likely with injury after the critical period of language development.
Perceptual and motor skill	a. Problems are common in the acute period of TBI.
	b. Psychomotor slowness and dyspraxia may develop after TBI, which can adversely affect social and scholastic functioning.
Executive functioning	a. Longer term difficulty with executive skill development.
	b. Frontal lobes are still developing late into the second decade of life.
	c. Difficulties may become apparent in later childhood and adolescence.

Table 2.
Effects of traumatic brain injury on cognitive functioning and development in children.

Among our pediatric patients, in the long term after moderate or severe closed TBI only 14% had speech and language problems, including aphasic symptoms in 8% and dysarthric symptoms in 6% of cases. Impairments in communication may include slowed speech, dysfluency, word-finding difficulties, insufficient quality of conversation (producing fewer words or sentences with simple structures, tendency to use gestures while speaking), and poor comprehension of complex or long expressions. Thus, a clear difference between children and adults is that while the effects of the TBI are immediately obvious in adults, children's development is disordered after injury and some deficits may take a considerable time to appear.

Motor disorders. Severe motor deficits, including hemiparesis and impaired balance and steadiness are common in the acute period of TBI in children, with rapid recovery occurring in the first weeks or months post-injury. It is only in children who sustain very severe TBI that such motor deficits persist. Although motor outcome in the mild end of the severe TBI group is generally good, abilities rarely return to normal. Even if a classic motor examination appears normal, there will usually be deficits related to speed of performance [29]. Balance problems are also very common after TBI.

In our cohort of patients, neurological assessment revealed hemiparesis in only 4% and symptoms of ataxia in 46%. The severity of these motor disorders was defined as mild or moderate. However, 100% of children in the long-term period following moderate or severe closed TBI manifested balance problems and subtle neurological signs when examined using Denckla's battery for gross and fine motor functions [30]. Like children with ADHD, they demonstrated poor performance in both types of this battery tasks, including walking a line and sustaining postures/stations, or repetitive or successive movements for hands and feet (fine motor proficiency).

Psychiatric disorders. Pediatric TBI is associated with increased risk for the development of psychiatric disorders. The rates of newly diagnosed psychiatric disorders among pediatric patients suffered TBI were as high as 49% compared with 13% in samples of children with orthopedic injury [31]. The psychiatric sequelae of TBI, both behavioral (externalizing) and emotional (internalizing), vary with the severity and location of injury, the phase of recovery, the premorbid conditions and personality of the patient, and the psychosocial environment [9, 32].

Our study included 104 adolescent patients (58 male and 46 female) aged 12 to 19 years, who were examined within 6 months to 4 years after undergoing closed TBI of moderate and severe degrees [19]. The presence and severity of psychiatric disorders was evaluated before and after the TBI. In the long-term period of TBI, emotional and behavioral disorders were diagnosed in 55% of the adolescent patients (**Table 3**). Among internalizing disorders, a high percentage (30%) of patients with anxiety disorders (simple phobias, obsessive-compulsive and generalized anxiety disorders) was found. Mood disorders in the form of depressive states (17%) were two times more common in girls than in boys. In the majority of cases mood disorders and anxiety disorders developed after TBI—that is, TBI served as a causative factor for their development.

Attention deficit hyperactivity disorder (ADHD) occurred in 30% of the examined patients, with less frequent conduct disorder (9%) and oppositional defiant disorder (6%). It should be noted that the manifestations of ADHD in all cases were observed even before TBI, as well as most cases of conduct disorder and oppositional-defiant behavior. Thus, the presence of externalizing disorders before TBI demonstrates their role as premorbid and predisposing conditions and a serious risk factor for TBI. On the other hand, in all those cases a significant deterioration of behavior was observed after the TBI compared with degree of behavioral problems before the injury.

