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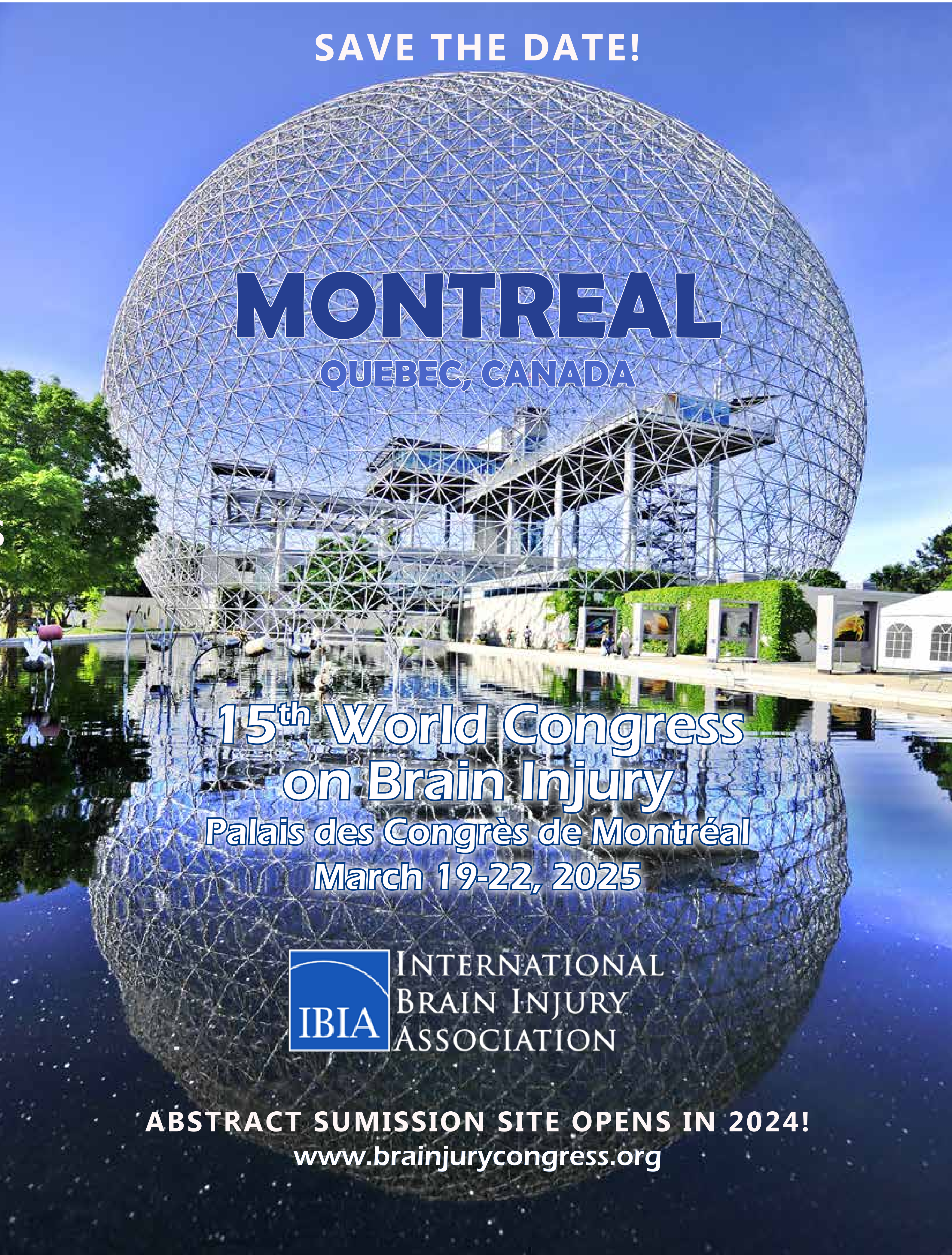
Advances in **Neurosurgical** Management of TBI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Dr. Juan Carlos Arango-Lasprilla

Editor Bio

Dr. Juan Carlos Arango-Lasprilla is currently an Ikerbasque Research Professor at BioCruces Vizcaya Health Research Institute affiliated with Cruces University Hospital in Bilbao, Spain. A neuropsychologist by training, his areas of expertise are neuropsychology, traumatic brain injury (TBI), and rehabilitation. Dr. Arango has received over 20 awards for his accomplishments in the area of brain injury and rehabilitation, including early career/emerging professional awards from the National Academy of Neuropsychology, the American Psychological Association's Division 22 Rehabilitation Psychology and Division 45 (Society for the Psychological Study of Ethnic Minority Issues), the International Brain Injury Association Young Investigator Award and Mid-Career awards such the Arthur Benton Mid-Career award from the International Neuropsychological Society and The Mitchell Rosenthal Mid-Career award From the American Congress of Rehabilitation Medicine. He has published more than 300 articles and book chapters and edited 10 books.

from the editor in chief

Every year, millions of people around the world suffer a traumatic brain injury. In those moderate or severe cases, the intervention of a neurosurgeon and having a unit specialized in neurotrauma is essential to save many lives, as well as for the future management of these patients and their subsequent quality of life. For this reason, it is with great pleasure that I introduce this issue of Brain Professional focused on Advances in Neurosurgical Management of TBI.

In this issue, we have the privilege of having authors with recognized international experience who address topics of great relevance in this field today. In the first article titled, "Pediatric Traumatic Brain Injury: A Global Perspective," the authors discuss the epidemiology of TBI in children, the differences between adult and pediatric populations, and the recent evidence-based guidelines in this area. The second article is titled "Non-Invasive Monitoring in Traumatic Brain Injury: New Insights and Future Trends." In this article, the authors provide an overview of the current and most frequently used modalities for Non-invasive Neuromonitoring- Transcranial Doppler (TCD), Optic Nerve Sheath Diameter (ONSD) by Ultrasound, Automated Pupillometry, Near Infrared Spectroscopy among others - in TBI. Their importance in helping to achieve a more precise diagnosis and improved management of TBI patients across the whole spectrum of severity is detailed. The third article, "The Intracranial Compartment Syndrome: A New Approach for Diagnosis and Treatment of Traumatic Brain Injury", offers an overview of the definition of the term Intra-Cranial Compartment Syndrome (ICCS) and a new approach for the diagnosis and its treatment. The fourth article is titled "The Role of Neurorehabilitation in Neurotrauma: A Global Perspective." The article highlights the global burden of neurotrauma, the importance of neurorehabilitation, and the challenges facing global neurorehabilitation. The last article, "Posttraumatic Epilepsy and TBI Biomarkers: New Insights", defines posttraumatic epilepsy and explains the link between trauma and epilepsy.

This issue includes two interviews with two worldwide renowned leaders in the area of neurotrauma. In the first interview, Gregory Hawryluk, MD, PhD. Director of the Brain Trauma Foundation, USA, describes his career in neurotrauma and how he became involved with the Brain Trauma Foundation projects. Also, he highlights his new position at the BTF and his forthcoming projects, such as the development of new guidelines, including prehospital TBI guidelines, penetrating TBI guidelines, and military TBI guidelines, among others.

In the second interview, Kee Park, MD., MPH, Leader of the Global Neurosurgery Team within the Program in Global Surgery and Social Change at Harvard Medical School, details how he became a leader in this field as part of his neurosurgery career, how important neurotrauma is in the global neurosurgery field, and how we can improve neurotrauma care systems. Finally, he emphasizes the need for international organization to work on advocacy and work together with government institutions around the world. We hope that you enjoy reading these articles and interviews and that you find them useful to increase your knowledge and clinical work.

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Andrés M. Rubiano,
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Editor Bio

Andrés M. Rubiano, MD, PhD, FACS, IFAANS, is the Chief of Neurological Surgery at Vallesalud Clinical Network in Cali, Colombia. He is also a Professor of Neurosciences and Neurosurgery at Universidad El Bosque in Bogota, Colombia, and a Professor of Neurosurgery at Universidad del Valle in Cali, Colombia. He is the Chair of the International Committee of the Neurotrauma and Critical Care Joint Section of the American Association of Neurological Surgeons and the Congress of Neurological Surgeons in the USA. He has been also appointed as Co-Chair of the Neurotraumatology Committee of the World Federation of Neurosurgical Societies (WFNS).

from the guest editor

Traumatic brain injury (TBI) is a critical condition and a public health problem worldwide. The burden of the disease affects the economically active population mostly in less developed areas like Latin America, Southeast Asia, and Africa. Conditions associated with less road safety infrastructure, less road safety literacy, and higher levels of social violence have been attributed to the higher levels of brain injury[1]. Traditionally, living in rural areas either in developed countries or in less developed countries has been associated as a risk factor for poor prognosis, especially because of prolonged transportation times, less infrastructure in prehospital services and post-operative advanced care[2]. Task shifting and task sharing in TBI care have been proposed as an alternative for having timely access to basic trauma surgery, based on military and rural surgeons' experiences in war theaters or in remote rural locations like some Australian towns[3]. A common aspect that affects transversally the outcomes, independent of the region of the world seems to be how to select in a timely fashion, patients who require aggressive medical or surgical therapy, especially in the first 4 to 6 hours[4]. This selection process cannot rely only on clinical factors like the Glasgow Coma Scale or the pupillary or motor response as has been traditional.

In our actual time moment, where precision and personalized medicine strategies learned from other types of health conditions, show us a more comprehensive and effective way of selecting these patients. Specific neuroimaging features (requiring new classifications), and biomarkers evaluation need to be attached to this selection process to really understand the specific damage load on every patient that has a unique response to the primary injury[5].

In this issue, we have invited a series of experts in TBI care, from different regions of the world who are involved in different activities supporting the development of protocols, guidelines, and translational strategies related to the acute care of TBI patients. Dr. Andrew Reisner, his team, and Dr. David Adelson present their extensive experience in the management of pediatric TBI care with a global perspective. Dr. Lina Becerra and Dr. Efrain Buritica, leaders of neuroscience training programs, discuss some of her lab findings in posttraumatic epilepsy research and how new insights into biomarkers are opening doors for translation into new therapies. Dr. Chiara Robba, a renowned expert in Neurosonology, and Dr. Sebastian Vásquez, a Neurotrauma and Neurocritical Care trainee analyze the different recent modalities for monitoring neurotrauma patients with non-invasive portable devices, a trend that is creating new options for protocol development in less-resourced areas of the world. Professor Virendra Sinha, a prominent leader in the treatment and rehabilitation process of TBI patients in India, in conjunction with his colleague, Dr. Jitin Bajaj shows a perspective for teamwork to improve results in these patients. I also will be presenting in conjunction with Dr. Daniel Godoy, a renowned neurocritical care expert from Latin America some of our recent work-related to the new concept of the intracranial compartment syndrome, proposing it as a new strategy for selecting urgent patients who will require emergency surgery.

Finally, but not less importantly we have key figures sharing their insights with the readers of brain injury professional, including Dr. Greg Hawryluk, Medical Director of the Brain Trauma Foundation, and Dr. Kee Park, promoter and developer of a new concept named Global Neurosurgery, that looks for the global care improvement over neurosurgical conditions like neurotrauma, and other prevalent neurosurgical emergencies.

I hope this issue will be of interest to the general audience motivated to improve the care of brain-injured patients worldwide.

Best regards and enjoy the content!
Andrés M. Rubiano MD, PhD (c), FACS, IFAANS

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Pediatric Traumatic Brain Injury: A Global Perspective

Andrew Reisner, MD [1,2,3,4] • Joshua J Chern, MD, PhD [2,3,4] • Sarah H Newman, MD [2,4]
Laura S. Blackwell PhD [3,4] • Olubunmi A. Fariyike, BS [6,7,8] • Youssef M. Zohdy [2]
Jacob R. Lepard, MD [2,3,4] • P. David Adelson, MD [5]

Introduction

Worldwide, traumatic brain injury (TBI) is a major health problem resulting in approximately 70 million deaths per year. However, this alarming statistic alone does not reflect the full extent of this disease. The morbidity among TBI survivors is wide-ranging and exerts a tremendous burden on public health services in all countries. In a recent Lancet Neurology Commission, it was noted that not only did TBI have the highest global incidence among the most common neurological conditions including stroke, Alzheimer's disease, Parkinson's disease and multiple sclerosis, but it also had the highest prevalence, a reflection of the massive disease burden conceived by the tens of millions of survivors (Mass et al., 2022). TBI is both an acute condition and a chronic condition. As an acute condition, immediate assessment and timely interventions are key steps that affect mortality, degree of recovery and long-term quality of life. Follow up care and rehabilitation are necessary to ensure the best possible outcome. Late onset neurodegeneration may occur, which would go undiagnosed and untreated without consideration of TBI chronicity. Traditionally and by necessity, neurosurgeons have focused more attention and research on those patients that sustain a TBI on the severe end of the spectrum (Glasgow Coma Score, (GCS), ≤ 8). These patients are more likely to require operative intervention. However, it is becoming increasingly apparent that patients with moderate (GCS – 9-12) and mild TBI (mTBI) (GCS 13 – 15) also suffer acute and long-term disabilities. These groups represent a substantial portion of the burden of TBI.

Although no age group is immune from TBI, the extremes of age are most vulnerable. The highest frequency of hospital admissions occurs among the elderly (age > 65 years) closely followed by the pediatric age group (< 21 years) (Hanalioglu et al., 2023). Although children and adolescents have an overall lower mortality than adults (approximately 5% of all TBI related deaths), the true burden of the disease in the young is significantly more substantial when measured in terms of years of lost life and years lived with disability (Majdan et al., 2016). Additionally, pediatric TBI has widespread consequences that not only affect the child, but also the family, community, overall healthcare system, as well as the health of future generations. Pediatric TBI is complex. This review is not meant to be a comprehensive summary of TBI related pathophysiology, rather, is an overview of pediatric TBI globally to describe the epidemiology of TBI in children, the differences between adult and pediatric populations, and provide an update on recent evidence-based guidelines.

Epidemiology of Pediatric TBI Globally

Although much about pediatric TBI remains unknown, three facts remain uncontested. First, TBI is the leading cause of death and disability in childhood (Dewan et al., 2016). Second, the burden of TBI to the public health system in every country is substantial. Third, data related to pediatric TBI is inadequate and incomplete especially in low and middle-income countries (LMIC).

It is estimated that 3 million children worldwide sustain a TBI annually. Globally, motor vehicle collisions (MVC) and falls cause the majority of TBIs in children and across countries, male children were disproportionally affected by TBI as compared to females. Regarding age, a bimodal distribution is apparent; the highest injury occurrence in very young children (<3 years) and older children (<15 years) (Dewan et al., 2016). Despite having global information on the disease, challenges and disparities exist globally, and individual countries have unique cultural, economic, political, and educational needs that affect the management, care delivery and data gathering of pediatric TBI patients. This makes it problematic to quantify the true enormity of TBI burden globally and these differences confound attempts to develop and deliver singular best practice guidelines worldwide.

It is noteworthy that almost 90% of TBI related deaths occur in LMICs where inadequate resources such as lack or insufficient pre-hospital emergency care and then post-acute intensive care contribute to less optimal care and outcomes. A patient suffering from a severe TBI in a LMIC has a two-fold higher mortality rate compared to a similar patients in high-income countries (HIC). Similarly, studies done in the United States (U.S.) and United Kingdom (U.K.), show a higher incidence of TBI in children from lower socioeconomic background compared to children from a higher socioeconomic background.

Unique regional and political circumstances also influence the epidemiology of TBI globally. For example, the number of gun-related deaths among children and adolescents in the U.S. rose almost 40% over the last two decades, especially since the onset of the COVID-19 pandemic. In areas of the world where armed violence is high, the Middle East and Central Africa for example, collateral gunshot injury is also notable as a cause of TBI.

While over 90% of TBI patients present to the emergency department with mTBI, just under 10% are estimated to have a severe insult. Annually, in the United States, over 1 million children and adolescents have mTBI. Despite a diagnosis of "mild TBI", these children are at high risk for repetitive concussions, prolonged cognitive deficits, psychiatric disturbances and inflicting self-harm (van Ierssel et al., 2021; Ledoux et al., 2022). Although sufficient data are lacking, it is strongly suspected that children in LMICs suffer similar post-TBI afflictions.

Unique Features of Pediatric TBI: Clinical Perspective

Despite the high incidence and long-term consequences of pediatric TBI, research in this population is lacking while adult populations have been the focus of most research efforts. Given the differences in physiology and pathophysiology between children and adults and the differences in sequelae following TBI, not all research inferences identified in adult TBI patients can be directly applied to children. The adage that children are not "small adults" holds true in the management of pediatric TBI.

While there are anatomic, biomechanical, physiologic, and pathologic differences between adults and children, there are also differences reflective of the stage of post-natal neurodevelopment, especially in the first 2 years of life. At birth, the brain weight is approximately 300 grams. There is a rapid increase in brain volume during the first 2 years of life such that the brain weighs approximately 1100 grams by the time the infant reaches 2 years. This massive growth reflects ongoing myelination, neuronal pruning, synapse formation and biochemical changes, which ultimately result in a normal adult brain. It is during this period of "plasticity" that neuro-regeneration is most likely to occur. Although the mechanism is unknown, clinicians have observed that infants with significant brain injuries may make unexpectedly good recoveries, presumably as new pathways develop in the non-injured area. Additionally, children sustain unique causes of TBI. Two examples are discussed here:

1. **Birth injuries:** Traumatic head injury may occur during birth due to various mechanical forces throughout labor and delivery, especially when specialized obstetrical care is unavailable. Most trauma to the fetal head is associated with a difficult delivery from abnormal presentation, cephalopelvic disproportion or operative delivery by forceps or vacuum extraction. The fetal head is vulnerable to injury during the birth process since in most deliveries, the cranium enters the birth canal first. Scalp injuries, which account for 80% of birth head trauma, include caput succedaneum, cephalohematoma, and subgaleal hematomas. Roughly, 46% of birth related skull fractures are associated with vacuum-assisted vaginal delivery. Refinement in obstetrical techniques and reduced use of delivery forceps have resulted in a decline in birth head trauma in HICs (Dumpa and Kamity, 2022).
2. **Abusive Head trauma (AHT):** AHT is uniquely disturbing. It crosses geographic, cultural, racial and social divides. While the constellation of injuries associated with AHT has been described in the literature for nearly 80 years, the American Academy of Pediatrics defines AHT as a constellation of cerebral, spinal and cranial injuries that result from inflicted head injury to infants and young children. AHT usually occurs in children less than five years of age and results from inflicted blunt impact and/or violent shaking resulting in an unique pathologic finding and excludes unintentional injuries resulting from neglectful supervision or penetrating trauma (i.e.) gunshot or stab wounds. Other terms such as inflicted traumatic brain injury, non-accidental trauma and most controversially, shaken baby syndrome have been used. AHT has become the preferred term as it encompasses the potential multiple biomechanical modes of injury and is unique in that it implies criminal intent.

The incidence of AHT in HICs is estimated to be between 13 and 40.5 per 100,000 in children < 1 year of age. In these infants that present with severe TBI (GCS < 9), mortality is approximately 25% in HIC. The incidence and mortality rates of AHT in LMICs are largely unknown, with relatively few reported cases in the literature. It is suspected though that the true incidence of AHT in LMICs is similar to that of HICs. It is not known if the discrepancies of reported incidences are due to failure to recognize AHT, inadequate data collection, barriers to reporting cases in different countries or differing cultural norms that preclude the acceptance of AHT as a distinct entity. Like child maltreatment more broadly, estimates of AHT are challenging due to data collection, legal implications, failure to seek treatment, lack of a definitive diagnostic marker and various methodologies to define and code AHT.

Unique Features of Pediatric TBI: Anatomic, Physiologic, and Pathologic Perspective

There is a wide range of anatomic, physiological and pathophysiological values across the age spectrum in children. This is critical for both neurosurgical and critical care management of post-traumatic intracranial hypertension and cerebral edema. A diffuse brain injury generally is more common in children than in adults, while focal bleeds, both intra-axial and extra-axial, are less common. These anatomical differences affect the pressure-volume curves as well as the metabolic response to injury, cerebral autoregulation and hemodynamics in children as compared to adults. Understanding that any (and multiple) areas of the scalp, skull, and brain can be affected in a child with a TBI, for descriptive purposes, we describe these individually and from superficial to deep:

- Bleeding from a scalp injury can be particularly dangerous in a young infant given the relatively low blood volume. This is especially deleterious in infants who typically have a high percentage of hemoglobin F with an attendant decreased oxygen carrying capacity.
- The skull of a newborn is relatively malleable and prone to deformation and fracture, but generally heals well. Unique to children, however, is a growing skull fracture, whereby a leptomeningeal outpouching insinuates itself in the fracture line not allowing adequate skull union.
- The skull matures and the sutures fuse in an organized fashion, typically with all sutures fused by 5 years of age. Prior to skull maturity and complete synostosis, the skull can expand at the fibrous bony unions and fontanelles, which allow partial dissipation of raised intracranial pressure (ICP).
- Generally, children have an exaggerated cerebrovascular response to TBI resulting in significant brain swelling. During infancy, the presence of an open anterior fontanelle and generous subarachnoid space does render a protective effect against ICP.
- Extra-axial hematomas include subdural and epidural hematomas. The epidural hematoma in a child can be both venous and arterial. Not infrequently, a venous injury can result in a slow bleed and consequent expansion of the epidural hematoma causing clinically significant mass effect days after the injury. Subdural hematomas are more common than epidural hematomas in cases of AHT. They are often associated with brain parenchymal contusions, swelling and injury.
- Intracranial vasculature is more pliable and elastic in children than adults. Children tend to be more prone to the rare but devastating post-traumatic aneurysm, a known complication of TBI, post-traumatic aneurysms. Post-traumatic aneurysms require treatment despite the associated risks of surgery and/or endovascular treatments as the natural history has a mortality approaching 50%.
- Upper cervical spine injuries are more common in younger children than adults. This is due to the traumatic vectors created by the relatively large cranium, focusing on the upper cervical spine, specifically C1 and C2. This level is especially vulnerable to fracture dislocations given the biomechanical factors of poor muscle support and more vertical orientation of craniocervical facet joints. Atlanto-occipital dislocation is particularly difficult to diagnose as often the subtle osseous disruptions are difficult to appreciate on initial radiographs. Note, there is a sentinel sign that an upper cervical spine injury is a posterior fossa hemorrhage, including cerebellar contusions and/or subarachnoid hemorrhage.

Unique Features of Pediatric TBI: Surgical Perspective

The technical aspects of operative management in the pediatric population are also different compared to adults. Anesthetic control, blood loss management and tissue handling are vital. Thinness of the skull during infancy requires a differential approach for craniotomy flap fixation, suture vs. permanent plating. The consistency of an infant's brain, prior to myelination, is such that it more resembles mucous requiring meticulous attention to anatomy intraoperatively.

Clinical Classification of TBI in Children

- As with adult populations, the spectrum of pediatric TBI are classified as mild, moderate or severe based on the GCS, a 15-point scoring system, used internationally based on the patient's response to eye opening, motor response and verbal response. A pediatric GCS is a modified version for children, but this has not been widely accepted. Despite widespread use of GCS, including inclusion in the NINDS TBI Common Data Elements, there are limitations with its use. Administration and scoring of the GCS is not standardized and its psychometric strength is moderate. Further, GCS is generally unreliable in very young TBI patients (<3 years), particularly the verbal domain. While arguably less relevant in pediatric patients, intoxicating substances, including common acute analgesic medications, has also been found to confound GCS scoring. GCS is also symptom-based and has poor correlation with specific intracranial pathology.