ADHD, defined by developmentally inappropriate and impairing levels of inattention and/or hyperactivity-impulsivity in multiple settings, is reported to be the most common externalizing psychiatric disorder among children with a history of TBI, with a prevalence of about 20–30% [31, 33], compared with the pediatric population prevalence of 5–8%. The studies have demonstrated that children with a history of TBI, even those with less severe injuries, have an increased risk for the development of new-onset attention problems even many years after injury. TBI severity was correlated with increased risk of secondary ADHD with strongest associations in severe TBI. Additional findings about the association of poor family functioning with the development of attention problems after TBI support the importance of allocating resources to the injured child's family throughout recovery [33].

Neurobehavioral effects from TBI differed by age at injury. Preschool children showed increasing ADHD and affective problems during the first year after injury [34]. Younger age at TBI was found to be a risk factor for adverse outcomes in specific psychosocial and EF domains. Preschoolers and school-age children were vulnerable to TBI adverse effects in terms of reduced emotional control, elevated emotional and affective symptoms, and behavior problems [35]. These

Emotional and behavioral disorders	Total (%) of patients with the disorder	% of patients with the disorder	
		Before the TBI	After the TBI
Anxiety disorders	30	5	25
Mood disorders	17	2	15
Attention deficit hyperactivity disorder	30	30	—
Oppositional defiant disorder	6	5	1
Conduct disorder	9	7	2

*Note: The gray shade in **Table 3** illustrates prevailing of firstly diagnosed externalizing psychiatric disorders in patients before the TBI and internalizing psychiatric disorders after the TBI.*

Table 3.
Emotional and behavioral disorders in adolescents aged 12–19 years, developed before and after closed traumatic brain injury.

findings regarding attention and emotional control are of particular importance for later self-regulation of behavior and academic achievements after TBI [36]. Executive dysfunction and psychosocial difficulties are likely to contribute to the lower functional academic skills in younger children and emergence of increased academic problems years after TBI [37].

Thus, TBI is a major cause of neurobehavioral disability among children and adolescents. Studies of outcomes 1 to 3–4 years post-injury reveal that moderate or severe pediatric TBI leads to difficulties in adaptive functioning, behavioral problems, deficits in academic and cognitive skills [9, 11–13, 15–29, 31–33]. Neurobehavioral sequelae frequently fail to resolve completely over time and thus are of particular concern to children's parents, teachers and health care professionals.

Poor outcomes of TBI sustained in early childhood may be explained considerably by the timing of injury in a period of rapid brain and behavioral development [24, 38]. Identification of vulnerability periods to the effects of TBI is crucial to promote awareness of appropriate referral for rehabilitation and school-based services [38].

4. Paroxysmal disorders in the long-term period of pediatric TBI

The vulnerability of structures of the immature brain associated with TBI can be also manifested in paroxysmal disorders: post-traumatic headache, post-traumatic epilepsy, subclinical epileptiform activity on the EEG. It is noteworthy, cognitive and behavioral disorders in children and adolescents in the long-term period of TBI significantly increase in the presence of paroxysmal disorders.

Post-traumatic headache (PTH). Headache following traumatic brain injury (TBI) of any severity has been the most common physical symptom described and is a focus of research and clinical attention [39–41].

It is easy to establish the relationship between a headache and TBI when the headache develops immediately or in the first days after trauma has occurred. On the other hand it is very difficult when a headache develops weeks or even months after trauma, especially when the majority of these headaches have the pattern of tension-type headache and the prevalence of this type of headache in the population is very high. Frequently, headache that results from head trauma is accompanied by other symptoms such as dizziness, difficulty in concentration, fatigue, anxiety and insomnia. This constellation of symptoms is known as the post-traumatic or post-concussion syndrome; among them, headache is usually the most prominent [42].