Severe TBI

The mainstay of contemporary clinical and surgical management of severe TBI is to reduce intracranial hypertension and ameliorate secondary injury to the brain. Although severe pediatric TBI guidelines have been developed with the original now 20 years old, level 1 evidence-based data is still unfortunately lacking. The most recent guidelines for the management of severe TBI in children were published in 2019 by the Brain Trauma Foundation only include 22 recommendations. There were no Level I recommendations, 3 Level II recommendations and 19 Level III recommendations. This points to the dearth of high levels of evidence-based studies related to the fundamentals of pediatric TBI management (Kochanek et al., 2019). As a result, proposed management of severe TBI in children is complex and resource-intensive with significant variability in its application and is difficult if not impossible to implement in lower-resourced settings. Resource-based stratified guidelines have been instituted in LMICs to better tailor severe TBI guidelines in adult populations based on available manpower and equipment (Griswold et al., 2022) but there are no pediatric-specific, resource-based guidelines for LMICs to date.

Mild TBI

Over 90% of all pediatric TBI fall into the "mild" TBI (mTBI) or "concussion" category, defined as GCS of 13 to 15. Although the term mTBI is used universally, it is a misnomer. It is becoming increasingly apparent that long-term consequences, especially after repetitive injuries, can be significant in some individuals.

Genetic as well as epigenetic factors that lead to this predisposition are not known.

The definition of concussion varies among experts. A 2017 multinational consensus meeting held in Berlin set guidelines for sports related concussion (SRC) and agreed upon a now widely used definition: “TBI induced by biomechanical forces”. Several common features that may be utilized in clinically defining the nature of a concussive head injury include: 1) a direct blow to the head, face, neck or elsewhere on the body with an impulsive force transmitted to the head, 2) a rapid onset of short-lived impairment of neurological function that resolves spontaneously, 3) neuropathological changes may occur, but the acute clinical signs and symptoms largely reflect a functional disturbance rather than a structural injury and, as such, no abnormality is seen on standard structural neuroimaging studies, and 4) a range of clinical signs and symptoms that may or may not involve loss of consciousness. Resolution of the clinical and cognitive features typically follows a sequential course.

Concussions in children can perplex clinicians. Often the diagnosis is elusory, as perceptible bedside signs are usually absent. The range of signs and symptoms with concussion, SRC and non-SRC, is broad, and standard radiographs and CT scans are usually normal. The Standardized Assessment of Concussion test identifies post-concussion deficits through cognitive screening based on orientation, concentration, memory and recall (SAC Form). With sports related injuries, sideline rapid assessment is valuable for initial treatment interventions followed by serial assessments to identify a progression of worsening symptoms. This can be challenging in the midst of competition, with an injured athlete is eager to keep going.

Annually, in the U.S., between one and two million children suffer mTBI. This is probably an underestimation as half of mTBIs go unreported, increasing the risk of untreated acute symptoms and the long-term sequelae related to the lack of immediate care and follow-up (Schmidt et al., 2023). As with severe TBI, data regarding the incidence of mTBI in LMICs is lacking. While concussion risk is higher and is associated with longer recovery times in female athletes compared with male athletes, the basis for these gender differences are unknown but are being actively investigated.

Preventative Measures and Programs

The best treatment for TBI is prevention of the injury. Targeted preventive measures could substantially lower the incidence and impact of TBI in children worldwide. Indeed, following institution of prevention practices, notably in motor vehicle safety resulted in a reduction in injuries (Thurman, 2016). The efficacy of TBI preventative programs also depends on cultural, geographic, economic and societal factors. Given that MVCs and falls cause the majority of severe TBIs in children, these have been the focus of preventative programs, to include improvements in road safety, personal restraints, and design of motor vehicles. Evidence supports the effectiveness of seatbelts and child car seats; therefore, promotion of proper use and effective education for parents and caregivers should be a priority. Child safety advocacy built into public policy and tailored to meet the needs of individual countries is vital for a broad, global reach.

The causes of mild and moderate TBIs in younger children are mostly falls followed by sports injuries in older children. Children ages 0-4 years are especially vulnerable to falls.

Prevention starts with pediatrician-to-parent/caregiver counseling to raise awareness around creating a safe environment for the child, which includes supervision. In an analysis of the clinicoepidemiologic profile of pediatric TBI in India (Cohort of 4833 children < 16 years of age), the most common mode of injury, 59%, was accidental falls (Madaan et al, 2020). with the most serious being balcony falls.

This prompted a preventative (# Safe Balcony Safe Child) campaign that included 5 simple measures (Increase balustrade height, netting between gaps, balcony furniture away from railings, minimize balcony play and encourage adult supervision), were taught to families resulting in a reduction of falls.

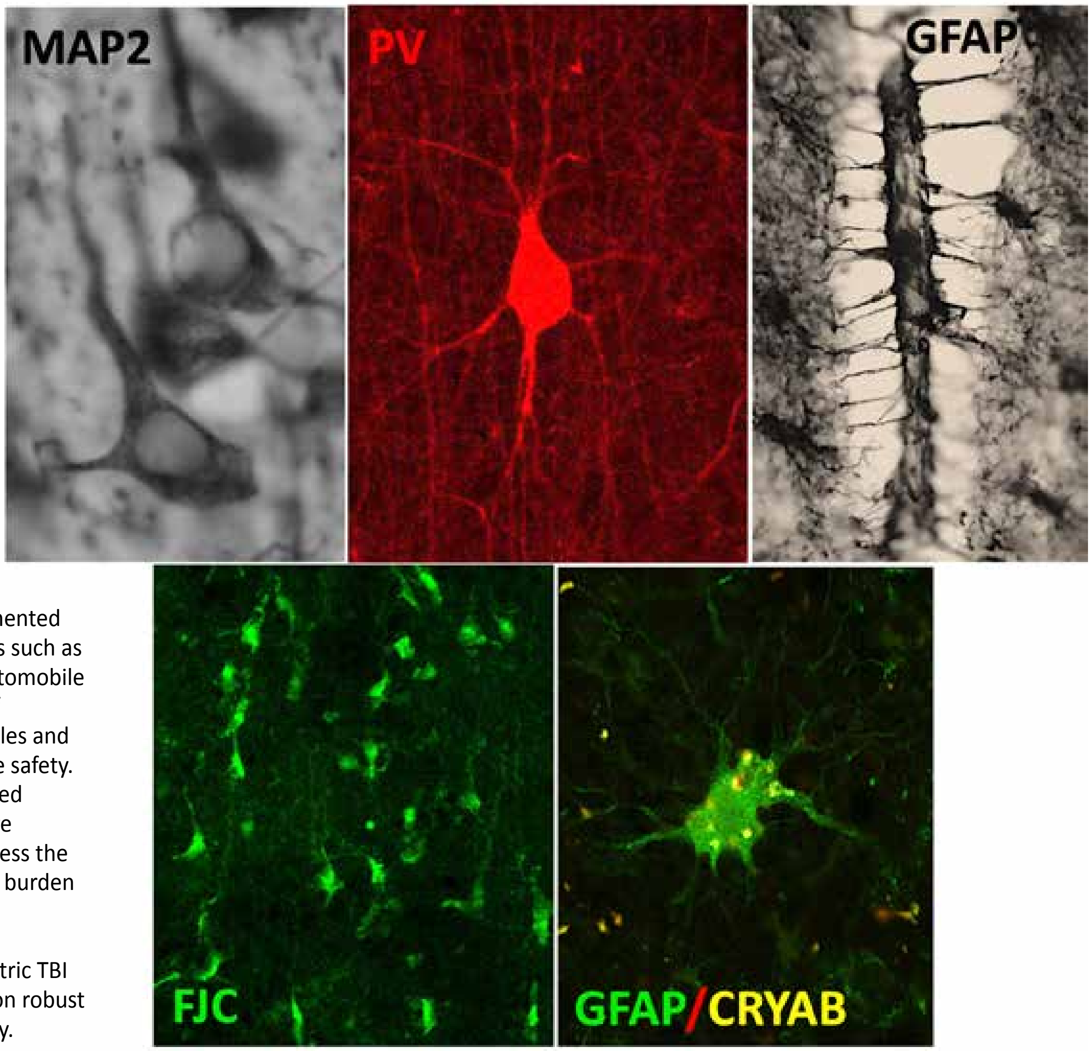
Strategies for contact sports injury prevention include the use of personal protective equipment such as helmets, which have improved over the years to provide optimal head and neck protection. In sports where tackling, body impact/collisions and restraining an opponent are expected, game rules now focus on safe play, disallowing aggressive physical impact and head/helmet contact (Berlin Concussion Guidelines).
Worldwide, governments have adopted an array of methodologies to regulate access to firearms, with the aim to reduce gun-related harm (Santaella-Tenorio, et al., 2016). The World Health organization considers child physical abuse, including AHT, a universal priority and has developed preventative programs globally. The outcomes of these efforts are mixed thus far.

Conclusion

TBI is a leading cause of mortality in children worldwide and the morbidity among survivors place a substantive burden on health care systems in every country. Challenges in diagnosis, treatment modality variations, reporting and data collection exist globally. Unique cultural, economic, political, and educational needs that affect the management, care delivery and data gathering of pediatric TBI confound these challenges. These inequities frustrate attempts to develop and deliver singular best practice guidelines worldwide.

Targeted preventative measures by individuals, institutions and professional organizations have addressed the issue of TBI in children. Further, with advocacy, some governments have implemented head injury prevention programs such as firearm regulation, improved automobile laws including mandatory use of seatbelts and improved game rules and protective equipment for athlete safety. However efficacious these focused programs may be locally, they are regional and inadequate to address the full extent of TBI related disease burden worldwide.

Improved management of pediatric TBI in tomorrow's victims depends on robust clinical and bench research today.



More research in TBI is needed, specifically in the pediatric population given the unique pathophysiology of TBI in children, challenges related to the different ontogenetic stages of brain development and the immense epidemiologic significance of TBI worldwide (Rostami et al., 2021).

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Non-invasive Neuromonitoring in Traumatic Brain Injury: Current Insights and Future Trends

Sebastián Vásquez-García[1-3]
Chiara Robba[4]

Introduction

Traumatic brain injury (TBI) represents a critical public health burden, with almost 50 million–60 million people having a TBI each year, and costing the global economy around US$400 billion annually[1]. The management of TBI patients is based on the prevention of secondary brain damage, and therefore a subsequent cascade of events following primary injury[2]. This necessitates a profound understanding of physiological derangements that take place across TBI severity spectrum, is influenced by the type of injuries (e.g cerebral edema, hematomas, contusions),and is associated extracranial injuries, patients comorbidities, among others. As such, multimodal neuromonitoring (MMN) is now a recommended practice parameter in order to understand physiological changes occurring after TBI[2,3], and research efforts are directed toward the development of management protocols based on individualized precision medicine. Despite invasive methods are considered the gold standard in TBI patients, noninvasive MMN (NI-MMN) offers the advantage of being widely available, particularly in low resource settings, is safe, and can be used when invasive tools are contraindicated (e.g coagulopathy)[4]. Here, we provide an overview of the current and most frequently used modalities for NI-MMN in TBI, with some considerations about the near future in this field (figure 1).

Transcranial Doppler (TCD): More Than a Noisy Signal

Transcranial Doppler was first introduced in 1982 by Aaslid et al. to record flow velocity in the basal cerebral arteries[5]. Implementation of transcranial color-coded duplex sonography allows the assessment of brain anatomy, real-time monitoring of essential (flow velocity (FV) and pulsatility index (PI))[6], as well as "advanced" TCD-derived parameters such as cerebral autoregulation[7].

Applications of TCD in TBI include the assessment of increased intracranial pressure (ICP)/intracranial hypertension (IH) assessment, which has been suggested using different methods: PI >1.3, diastolic FV (FVd) <20 cm/s, and a formula-derived from flow velocities for ICP estimation[7, 8], which showed a high negative predictive value (NPV) in ruling out intracranial hypertension, even in patients in whom craniotomy was carried out[8]. Most importantly, the trends rather than the absolute values of these metrics are of greater importance for therapeutic decision-making processes in such patients.

Other potential applications of TCD in TBI are vasospasm screening (evaluated through increased FV and a Lindegaard ratio >3)[6,9], carbon dioxide vasoreactivity monitoring[4,11], static cerebral autoregulation (CA) assessment using the transient hyperemic response test[10], and dynamic CA using different indices[11], that consider a surrogate of cerebral blood flow (TCD measured FV) and their correlation with mean arterial pressure[11,12].

Optic Nerve Sheath Diameter (ONSD) by Ultrasound: Eyes are Still Windows into the Brain

The optic nerve is surrounded by the meningeal space, where cerebrospinal fluid (CSF) is contained. Therefore, when the pressure in the CSF increases, this causes an enlargement of the elastic membrane which surrounds the optic nerve. On this basis, ONSD has emerged as a useful tool in NI-MMN in TBI patients. In fact, Ultrasound based ONSD assessment may be considered, when technically-appropriate done, a reliable method for detecting high ICP[13,14].

To date, many cutoffs for ONSD-estimated high ICP have been proposed[13,15, 17]; however, there is still no widely defined value for that purpose.

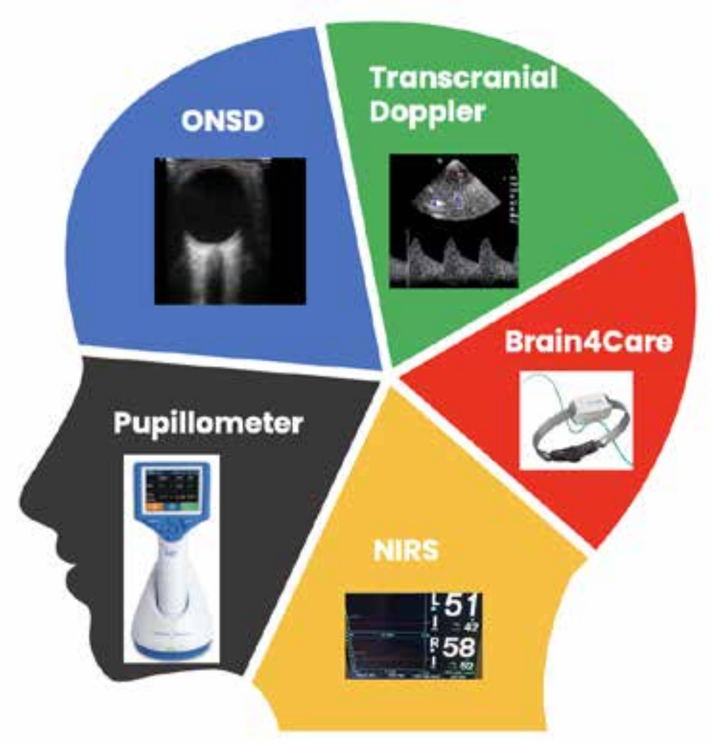

Figure 1. Most frequently used modalities for NI-MMN in TBI.

According to the available evidence[14], and from information analyzed by authors' own work, an ONSD value >5.8 mm (either as a mean value or in a single eye) can be suggestive of high ICP in the appropriate settings, again, with more importance given to trends rather than absolute values. Finally, although there are some interesting protocols for ONSD measurement related to technique[16,17], training in ONSD measurement and standardization of cutoffs is an urgent need for the proper management of TBI patients worldwide[19].

Automated Pupillometry (AP): Is it ready for forecasting in TBI?

The pupillary response involves different processes that lead to a qualitatively visible result: the change in pupil size, mediated by two pathways that are coupled; constriction due to parasympathetic activation and dilatation due to sympathetic activation, both influenced by different physiological stimuli.[18,19] For this reason, the use of a tool that allows an objective evaluation of pathological pupillary changes is of utmost importance, given the challenge represented by the subjectivity of the results of the neurological examination from the naked-human eye perspective.[19]

The pupillometer is a tool that assesses dynamic variables of the pupillary response for each eye, such as maximum and minimum pupil size, maximum constriction velocity, dilation velocity, percentage of constriction and latency, as well as the neurological pupillary index (NPi) which is a proprietary variable that uses an algorithm that brings together all the aforementioned variables, comparing them with a mean derived from results in healthy individuals, and whose normal value is >3, and with a value <3 or a difference >0.7 between each eye indicative of abnormal pupillary responses.[21,23] The role of NPi in TBI stands out in the detection of ICP changes, with an inversely proportional relationship, and it is the most reliable variable in pupillometry for this purpose. By monitoring the trend of the results, it allows the prediction of ICP increments, even before other non-invasive methods, and a serial cumulative abnormal-NPi is a predictor of poor prognosis in TBI patients according to the recently published ORANGE trial.[24,25,26,27]

Near Infrared Spectroscopy (NIRS): Let's Track Hemoglobin

By applying Beer-Lambert law, which states that the concentration of the substance and the path length is directly proportional to the absorbance of the light, NIRS has been used since 1970's to measure oxyhemoglobin[28], being one of the most easily available tools for regional brain oxygenation monitoring. Indeed, there appears to be a close relationship between regional hypoxia (regional O2 saturation (rSO2) <60%)) during the initial stages of TBI and in-hospital mortality and functional outcome[29]. NIRS values are also correlated with partial pressure brain tissue oxygen (PtiO2) values, and low rSO2 values have been demonstrated during increases in ICP[29], reflecting a disturbed brain oxygenation secondary to intracranial hypertension. However, NIRS has also important disadvantages, such as extracranial noise[30], patient's skin-device poor adherence due to sweating or movement, and the focal nature of measurements, which limits the assessment of a globally or more widely spread dysoxic insult.

Finally, NIRS can be used as a triage tool in TBI patients[31], when intracranial bleeding (e.g epidural or subdural hematomas) is suspected32, by identifying higher light absorbance in the affected side due to higher hemoglobin concentrations, and with the ability to detect a hematoma volume of 3.5 ml, with up to 3.5 cm of depth from the scalp, with a negative predictive value reaches 93.9% when evaluated under this conditions[33].

Brain4Care®: Do skull pulsations really exist?

Sergio Mascarenhas, a brazilian professor of physics, underwent a ventriculo-peritoneal shunt procedure for normal pressure hydrocephalus (NPH) in 2006, when he realized that more efforts in the diagnosis of NPH were needed[34]. Since then, and with the work of one of his mentees, Gustavo Frigieri, they progressively demonstrated the presence of skull microexpansions related to ICP changes[35], which were transmitted to the cranial vault, with subsequent acquisition of ICP waveform (ICPW)[34,35] by a thiara-like device, named Brain4Care®[34].

Although a deep explanation about ICPW is out of the scope of this paper, it is crucial to recall that P2 component results from changes in compliance of the cerebrovascular bed (as changes in cerebral blood volume (CBV))[36]. With increasing CBV, P2 is increased in comparison with short extension of P1, given that the latter is correlated with pulse amplitude of systolic pressure[37]. Based on these principles, a P2>P1 pattern is suggestive of a loss of intracranial compliance (ICC) (from the "arterial side"), and thus, P2:P1 ratio, and time-to-peak (TTP), are the analyzed components by the Brain4Care® technology, with P2:P1=1 being a sort of "warning" of risk of ICC loss; and P2:P1= >1 suggesting "in progress" or actual loss of ICC[35]. Even though the evidence in this field has been increasing over the past years, more studies are needed for considering this promising tool as standard of care for NI-MMN in the TBI population.

Is there a role for simultaneous multiparameter monitoring using NI-MMN methods?

The management of TBI is highly complex, and information extracted from simultaneously-monitored physiological variables that are correlated with each other at the same time, may reflect an interplay of the different phenomena affecting patient's clinical condition, which may translate into better management and precision medicine approaches[38].

Different comprehensive softwares, like ICM+® (Cambridge Enterprise, Cambridge, UK), collect different digital signals and translate them in clinically relevant data obtained in real time at the bedside, allowing the integration of multiple signals and the acquisition of complex information that can drive changes in therapeutic strategies[39], or give information about patient's outcome[38,39]. Some NI-MMN modalities have been analyzed using these softwares, particularly TCD[40-43], and, although NIRS signals have been included in those analysis44,45, it would be very interesting to see in the near future the inclusion of Brain4Care® derived-signals in softwares like ICM+®, and see how well they behave in comparison with invasive ICP-derived signals.

Conclusions

NI-MMN in TBI follows the common premise of "the more you look, the more you find". The proper use of each modality, oriented-toward a physiological-based interpretation, and advantages of their noninvasive nature, will allow a more precise diagnosis and management of TBI patients across the whole spectrum of severity. Inclusion of novel NI-MMN modalities into actual multiparameter-analysis systems may be considered as revolutionary and practice-changing strategies in the near future.

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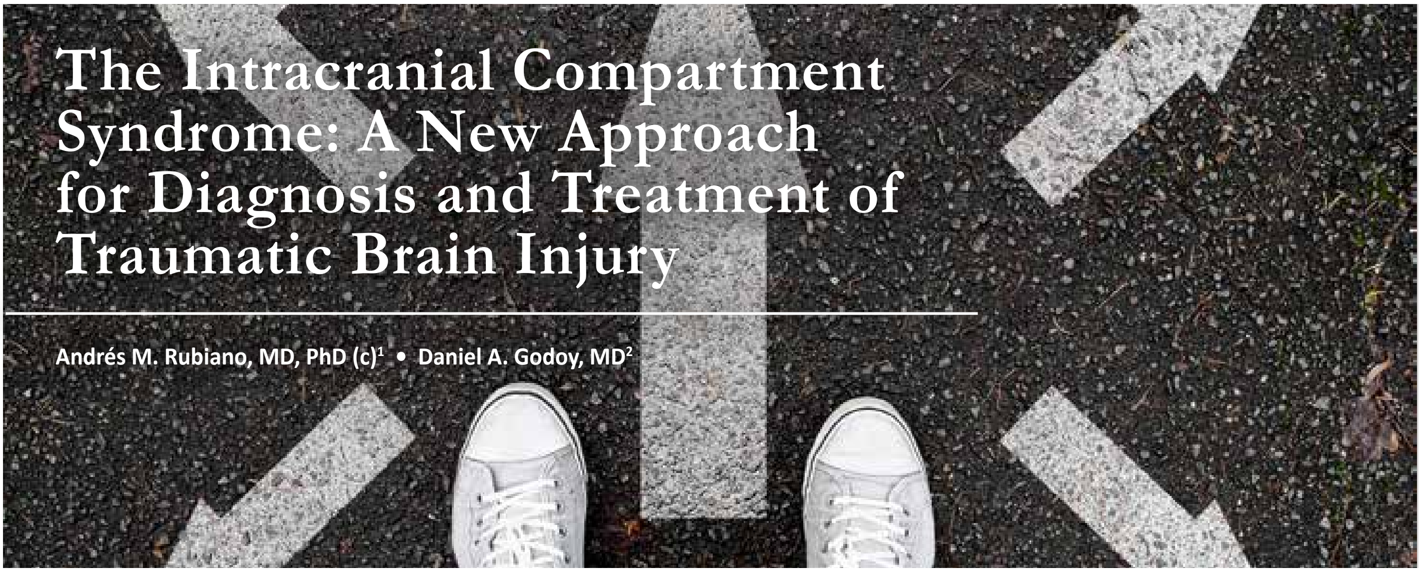
> **Traumatic brain injury (TBI) represents a critical public health burden, with almost 50 million–60 million people having a TBI each year, and costing the global economy around US $400 billion annually[1].**