In the International Classification of Headache Disorders (3rd edition) [43], PTH is considered a secondary headache defined by the onset of headache "within 7 days following trauma or injury, or within 7 days after recovering consciousness and/or within 7 days after recovering the ability to sense and report pain" [43]. PTH is further subdivided into "acute headache attributed to traumatic injury to the head" and "persistent headache attributed to traumatic injury to the head." If the headache resolves within 3 months of onset, it is characterized as acute PTH, whereas headaches that occur beyond 3 months are defined as persistent PTH.

The most common headache phenotypes in PTH are tension-type-like headache and migraine-like headache. In our cohort of patients suffered closed TBI of moderate and severe degrees persistent PTH were observed in 268 of 283 patients (95% of cases) recurring from one episode in a week to daily attacks [18, 19]. Headaches usually affected the lifestyle of the children, resulted significantly on their mood, behavior, intellectual and physical endurance, school learning. Headaches causation was established by their onset in temporal relation to TBI and persistence for more than 3 months after head trauma. The most commonly seen pattern, resembling tension-type headache, occurred in 72.4% of patients. Headache associated with the increase of intracranial pressure due to long-lasting disorders of cerebrospinal fluid circulation was confirmed in 12.3% of cases. Migraine-like headaches were diagnosed in 11.9% and neuralgic pains in the frontal or occipital regions in 3.4%. Thus, our data evidence for the involvement of different causative mechanisms in PTH in children.

PTH pathophysiology remains largely unclear, but several possible mechanisms have been proposed, including impaired descending modulation, neurometabolic changes and activation of the trigeminal sensory system [39]. When indicating severe brain damage due to TBI and persistent PTH, it is necessary to exclude the epileptic origin of paroxysms. The combination of PTH and epilepsy, as well as epileptiform activity on the EEG in patients with PTH was firstly reported in 1963 by D.W. Cooper and D.C. Cavicke based on two cases [44]. Formisano et al. [45] revealed a high incidence of paroxysmal abnormalities on the EEG with the presence of sharp waves in 84.6% of patients with chronic PTH, which was also associated with the presence of fractures or damages to the skull and dura mater, either due to TBI or as a result of craniotomy.

Not only routine EEG, but also video-EEG monitoring with the recordings in different functional states (especially all phases of sleep) should be used in the examination of patients with chronic PTH. Studies on the use of multichannel EEG monitoring in combination with evoked brain potentials to assess the disruptions and delay of activation of neuronal networks in PTH, especially in posttraumatic migraines, is promising [46].

Post-traumatic epilepsy is one of the most threatening consequences of TBI. High risk of post-traumatic epilepsy is characteristic for patients with penetrating head injuries—as much as 50% of them develop seizures. Patients with focal neurological deficit and large cerebral lesions immediately after injury have the greatest risk for post-traumatic epilepsy. It is believed that post-traumatic epilepsy is much less common with closed head injuries.

We have determined the incidence of post-traumatic epilepsy in our cohort of children suffered moderate or severe closed TBI. A total of 18 cases of epilepsy were revealed in a total of 283 patients. A total of 16 patients (10 boys and 6 girls) or 5.7% developed secondarily generalized seizures, all in the period from 4 to 12 months post-injury; the severity of head injury was moderate in 12 and severe in 4 of them. In 2 of 18 patients head injury precipitated idiopathic generalized epilepsies: childhood absence epilepsy in a boy of 7 years of age and idiopathic epilepsy with grand mal seizures on awakening in a boy of 10 years of age. Although symptomatic post-traumatic epilepsy developed in 5.7% (16 of 283) of children suffered closed TBI of

moderate or severe degree, this incidence appears to be rather high. The findings are indicative of long-term follow-up in cases of moderate or severe TBI with the necessity of repetitive EEG recordings.