The Intracranial Compartment Syndrome: A New Approach for Diagnosis and Treatment of Traumatic Brain Injury

Andrés M. Rubiano, MD, PhD (c)[1] • Daniel A. Godoy, MD[2]

The term Intra-Cranial Compartment Syndrome (ICCS) has been mentioned occasionally in the brain injury literature associated with different perspectives based on the similarities between the systemic compartment syndromes (extremities, abdomen, etc.) and the intracranial hypertension pathophysiology. One of the early mentions was discussed by Dr. Richard G. Fiddian-Green as a rapid response to a letter to the editor entitled Brain death is a recent invention, published in the BMJ on September 14, 2002[1]. This letter was a response to the analysis of the book Brain Death by Dr. Eko Wijdicks, published in 2001[2]. Dr. Fiddian-Green goes over a detailed discussion regarding similarities between the pathophysiology of the muscle and abdominal compartment syndromes and the consequences of primary and secondary brain injuries leading to brain death. His commentary entitled "intracranial compartment syndrome" is still available on the BMJ website[3]. In the neurosurgery literature, the term was originally mentioned by Dr. Anthony Figaji in a case series report related to the surgical management of severe TBI in pediatric patients as "brain compartment syndrome"[4]. In 2020, in a systematic review article by Coccolini et al, related to the timing of surgical interventions for compartment syndrome in different body regions, the term was used as "compartment syndrome of the brain" to correlate articles of early vs. late cranial decompression and outcomes[5]. After this review, Coccolini edited a book entitled: "Compartment Syndrome" in a series of "hot topics in acute care surgery and trauma"[6], and two chapters were related to discussing the similarities between intracranial pressure complications mimicking the complications of the abdominal or extremities compartment syndromes[7,8].

Taking these previous literature concepts, we were digging into the more recent trends of advanced neuromonitoring in traumatic brain injury (TBI), which includes aspects of basic and advanced engineering for better comprehension and understanding of phenomena like intracranial compliance and the autoregulatory response in acute brain injury and especially in TBI patients. Some of these concepts were described in the article entitled: "Intracranial pressure management: moving beyond guidelines" where we call attention to the mechanisms of fluids and solid dynamics and how these principles affect the compliance inside the three main anatomical compartments of the skull (left and right supratentorial and the infratentorial spaces) after primary injuries in TBI patients[9]. Traditionally the triggering aspect for defining treatment intensity in TBI patients relies on an ICP number threshold that has been considered between 20 to 25mmHg.

We consider, based on clear physiological processes inside the skull, that fundamental concepts of the mechanics and the dynamics of fluids and solids demonstrate that an ICP number, or an ICP range, does not fully explain the intracranial dynamics. We need to remember that ICP is derived from interactions of elements such as brain elements pulsatility, flow velocity, compliance of the CBV/CSF, and the compliance of the brain tissue[10,11].

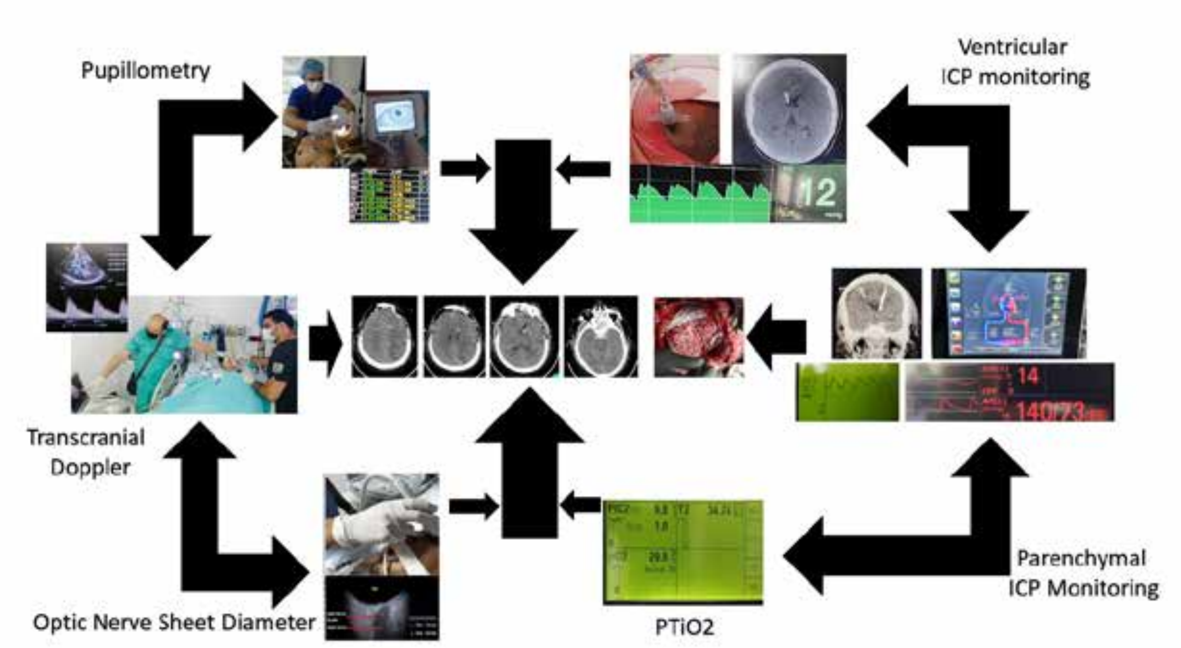
Based on the introduction of non-invasive techniques that we can use for being correlated with compliance reduction into the cranial vault, and specifically on each anatomical compartment, we start applying on TBI patients, simultaneous measurements of invasive ICP systems and non-invasive ones, including neuro sonography techniques (optic nerve sheet diameter and transcranial doppler) and digital pupillometry[12].

We were really surprised about the interactions and differences between non-invasive and invasive systems in specific cases where traditional ICP values (in terms of thresholds) on invasive monitoring did not correlate with an actual decrease of compliance, diagnosed by non-invasive systems, even after correction of systemic disorders that affects the dynamic response of the intracranial components that generate the pulsatile wave of the ICP.

It was more interesting when adding the evaluation of the invasive brain oxygenation, and in some specific types of patients, there was present oxygenation impairment associated with specific patterns of compliance disturbances showed by the non-invasive ICP evaluation methods, even in the presence of "normal" ICP values but with clear affection of the ICP waveform suggesting lost of compliance in the invasive monitored side (Figure 1).

Looking into the actual protocols and guidelines for the treatment of moderate and severe TBI, there was no option for selecting patients who require aggressive therapy in the presence of a "normal" number of ICP. This was illustrative, and an analogy came to us: we never treat with anti-hypertensive therapy a patient with a normal range of systemic blood pressure. Due to this, patients with TBI who lose compliance (putting at risk the viability of the brain tissue) will never receive aggressive therapy if their ICP numbers are in a "normal" range. Understand that this situation can happen, and it is critical to define how we can overcome such a situation for defining candidates for more aggressive therapy, fortunately, the non-invasive systems can show abnormal results in any of the

Figure 1. Integration of invasive + noninvasive systems in TBI for better decision-making on aggressive medical and surgical therapy in TBI patients who present an intracranial compartment syndrome.



anatomical compartments. We consider that if this is the case, the "intracranial hypertension" definition is not accurate as the ICP number will be in a normal range. So, the occasionally discussed but not well-understood ICCS will generate a better understanding of the situation to move faster in decreasing primary and secondary injuries in these patients.

That is why we have proposed recently, a new approach to treating early patients who have loose compliance, and the cause is not a systemic issue that can be medically managed. We recently published the proposed model, and we will be soon testing it on a clinical trial comparing standard protocols of care with the new approach[13]. In this approach, 4 stages can be defined, and the last one, where the ICP waveform is abnormal (P2 > P1), the PtiO2 is low, the optic nerve diameter is high, the maximum contraction velocity in digital pupillometry is low and the transcranial doppler waveform is decreasing in diameter, will be a surgical emergency requiring emergency cranial decompression[13].

To know more about the model, we encourage readers to go over the full article in detail, explaining the new concept and how it could be an option for selecting better patients for acute aggressive therapy to reduce tissue damage after TBI.

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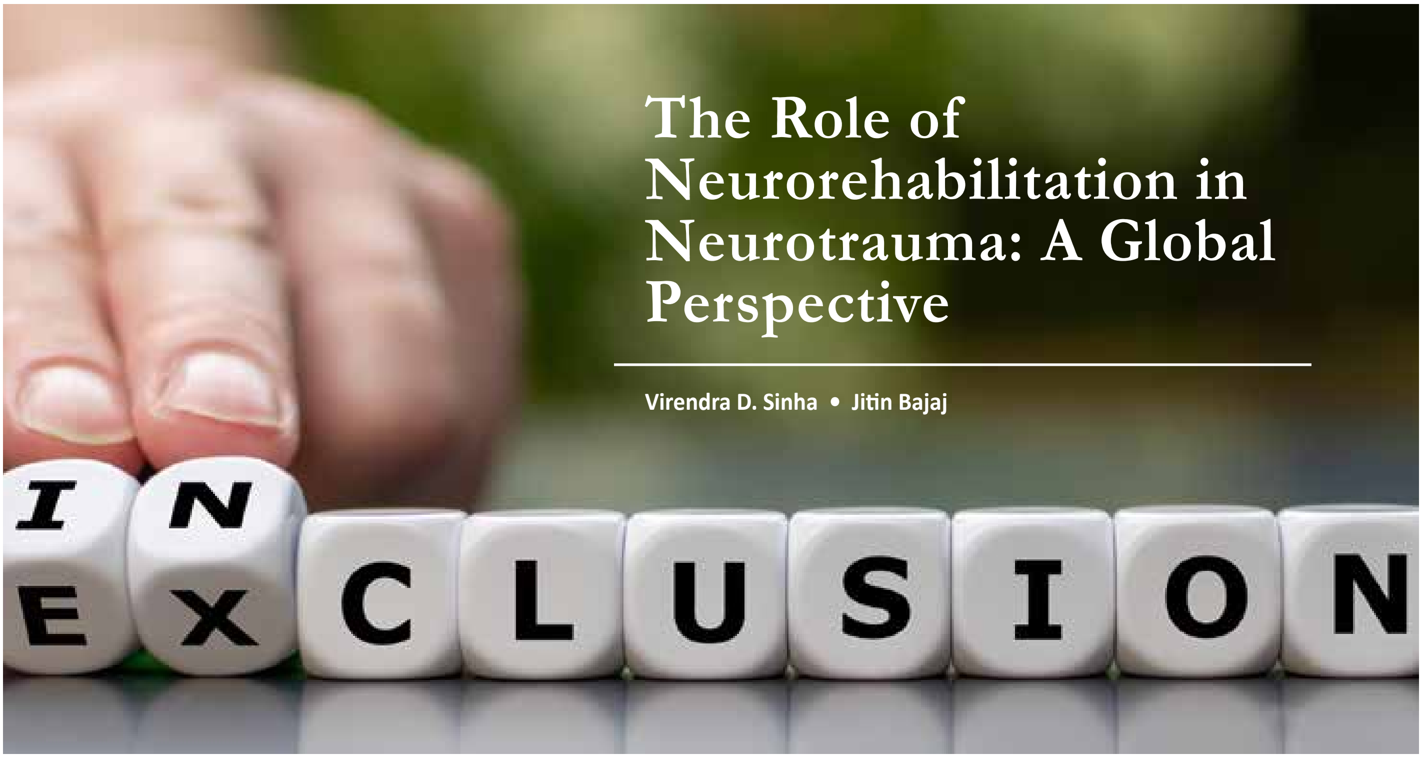

The Role of Neurorehabilitation in Neurotrauma: A Global Perspective

Virendra D. Sinha • Jitin Bajaj

Introduction

Neurotrauma, encompassing traumatic brain injuries (TBI) and spinal cord injuries (SCI), is a global healthcare challenge with profound consequences for individuals and societies.[1] The aftermath of neurotrauma often leaves survivors with physical, cognitive, emotional, and social impairments, necessitating comprehensive care and rehabilitation. Neurorehabilitation plays a pivotal role in improving the quality of life and functional outcomes for those affected by neurotrauma, offering hope and recovery.[2]

The Global Burden of Neurotrauma

Neurotrauma is a global health concern that affects millions of individuals annually. Causes range from motor vehicle accidents and falls to sports injuries and violence. According to the World Health Organization (WHO), TBI is a leading cause of death and disability worldwide. Spinal cord injuries are less common but equally devastating, resulting in long-term physical disabilities.

Low- and middle-income countries often bear a disproportionate burden of neurotrauma due to limited access to healthcare resources, inadequate preventive measures, and high rates of road traffic accidents. The economic burden poses a significant challenge for developing countries. This burden encompasses both direct costs, such as medical expenses, and indirect costs like unemployment. Additionally, there are intangible costs associated with factors like pain and disability, which further compound the overall economic impact.

The Role of Neurorehabilitation

Neurorehabilitation is a multidisciplinary approach aimed at helping individuals with neurotrauma regain function, independence, and quality of life. It involves a comprehensive and personalized plan of care that addresses the physical, cognitive, emotional, and social challenges faced by survivors. Key components of neurorehabilitation include physical therapy, occupational therapy, speech therapy, psychological support, and social integration. Cognitive impairment significantly affects long-term outcomes in TBI survivors, impacting daily life and imposing an economic burden. Evaluating cognitive impairment is essential, even after mild TBI, with tools like Montreal Cognitive Assessment. Commonly affected functions are visuospatial/executive function, memory, and attention, differentiating mild from moderate impairment.[3] We need to prioritize nationwide neurorehabilitation programs for post-TBI individuals.

Challenges in Global Neurorehabilitation

Despite the importance of neurorehabilitation, there are several challenges that hinder its effective implementation on a global scale. These include:

- Access to Care: In many low- and middle-income countries, access to neurorehabilitation services is limited, leading to unmet needs for millions of neurotrauma survivors. Even in high-income countries, disparities in access exist, particularly in underserved rural areas.
- Health Inequities: Neurotrauma disproportionately affects vulnerable populations, including those with lower socioeconomic status and limited access to healthcare. These disparities exacerbate health inequities, leading to unequal outcomes in neurorehabilitation.
- Workforce Shortages: A shortage of trained healthcare professionals, including physical therapists, occupational therapists, and rehabilitation specialists, is a global issue that impedes the delivery of quality neurorehabilitation care.
- Financial Barriers: The cost of neurorehabilitation services, including therapy sessions, assistive devices, and medications, can be prohibitive.

Insurance coverage and reimbursement policies often do not adequately address these expenses, leaving many individuals without essential care.

- Infrastructure and Facilities: Inadequate infrastructure and rehabilitation facilities in many regions hinder the provision of comprehensive neurorehabilitation services. This includes accessible buildings, transportation, and rehabilitation equipment.
- Cultural and Linguistic Barriers: Cultural beliefs, stigmatization, and language barriers can impact the effectiveness of neurorehabilitation, making it essential to provide culturally competent care.
- Long-Term Care and Support: Neurotrauma often requires long-term care and support, but healthcare systems are frequently designed for acute care rather than the extended needs of survivors.

Rehabilitation Team
Interdisciplinary Approach

Figure 1. Interdisciplinary approach is fundamental for the success in the rehabilitation process.

Global Initiatives in Neurorehabilitation
Despite these challenges, there is a growing recognition of the importance of neurorehabilitation on a global scale. Several initiatives aim to improve access to and the quality of neurorehabilitation care, the prominent which include the WHO Rehabilitation 2030 initiative. It seeks to strengthen health systems' capacity to provide rehabilitation services, emphasizing the importance of rehabilitation for all, including neurotrauma survivors.[4] It has given technical support to over 35 countries, which is increasing, to strengthen their health systems for rehabilitation services. The use of technology, such as mobility aids, communication devices, and adaptive equipment, can significantly enhance the independence and quality of life for neurotrauma survivors.

Global Collaboration: It is essential for advancing the field of neurological recovery and enhancing the quality of life for individuals affected by neurological conditions. By bringing together experts, researchers, and healthcare professionals from around the world, we can pool our knowledge, share innovative techniques, and conduct collaborative research to develop more effective rehabilitation strategies. This collaborative effort promotes the exchange of ideas, the standardization of best practices, and the development of accessible and personalized therapies that can benefit people across diverse cultural and geographic boundaries (Figure 1). Ultimately, global collaboration in neurorehabilitation holds the promise of improving outcomes and providing hope for individuals striving to regain their independence and function after neurological injuries or illnesses.

Conclusion

Neurotrauma is a global healthcare challenge with far-reaching physical, cognitive, emotional, and social consequences. Neurorehabilitation plays a pivotal role in helping individuals affected by neurotrauma regain function and improve their quality of life. However, challenges in access, equity, and infrastructure persist, hindering the delivery of comprehensive care.

Global initiatives and collaborative efforts are working to address these challenges and expand the reach of neurorehabilitation services. As we move forward, it is imperative to recognize the universal significance of neurotrauma and invest in the development of inclusive, culturally competent, and accessible neurorehabilitation programs. By doing so, we can offer hope and support to millions of neurotrauma survivors worldwide, helping them on their journey to recovery and reintegration into society.

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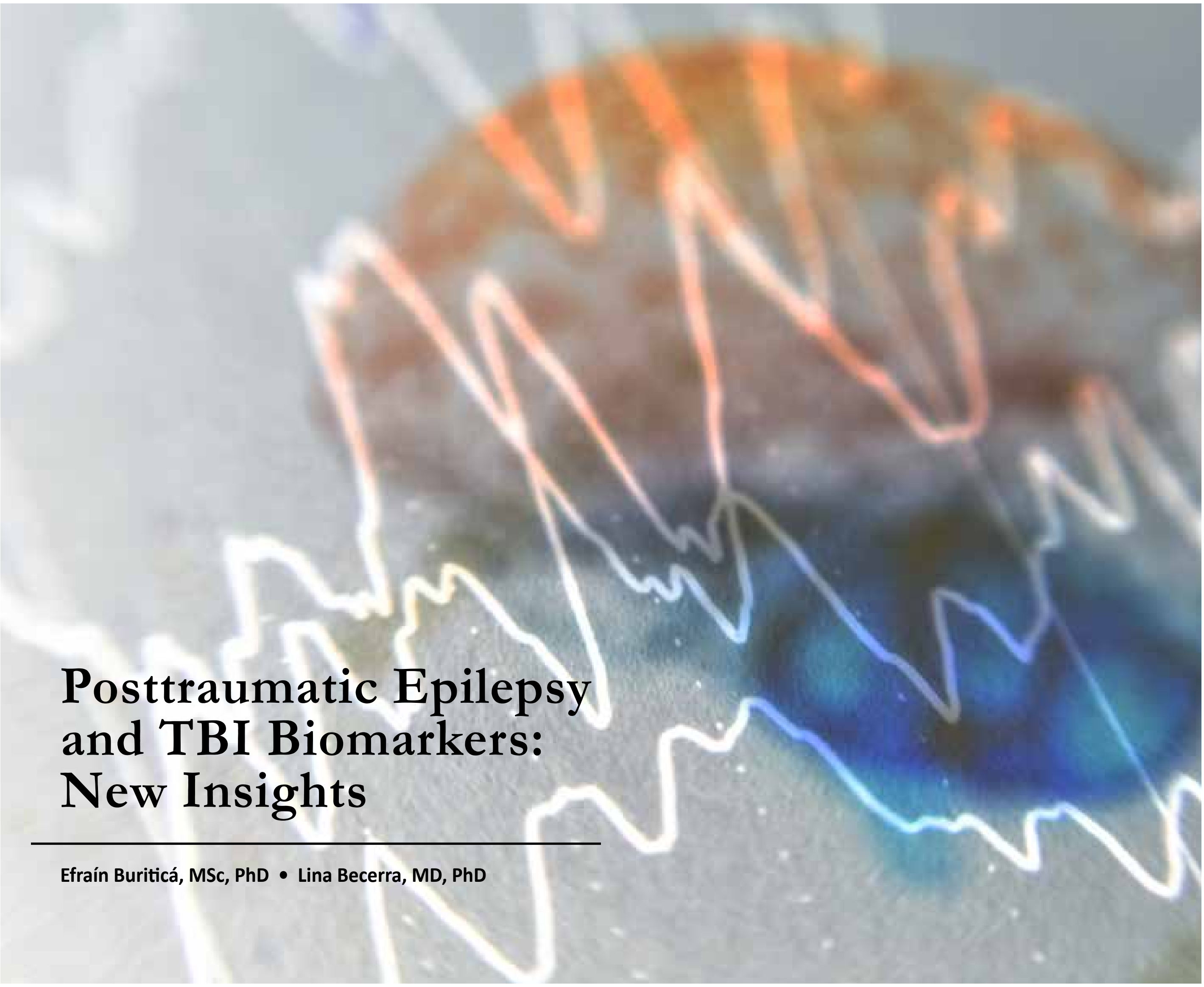

Posttraumatic Epilepsy and TBI Biomarkers: New Insights

Efraín Buriticá, MSc, PhD • Lina Becerra, MD, PhD

Post-traumatic epilepsy (PTE) is defined as the presence of at least two episodes of epileptic seizures in less than one year after a traumatic brain injury (TBI). This represents 6% of all epilepsies and 20% of symptomatic epilepsies. PTE appears in 5% of all TBIs and 15-20% of severe TBI (Pitkänen et al., 2021).

Most of the studies on TBI use animal models under controlled situations that, although they generate fundamental contributions, do not accurately reflect the intrinsic heterogeneity of TBI in humans. These preclinical studies have suggested several mechanisms influencing ictiogenesis following TBI. Among these, the most documented includes a primary mechanism of post-TBI damage that involves mechanical changes within the first few minutes after trauma and occurs in axons, glial cells, and blood vessels, which can be lacerated and cause extravasation of blood and cell death. Minutes, hours, or days after TBI, a secondary lesion has been described (McGinn and Povlishock, 2016) that involves, among others, the release of glutamate by neurons and glial cells affected, which produces excitotoxicity, as well as inflammation, which affects the subdural space due to the migration of activated lymphocytes and an increase in proinflammatory mediators (Klein and Tyrlikova, 2017). It has also been described that the increasing levels of glutamate in the extracellular space modify the function of the cysteine-glutamate antiporter, which is necessary for the creation of the main antioxidant of the cell, glutathione (Barger and Basile, 2001). After this, there is a repair with neurogenesis, axonal sprouting, synaptogenesis, and changes in the composition of neurotransmitter receptors. It has been suggested that all these side effects would facilitate the onset of seizures since they contribute to the excitation/inhibition imbalance. Some studies have shown that cell death in TBI mainly affects hippocampal GABAergic interneurons, since they seem to be vulnerable to lesions related to hypoxic and oxidative states, contributing to the excitation/inhibition imbalance (Hunt et al., 2013).