One of the most well-known population studies on post-traumatic epilepsy risk factors conducted to date [47] included 4541 patients who were divided into four age groups: from birth to 4 years (n = 542), from 5 to 14 years (n = 1184), from 15 to 64 years (n = 2546), 65 years and older (n = 269). The total 5-year probability of developing epileptic seizures was 0.5% among patients with mild TBI (loss of consciousness or amnesia lasting less than 30 minutes and no skull fractures), 1.2% for those with moderate TBI (loss of consciousness for 30 minutes to 24 hours or a skull fracture), and 10% among patients with severe TBI (loss of consciousness or amnesia for more than 24 hours, brain contusion or subdural hematoma). Thirty years post-injury, the corresponding figures were 2.1% for mild TBI, 4.2% for moderate TBI, and 16.7% for severe TBI. Thus, the increased risk of seizures after TBI varies greatly according to the severity of the injury and the time since the injury. The probability of developing epilepsy after a mild TBI does not exceed the average population risk, but severe or moderate TBI with focal damage to the cerebral cortex leads to formation the substrate of post-traumatic epileptogenesis.

The complexity and polymorphism of clinical manifestations of post-traumatic epilepsy are determined by the variety of injuries in TBI, which include both focal and diffuse components, blunt closed head injuries with or without a skull fracture, contusions, hematomas, and penetrating injuries to the brain [48]. Mostly focal injuries are accompanied by contusion of the hemispheric surface structures and the involvement of various epileptogenic zones of the brain. The subcortical structures are affected by strong mechanical impact; the superficial focal injuries often damage the frontal and temporal lobes, which have high epileptogenic potential. Therefore, the epileptic syndromes that occur with these lesions will correspond to frontal or temporal lobe epilepsy. During the course of post-traumatic epilepsy seizures remain focal in about one quarter of patients, in half they become secondary generalized with a focal onset, and in another quarter they are manifested by generalized convulsions only (after a closed TBI with diffuse damage to the deep brain structures) [49].

Meanwhile, in recent years, the use of long-term video EEG monitoring allows to identify subclinical forms of seizures, as well as epileptic status in some patients with post-traumatic epilepsy [50].

5. Treatment of neurobehavioral consequences of pediatric traumatic brain injury

The long-term consequences of TBI are often more obvious in children because their longer life span and need for schooling make such deficits all the more apparent. The overall disability in children is often less than that in adults suffered TBI. However, in the majority of head-injured children neuropsychological studies have shown deficits in cognitive functions and learning skills ranging from subtle to obvious. Special supportive measures, including educational intervention, behavioral modification and medical treatment, are therefore important issues. Thus, the treatment of TBI cognitive and behavioral sequelae must be planned as multimodal.

The study of cognitive functioning and recovery 10 years after TBI in young children by Anderson et al. [51] confirmed the high risk of persisting functional deficits associated with severe early brain insult but demonstrated an "injury threshold" beneath which children may escape serious sequelae. In contrast to the "severity"-specific recovery observed in acute and subacute periods, findings

illustrate that recovery trajectories plateau from 5 to 10 years for all groups, regardless of injury severity. This result is important because it questions previous speculation that children with severe brain insults "grow into deficits" with time since injury. After a protracted recovery period, these children gradually stabilize and begin to make some developmental gains, suggesting that even many years post-injury, intervention may be effective [51].

Children with TBI represent a challenge to pediatric rehabilitation professionals as they may improve neurologically for months or years after the injury and may recover much of the knowledge and skills acquired before their injury despite substantial new problems of learning and behavioral self-regulation.

A child with a TBI is unique not only in comparison with peers of the same age, but also to other children with brain injuries. Each child's recovery process and outcomes are different and individual. Outcomes from pediatric TBI are rarely predictable and neither is the student's progress in school. Therefore, before the child returns to school, it is necessary for him, his parents, educators and rehabilitation professionals to develop an Individual Education Program (IEP). An IEP is essential for the successful academic progress of a child suffered TBI. An IEP is an educational plan outlining the special learning needs of a child, including:

a. The amount of special education or resources which needs to be provided

b. The educational and learning goals

c. The frequency of the interventions within and without the school (usually revised yearly)

Cognitive rehabilitation refers to the process of retraining individuals in the way they take in, store, and use information. Cognitive rehabilitation therapy is sometimes provided through hospitals or rehabilitation facilities immediately following acute hospitalization. When the student is reintegrated into school, it is necessary to continue some form of cognitive training. Cognitive rehabilitation and training help the student function within the environment. Although this treatment may initially be coordinated between an outpatient rehabilitative program and school, eventually it will become a school-based intervention program.