Our research group has contributed to describing the cellular and subcellular landscape of TBI by evaluating the contused human cerebral cortex using histological and Western-Blot (WB) techniques. This work called “Qualitative and Quantitative Study of Traumatic Brain Injury in Humans” (Colciencias, 11060416329) analyzed temporal and frontal cortical tissue of subjects who suffered a severe TBI and underwent decompressive craniectomy with extraction of the contusion in the Neurosurgery Unit of the Hospital Universitario del Valle. This research has made it possible to study the distribution by cell types in the cortical layers and the white matter of some markers and, on sometimes, the subcellular localization of the proteins in these cells.

The integration of data from classical histology, immunohistochemistry, double immunofluorescent labeling, and WB allowed us to understand possible functional relationships of the markers used, and likewise conclude about cell viability and homeostasis in events secondary to TBI.

In our study, we recognized that TBI is a microscopically heterogeneous phenomenon within the same contusion, and molecularly and cellularly heterogeneous, as is its clinical manifestation. In tissues with NeuN labeling to verify the preservation of cytoarchitecture and cortical lamination, we found that immunoreactivity for NeuN (NeuN-IR) was abnormal in all samples. In the same sample, we found microscopic sectors that presented slightly altered NeuN-IR but preserved cytoarchitecture (called SPC), and others with partial loss of the supragranular layers in the form of "patches" (especially layer III) or with drastic loss of the IR in all layers, that is, sectors with loss of cytoarchitecture (called SLC). MAP2 labeling was also altered in all samples with varying degrees of involvement, in the same sectors as NeuN labeling but to a greater extent than it. The apical dendrites of pyramidal cells were difficult to follow, especially those coming from layer V, which were observed as tortuous, fragmented, and with aberrant orientation (Escobar et al., 2008).

In a later phase of the study, we determined that SLCs represented at least 25% of the area of contused tissue in which there was a 67% decrease in NeuN protein by WB; and that the SPCs only had 39% of their neurons with the classic pattern of normal subcellular labeling for NeuN. Using Fluoro-Jade C labeling, we identified a 16-fold increase in the density of dying neurons in SPC sectors and a 5-fold increase in SLCs sectors (Riascos et al., 2013).

GABAergic Interneurons and Post-traumatic Epilepsy

The increase in cortical excitatory activity, associated with impaired inhibition mediated by GABA, constitutes one of the most frequently invoked hypotheses to explain ictiogenic activity in human epilepsy. Several studies have observed in frontal and temporal neocortical regions of subjects with drug-resistant epilepsy the loss of GABAergic cells that express the calcium-binding protein (CaBP) parvalbumin (PV), as well as the decreased expression of glutamate decarboxylase (Marco et al., 1996; Arellano et al., 2004). Interneurons that express Calretinin (CR) and Calbindin (CB) have always been considered to be more resistant to epileptic phenomena than those that express PV, but recently several authors have reported a decrease in the number of CR+ and CB+ neurons in the hippocampus and the neocortex of human subjects diagnosed with temporal lobe epilepsy (TLE) and focal cortical dysplasia (FCD) (Tóth et al., 2010; Barinka et al., 2010),as well as a significantly higher number of PV+, CB+, and CR+ neurons in layers II, IV, and V have also been reported in type Ia/IIIa FCD (Kuchukhidze et al., 2015). Therefore, the discussion remains open, and there is no consensus regarding the changes observed in populations of interneurons in the different types of epilepsy.
Our studies in contused human cortical tissue have also shown cytomorphological alterations in neocortical pyramidal cells of layers III and V and loss of interneurons, specifically those PV+. Both the loss of some interneurons and the cytomorphological alteration of others could be related to the functional alterations observed in pyramidal cells in PTE models, such as decreased control of electrical activity. Our study was carried out in both the SLC and SPC sectors evaluating the NeuN-IR.

In SLC, the results showed an almost total loss of the CaBP-IR, and therefore of the interneuron subpopulations. Less drastic changes in CaBPs-IR were observed in SPC, including cytomorphological alterations in the soma and processes of all interneuron subpopulations, a decrease in PV+ neurons in layer II, an increase in CB+ neurons in layers III, and V, and an increase in CR+ neurons in layer II. These latter findings may reflect dynamic activity due to changes in the microcircuitry of hyperactivated pyramidal cells in response to primary impact or secondary events such as hypoxia-ischemia. The time course of these changes may be the substrate linking the severe cortical contusion and resultant epileptogenic activity seen in some patients. The increase in CR+ cells reported in the contused tissue would contribute to the excitation/inhibition imbalance since some neurons of this subpopulation have a disinhibitory role that would accentuate the effect of the loss of those PV+ (Buriticá et al., 2009).

Reactive Astrogliosis: Link Between Trauma and Epilepsy

Different studies on human epilepsy have shown microglial reactivity as well as severe reactive astrogliosis through the expression of glial fibrillary acidic protein (GFAP). Expression of proinflammatory cytokines by typical neurons, dysmorphic neurons, balloon cells, and reactive astrocytes, such as TNF, IL1β, NF-κB, and inflammation-induced proteasome proteins, among others, have been reported in human brain tissue from patients with TLE, FCD, glioneuronal tumors and tuberous sclerosis (Richter et al., 2016; Chamberlain, 2008).

In our research group, we observed an overexpression of GFAP in the deep white matter, in the transition from gray matter to white matter, and around the SLC cortical sectors of contused subjects (Buriticá et al., 2009). We also assessed the expression of Crystalline-a-B (CRYAB), a molecular chaperone that stabilizes the rapid thickening of the intermediate filaments during the process of reactive astrogliosis in response to TBI. We found that astrocytes that overexpress GFAP also overexpress CRYAB, a finding corroborated by the double-labeling immunofluorescence. Additionally, we observed the expression of CRYAB in some pyramidal cells of layer V, which could be related to the selective vulnerability of this layer to TBI (Becerra-Hernández et al., 2022). This protein had previously been described as a tissue marker of epileptic foci in a study that examined the brain tissue of children with epilepsy. In all study samples, CRYAB was overexpressed in astrocytes and oligodendrocytes, and occasionally labeled neurons of the neocortex, hippocampus, and amygdala. The CRYAB-IR was more intense near the epileptic focus, being able to delimit its extension, and was independent of the presence of structural histological lesions, gliosis, or inflammation. Balloon cells and atypical giant cells characteristic of tuberous sclerosis samples had strong CRYAB-IR (Sarnat and Flores-Sarnat, 2009).

Conclusion and Future Directions

Although the search for biomarkers for TBI and PTE aims to determine the severity of the diagnosis or the prognosis of the patients who suffer from them, most of the findings in the matter have been obtained in plasma and in cerebrospinal fluid (CSF), and predominantly in non-human models. The recognition of the cell type that expresses them and the physiological role of these in the healthy or pathological brain tissue of humans is just beginning.

Perhaps in this direction we should soon aim to identify the mechanisms underlying the sequelae of TBI, the epileptogenesis of PTE, and refractoriness in epilepsy. Our research group is just now working on assessing several of the markers for TBI, PTE, and drug-resistant epilepsy that have been identified in plasma and CSF, or in animal models.

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Authors Bio

Efraín Buriticá, MSc, PhD, received his Master's and PhD in Biomedical Sciences from Universidad del Valle. He is the current executive director of the Colombian College of Neurosciences and the director of the Master's and Doctorate training programs in Biomedical Sciences at the Universidad del Valle. He is an Associate Professor and researcher at the Centro de Estudios Cerebrales of the Universidad del Valle, an expert in the cerebral cortex and in cortical GABAergic systems, he uses histological, immunohistochemical, immunofluorescent and western blot techniques to evaluate neurotypical and pathological tissue, focusing on traumatic brain injury, cerebral ischemia, autism spectrum disorders, and epilepsy.

Lina Becerra, MD, Ph.D., received her Ph.D. in Biomedical Sciences from the Universidad del Valle. She is the current president of the Colombian College of Neurosciences and works as a professor at the Universidad del Valle and the Pontificia Universidad Javeriana in Cali, Colombia. Her research involves the human cerebral cortex, using immunohistochemical techniques for assessing neurotypical and pathological tissue, focusing on traumatic brain injury, autism spectrum disorders, and epilepsy.

BIP expert interview

Interview With Kee Park MD, MPH

Lead of the Global Neurosurgery Team at the Program in Global Surgery and Social Change at Harvard Medical School

Related to the Global Neurosurgery Science in the Brain Injury Area, we interviewed Dr. Kee Park, from the Harvard Medical School. Dr. Park is the Lead of the Global Neurosurgery Team at the Program in Global Surgery and Social Change at Harvard Medical School. He is also Chair of the Global Neurosurgery Committee of the World Federation of Neurosurgical Societies and Editor-in-Chief of the Journal of Global Neurosurgery. Dr. Park practiced private neurosurgery for 12 years in the US before spending the next decade teaching neurosurgery in Nepal, Ethiopia, and Cambodia. He then returned to the US to obtain his MPH at the Harvard Chan School of Public Health. He joined the Program in Global Surgery and Social Change in 2016 where he leads the policy and advocacy aspects of global surgery as well as the global neurosurgery initiative.

Question 1. We know you have been dedicated to Global Neurosurgery development in different contexts. Can you briefly mention how you became a leader in this field as part of your neurosurgery career?

When I started devoting my time to serving the unmet neurosurgical needs in 2007, the term "Global Neurosurgery" did not even exist. Having trained neurosurgeons in Ethiopia and Cambodia, I realized that adding more neurosurgeons into a system that is unable to absorb them is pointless. I was trying to solve a public health problem through medical training – important but insufficient to make sustainable changes. In 2016, I returned to the US to obtain a master's in public health and completed a fellowship in global surgery. These additional skills allowed me to approach the problem more comprehensively. Thus, the concept of Global Neurosurgery was started. As the pioneer in the field, I naturally became a leader in the field.

Question 2. From your perspective how important is neurotrauma in the global neurosurgery field?

Our priority was to estimate the number of neurosurgical conditions around the world each year and how many were not being treated as the result of limited capacity. Of the 5 million neurosurgical operations that are needed each year but not being done, more than 50% were traumatic brain injuries. If we are going to address this massive gap, neurotrauma care capacity building in LMICs should be at the top of the list.

Question 3. Can you describe to us the proposed strategy for improving neurotrauma care systems at different country levels, from the Global neurosurgery perspective?

Global Neurosurgery is the clinical and public health practice of neurosurgery with the primary purpose of ensuring timely, safe, and affordable neurosurgical care to all who need it. Clinical care at country levels should be tailored to the resources available. This means clinical guidelines should not be "one size fits all" but rather contextualized to each country and its resources. The public health approach means the country should manage neurotrauma in a comprehensive way, from surveillance, prevention, prehospital care, hospital care, and rehabilitation.

In 2019, we published the "Comprehensive Policy Recommendations for the Management of Head and Spines Injuries in LMICs" (https://docs.wixstatic.com/ugd/d9a674_1ba60c38a07341a7bbbe8b1e3f0ff507.pdf) to help health ministries in this regard.

Question 4. You have published different studies analyzing data from LMICS related to infrastructure, manpower, and strategies of care for neurotrauma. Can you give us the most relevant conclusions of this great work?

Our research showed that the counties should strive to have at least 1 neurosurgeon per 200,000 persons to manage the neurotrauma burdens. Further, neurotrauma facilities should be no more than 4 hours away from the pace of injuries as the risk of poor outcomes increases significantly after the 4-hour window. Lastly, prevention is key to reducing the burden of neurotrauma cases, this helps the often-overworked neurosurgical workforce by reducing their workload so that they can care for other neurosurgical conditions such as tumors and strokes.

Question 5. You have discussed the controversial topic of task shifting and task sharing in acute neurosurgical care, including trauma. What is your perspective related to the utility of this strategy, especially in LMICs?

The practice of non-neurosurgeons caring for neurosurgical patients is already widespread, especially in LMICS. This makes sense. General surgeons are quite capable of being upskilled to care for neurotrauma patients. What's needed is for the authorities to formally recognize and institutionalize the practice, so these doctors are not working in the "grey area" of medical practice.

Question 6. As a final question, do you think that there is more specific work that international associations of professionals, working in this field, need to do in terms of advocacy and working at government levels in different regions of the world? If yes, do you have some final recommendations based on your experience working at this level?

We are just scratching the surface. Neurosurgeons entering the public health practice are too few and we need to formally recognize global neurosurgery practice as an important subspecialty within neurosurgery. I'm so encouraged by the sheer number of students and trainees showing their interest in Global Neurosurgery.

The training programs are playing catchup to meet this demand. I predict that global neurosurgeons will one day be respected for their excellence and impact as much as the scientists and surgical masters we all respect. The social change is already happening. Journals are creating global neurosurgery sections, departments are hiring global neurosurgery faculty, and national and international associations are creating global neurosurgery committees. The transformation of the neurosurgical profession has been incredibly satisfying both professionally and personally.

About the Interviewer

This interview was obtained by Dr. Andrés M. Rubiano, Neurosurgeon, Critical Care Physician, Co-Chair of the Neurotraumatology Committee of the World Federation of Neurosurgical Societies (WFNS), and Chair of the Neurological Surgery Service of Vallesalud clinical Network in Cali, Colombia. He acts as Guest Editor for this issue of Brain Injury Professional.

BIP expert interview

Interview with Gregory Hawryluk, MD, PhD

Medical Director, Brain Trauma Foundation, USA

Related to the Brain Trauma Foundation Guidelines projects, we interviewed Dr. Gregory Hawryluk, Medical Director of the Brain Trauma Foundation. Dr Hawryluk is a Canadian neurosurgeon, currently working with the Cleveland Clinic in Akron (OH) at the Akron General Medical Center and in Canton (OH) at the Mercy Hospital. Dr Hawryluk was trained as a BSc (Med) and MD at the University of Alberta, and posteriorly as a PhD at the University of Toronto and obtained a Neurotrauma Fellowship at the University of California in San Francisco.

Question 1. How did you develop your neurotrauma care career and become involved with the BTF projects?

I wanted to do meaningful medicine. For that reason, I enter the pathway of trauma care specifically into brain injury care, as this area impacts people's lives. When I went to medical school, I was always thinking about emergency medicine because of my type of personality, trying to solve complex situations in a very short period. I discovered then that I enjoy playing with my hands in small surgical procedures in the emergency room. I decided then to go for neurosurgery because leading with the brain was always a puzzle and I perceived that as a personal challenge. When I was an undergrad, I was fortunate to pick specific rotations in neurosurgery, especially in Toronto, doing a Ph.D. in parallel with my medical training with Professor Michael Fehlings in basic science for spinal cord injuries. Then I was able to have a rotation with Professor Ross Bullock, in Richmond (VA), understanding how important was to pursue a career in neurotrauma, as he was one of the leading stars in the field.

After finishing my residency, I performed a specific fellowship in neurotrauma with Professor Geoffrey Manley at UCSF, also having the opportunity to be trained in critical care of neurotrauma patients. This pathway of training allows me to have my first job in the United States as a neurotrauma specialist in Salt Lake City at the University of Utah, working also in the neurocritical care unit. During my residency, I participated in some of the Guideline's developments of the BTF, understanding this important process firsthand. After Utah, I was recruited by the University of Manitoba, as a neurosurgeon and researcher, being one of the leads with Professor Randall Chesnut from the University of Washington of the SIBBIC algorithms project for developing pathways of care based on expert consensus for TBI care. More recently I moved my practice to Cleveland Clinic, and I received an invitation from Professor Jam Ghajar, President of the Brain Trauma Foundation to be appointed as medical director of the Foundation, aiming to lead the coming guidelines development projects.

Question 2. How is your new position at the BTF moving ahead with the forthcoming projects?

A couple of things happened. After releasing the 4th edition of the BTF guidelines there was a concern regarding the applicability of their recommendations due to the rigid structure of the methodology. Suggestions for the development of algorithms to facilitate daily clinical practice were present in the different meetings where the guidelines were presented.

There was then the question about the relevance of guidelines development in the era of personalized and precision medicine. Important discussions show up inside the BTF regarding the future of the process and how to evolve in the future. We had a conversation with Dr. Ghajar, and he asked me about generating that future. My role was also bringing a sound advisor committee of experts to brainstorm about future guidelines and the innovation in methodology, to also develop consensus and algorithms associated with the guidelines.

Question 3. You recently have been in a leadership role of developing consensuses of care for TBI. How was this experience linked with the new trends in BTF projects?

I was fortunate to have a great opportunity to lead the SIBICC consensuses with Dr. Randall Chesnut. The "Seattle International Brain Injury Consensus Conference" was an initiative to build based on expert opinion and consensus, two practical algorithms for managing TBI under specific circumstances, either guided by invasive ICP monitoring or in a dual fashion, guided by invasive ICP and brain oxygen pressure. We use facilitators to decrease bias using a Delphi method and after publishing it, there have been other consensuses where I have participated. I think the enthusiasm is great and in general, people feel these types of exercises are useful. But consensuses are not the final word, and we need to understand that the rigor of evidence-based medicine is still needed. After the experience with these exercises, the new BTF projects involving guidelines development have considered the possibility of using consensuses in some of them as an additional process to turn recommendations into a more practical tool for use daily.

Question 4. The BTF is working on new different guidelines, including the prehospital TBI guidelines, penetrating TBI guidelines, military TBI guidelines, etc. Did you think something is still missing?... like TBI rehabilitation guidelines or some other topics?

Well, yes, there are absolutely gaps in evidence-based medicine guidelines in TBI. There is no question we want to have an evidence-based document about rehabilitation in TBI, but I think if we think about it, maybe there is not enough evidence to look for funding that supports a project on this topic. Your point is very much on targets also. In BTF we think we need to update the existing guidelines also as a regular process, but people need to be aware that we are always looking to fill gaps. There are other BTF guidelines that are not as recognized as the adult TBI ones, and as examples, we have guidelines on military TBI, and other documents related to TBI prognosis.

The BTF has been successful in understanding where the priorities are, and we are regularly evaluating new opportunities for closing gaps of knowledge in the field. Anyone interested in what the BTF is doing can access the website at: https://braintrauma.org/

Question 5. You have important experience in clinical trials, including basic research and human research. Do you think there is still something missing in the TBI studies to improve the evidence available for guideline development?

I think TBI research is an open field. Every time that we develop some guidelines few recommendations are level I due to the lack of studies with good quality available for most of the topics. Head injury researchers need to keep focused on the big picture. If we think something is missing, we need to move to translational medicine, because as an example, basic physiological changes evaluation is fundamental and sometimes we don't focus enough on these aspects. For example, the difference between the Monro-Kellie doctrine approach and the Rosner vasoconstriction and vasodilatory cascades sometimes is not well understood and deserves to be studied in deep to move for applicability in clinical practice and how these approaches correlate with outcomes.

Thanks for your kind answers to these questions. Finally, do you have some message for the audience of Brain Injury Professional?

Yes, sure. TBI is a common but profound health problem that affects several functions of the human being, including mood changes, personality changes, impairment of speech, etc. Taking care of these patients is an inspiring process because there are not so many stones that we can walk on to resolve these critical problems. There are not so many people devoted to understanding and treating these problems worldwide and having people looking to solve them, shows that they have this issue as their passion, bringing intense curiosity to seek and question the fundamentals for moving into advancements in the field. This inspiration is needed, and I will encourage people to move into this pathway to create a new paradigm for the current strategies of care in brain-injured patients.

About the Interviewer

This interview was obtained by Dr. Andrés M. Rubiano, Neurosurgeon, Critical Care Physician, Co-Chair of the Neurotraumatology Committee of the World Federation of Neurosurgical Societies (WFNS), and Chair of the Neurological Surgery Service of Vallesalud clinical Network in Cali, Colombia. He acts as Guest Editor for this issue of Brain Injury Professional.

events

2023

December

8 - 9 - *AOTA Specialty Conference: Children & Youth*, December 8 – 9, 2023, New Orleans, Louisiana. For more information, visit www.aota.org.

2024

February

15 - 17 - *Combined Section Meeting*, February 15-17, 2024, Boston, MA. For more information on the event, visit https://www.apta.org/csm

March

21 - 24 - *2024 American Occupational Therapists Association Conference and Expo*, Mach 21 – 24, Orlando, Florida. For more information, visit www.aota.org.

27 - 30 - *ABI2024*, March 27-30, 2024, Las Vegas, Nevada. For more information, visit www.abi2024.org.

April

18 -20 - *ACRM Spring Meeting*, April 18 – 20, 2024, Dallas, Texas. For more information, visit springmeeting.acrm.org.

May

1 - 3 - *Canadian Association of Occupational Therapists Conference 2024*, May 1 - 3, Halifax, Nova Scotia. For more information, visit caot.ca/site/prof-dev/pd/conference?nav=sidebar&banner=3.

22-25 - *13th World Congress for Neurorehabilitation*, May 22 – 25, 2024, Vancouver, Canada. For more information, visit www.wfnr.co.uk.

June

1-6 - *ISPRM 2024* – 18th World Congress of the ISPRM, June 1 – 6, 2024, Sydney, Australia. For more information, visit isprm.org/events/isprm2024/

September

19 - 21 - *Fifth Biennial Conference on Paediatric Brain Injury*, September 19-21, 2024, Glasgow, Scotland. For more information, visit internationalbrain.org.


CRAIG

PHOTO BY HERMAN PRIVETTE

SCARLETT LAW GROUP

Scarlett Law Group is a premier California personal injury law firm that in two decades has become one of the state's go-to practices for large-scale personal injury and wrongful death cases, particularly those involving traumatic brain injuries.

With his experienced team of attorneys and support staff, founder Randall Scarlett has built a highly selective plaintiffs' firm that is dedicated to improving the quality of life of its injured clients. "I live to assist people who have sustained traumatic brain injury or other catastrophic harms," Scarlett says. "There is simply no greater calling than being able to work in a field where you can help people obtain the treatment they so desperately need."

To that end, Scarlett and his firm strive to achieve maximum recovery for their clients, while also providing them with the best medical experts available. "As a firm, we ensure that our clients receive both the litigation support they need and the cutting-edge medical treatments that can help them regain independence," Scarlett notes.

Scarlett's record-setting verdicts for clients with traumatic brain injuries include $10.6 million for a 31-year-old man, $49 million for a 23-year-old man, $26 million for a 7-year-old, and $22.8 million for a 52-year-old woman. In addition, his firm regularly obtains eight-figure verdicts for clients who have endured spinal cord injuries, automobile accidents, big rig trucking accidents, birth injuries, and wrongful death.

Most recently, Scarlett secured an $18.6 million consolidated case jury verdict in February 2014 on behalf of the family of a woman who died as a result of the negligence of a trucking company and the dangerous condition of a roadway in Monterey, Calif. The jury awarded $9.4 million to Scarlett's clients, which ranks as one of the highest wrongful death verdicts rendered in recent years in the Monterey County Superior Court.

"Having successfully tried and resolved cases for decades, we're prepared and willing to take cases to trial when offers of settlement are inadequate, and I think that's ultimately what sets us apart from many other personal injury law firms," observes Scarlett, who is a Diplomate of the American Board of Professional Liability Attorneys.

In 2015, Mr. Scarlett obtained a $13 million jury verdict for the family of a one year old baby who suffered permanent injuries when a North Carolina Hospital failed to diagnose and properly treat bacterial meningitis that left the child with severe neurological damage. Then, just a month later, Scarlett secured an $11 million settlement for a 28-year-old Iraq War veteran who was struck by a vehicle in a crosswalk, rendering her brain damaged.

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