Cognitive training focuses on the foundation skills necessary for learning. The treatment goals are improvement in these skills as well as development of compensatory strategies. Skill development should be addressed both in individual and group settings where abilities such as social/verbal pragmatic competence can be addressed more suitably. Academics as well as functional life activities need to be included within the treatment to aid with generalization of identified skills.

The home environment and parenting style have long-term impacts on functional outcomes of children recovering from TBI. Interventions to promote more effective parenting may be useful for preventing or ameliorating morbidity following TBI [52].

The brain preserves a capacity to recover and adapt secondary compensatory mechanisms when neural tissue is compromised. This capability is due to neuroplasticity, a unique feature that makes the neural circuits malleable and is at the basis of memory formation and learning as well as in adapting to injuries and traumatic events throughout life [53–56].

Neuroplasticity is a process of biological adaptation based on brain structural and functional reorganization, aimed at restoring lost or impaired functions after brain damage [54, 55]. Neuroplasticity can be implemented at the molecular,

synaptic, neuronal or multiple levels. It is based on modulating the functioning of neurons, restoring synaptic transmission, and activating inter-neuronal connections. To varying degrees, activation of neuroplasticity is accompanied by stimulation of the expression of certain genes, biosynthesis of receptor and ion channel molecules, filamentous proteins of the synaptic cytoskeleton, neurotransmitter, synaptic membrane components, intercellular adhesion molecules, formation of immature contacts, their maturation, activation, hypertrophy, and reorganization of active synapses [54]. Reparative neuroplasticity provides restoration of functional systems of the brain after their damage and is implemented by the entire spectrum of increasing the efficiency of the synaptic pool, from activation of preserved synapses to neosynaptogenesis and growth of nerve processes-a phenomenon of synaptic sprouting [54, 55].

The goal of TBI treatment is to restore normal neuroplasticity. Important tasks of neuroprotection in patients with TBI are prevention of secondary damage processes, blocking of biochemical cascades that lead to the death of neuronal cells, as well as stimulation and maintenance of neuroregeneration and neurogenesis. The discovery of neurotrophic peptide factors served as a justification for peptidergic neurotrophic therapy of many brain diseases and the consequences of TBI in particular [55, 56]. The pharmacological potential of neuropeptides is linked with the treatment of cerebral diseases associated with secondary brain damage, including TBI. Specifically, in the area of "traumatic penumbra," neurotrophins may offer protection from a secondary injury by stimulating growth and differentiation and promoting recovery of injured brain neurons [53].

Novel therapeutic strategies for TBI should attempt to stimulate endogenous repair-regeneration mechanisms while antagonizing deleterious processes. Peptide extracts from animal brains have been used as the basis for several multicomponent organ-specific medicinal formulations which are currently use in the treatment of brain diseases, including TBI [55–58]. These formulations have one very important property in common: they contain hundreds of potentially active peptide components extracted from the brain. The complex peptide formulations from the brain are optimal for simultaneous actions on different targets in the brain maintaining optimal neuroplasticity, which can in turn be regarded as a global multicomponent target.

Cortexin is a complex of polypeptides and L—amino acids with a mass of 1 to 10 kDa. Mechanisms underlying the neuroprotective properties of cortexin as well as its numerous positive effects in cerebral diseases in clinical and experimental studies have been reported [56–62]. Experimental studies have shown that cortexin's neuroprotective and nootropic actions are based on its ability to reduce neuroapoptosis and mitochondrial dysfunction, which are complex pathological processes leading to persistent cognitive disorders [57, 58].

The neuroprotective and neuroregenerative properties of this peptidergic drug are based on the ability to influence the neurotrophins system and, indirectly, neuroplasticity, neurogenesis, and degenerative changes in neurons [58, 59]. The potential molecular mechanisms of cortexin's neuroprotective properties are diverse and relate to key processes underlying neuroplasticity: signal transduction, energy metabolism, protein proteolytic modification, brain cell structure, and neuroinflammation processes. Tissue specificity is important, as well as the multicomponent nature of the drug's action, which determines its potential beneficial effect on different targets in the brain simultaneously [56].

Since neuroinflammation is a significant factor in the pathogenesis of TBI consequences, the results of animal experiments that confirmed the anti-inflammatory effect of cortexin, which had both a systemic and tissue-specific character, are of particular interest [60]. At the CNS level, its action led to normalization of free

radical balance and prevention of excessive inflammatory processes, which is the basis for potential optimization of neuroplasticity.

Another study identified four brain proteins that interact with cortexin peptides [61]. The identified molecular partners of cortexin peptides are the cytoskeletal proteins actin and the brain-specific isoform of tubulin, the brain-specific adaptive protein 14-3-3 and creatine kinase—the first potential primary targets of the drug. All these proteins are involved in fundamentally important processes. The actin cytoskeleton is known to regulate important cellular processes in the brain, including division and proliferation, cell migration, cytokinesis, and differentiation. The neuron-specific protein tubulin β5, a component of the cytoskeleton microtubules, is critical for the emergence and maturation of neurons, their migration, differentiation, and integration into neural networks. Protein 14-3-3 (alpha/beta) is the important adaptive protein of the brain that interacts with a large number of proteins, determining their localization and function in the cell, and thereby affecting a variety of cellular and physiological processes. Regulating the activity of enzymes, protection from dephosphorylation of proteins, the formation of triple complexes and sequestration processes, protein 14-3-3 participates in pathogenesis and performs neuroprotective functions in neurodegenerative diseases and other neurological and mental disorders. If we assume that binding to cortexin peptides modulates the activity of creatine kinase type B, another molecular partner identified in this study, then the positive effect of the drug on the energy supply of brain tissue becomes clear [61].

Cortexin was demonstrated to be effective in the treatment of neurological, cognitive consequences of TBI and PTH in both pediatric and adult patients [56, 58]. Taking into account the risk of post-traumatic epilepsy in the long-term period of TBI, data on the dose-dependent antiepileptic activity of cortexin obtained in experiments in animals when modeling chronic convulsive activity (model of temporal epilepsy) are important [59, 62].

The potential multicomponent nature of cortexin, containing a multitude of different neuropeptides, may be favorable for simultaneous actions on multiple targets [58, 59]. The brain tissue specificity of these molecular mechanisms is important, as to a significant extent it determines the efficacy of the formulation in cerebral diseases, including consequences of TBI.

6. Conclusions

Childhood and adolescence are periods of rapid physical and psychological growth, endocrine adjustment, and, at the same time, high risk of injuries. TBI is the most common and potentially the most deleterious type of injury in pediatric population. The consequences of TBI in children and adolescents can be represented in cognitive, behavioral, and paroxysmal disorders. These disorders may have a long-term and significantly negative impact on the success of school education and social adaptation in pediatric patients. Meanwhile, high levels of neuroplasticity in children and adolescents may determine favorable outcomes of TBI.

Conflict of interest

The authors declare no conflict of interest.

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Author details

Nikolay Zavadenko*, Yuriy Nesterovskiy, Alexey Kholin and Irina Vorobyeva
Neurology, Neurosurgery and Medical Genetics Department Named After Academician L.O. Badalian, Faculty of Pediatrics, N.I. Pirogov Russian National Research Medical University, Moscow, Russian Federation

*Address all correspondence to: zavadenko@mail.ru

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