Introduction: Pediatric traumatic brain injury: New frontiers in clinical and translational research

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Introduction

Traumatic brain injury (TBI) is a major public health problem among children and adolescents. Surveillance data reveal that 1 in every 20 emergency department presentations at pediatric hospitals is for a TBI, making TBI more common than burns or poisonings. For children, such injuries represent a common interruption to normal development, with population estimates ranging from 200 to over 500 per 100 000 a year, and with well-established variations across age and gender (Crowe et al., in press; Langlois et al., 2006). The majority of TBI in children and adolescents are mild, typically with few long-term consequences; however, a significant proportion of children will suffer more serious injuries and will experience a range of residual physical, cognitive, educational, functional, and social and emotional consequences, requiring the lifelong involvement of health professionals across a range of disciplines and leading to a significant social and economic burden for the children’s families and for the community more broadly (Cassidy et al., 2004).

This book, New Frontiers in Pediatric Traumatic Brain Injury, aims to evaluate what we have learned about TBI in childhood to date and, perhaps more importantly, to articulate the challenges we face and how we should go forward in the future. Over the past two or three decades, researchers and clinicians working with children with TBI have become aware that injuries to the developing brain cannot be understood or treated in exactly the same manner as those occurring in adulthood. Although we may be guided by science and practice in adult TBI, unique developmental and contextual issues need to be taken into account at all stages of recovery and treatment in children. Thus, a separate knowledge base is needed for pediatric TBI. As a consequence, until recently our understanding of recovery and outcomes in pediatric TBI has lagged behind that for adults. This is changing. Research in pediatric TBI now has more solid foundations. A number of principles have been established, some consistent with the adult literature, such as the predictive value of injury severity (Anderson et al., 2004; Taylor et al., 2008). Others are specific to early brain injury, such as the unique mechanics and characteristic pathology of inflicted injury in children (Coats & Margulies, 2006; Prange & Margulies, 2002), or reflect the importance of developmental and contextual factors, such as the age at injury, developmental stage of brain development, and functional maturation (Anderson et al., 2005; Taylor & Alden, 1997), the key role of the family, and implications of life tasks specific to children (Yeates et al., 1997).
To this point, we have been reasonably successful in describing the consequences of pediatric TBI. The natural history of pediatric TBI has also been studied extensively, and we have a working understanding of the acute and long-term effects of injury for the child and family. At a group level, research has demonstrated that children with milder injuries are likely to recover well, with few residual problems. With increasing severity, recovery is less complete, and we know that those with severe injury are at risk for ongoing difficulties across a range of physical, cognitive, and socio-emotional domains, and that these difficulties may persist through childhood and into adulthood (Hessen et al., 2007; Jaffe et al., 1995; Yeates et al., 2004). In contrast, at the individual level, these trends may not necessarily apply, and clinical reports confirm that outcomes are highly variable, leading to uncertainty with respect to prognosis and key predictive factors. More precise information is critical to determining which children are at high risk and to effectively allocating limited resources for management and treatment. To date, our research has been only modestly successful in providing guidance with respect to which factors contribute most to recovery and outcome, with much past research focused within specific domains or silos. For example, medical researchers may examine the impact of raised intracranial pressure or neurological signs on long-term outcome, while others may look at biochemical markers, radiological results, or environmental factors. To date, progress using this narrow focus has been disappointing, suggesting that a more multi-dimensional model is required, in which researchers across disciplines come together with a more holistic view of the child.

A further challenge exists in the area of management and treatment. At present, the evidence base for effective treatment, at both acute and more chronic stages of recovery post-TBI, is largely lacking, across medical, pharmacological, and behavioral domains (Anderson & Catroppa, 2006; Laatsch et al., 2007; Ylvisaker et al., 2005). As a result, health professionals have little direction with respect to which interventions may lead to better outcomes. Reflecting this problem, clinical practice guidelines, where established, vary dramatically across the world, and even within individual centers. As a result, care pathways are disparate and clinical decisions are typically made on the basis of previous training and experience, rather than on empirical grounds. Treatment research and clinical trials in this domain are costly and difficult, but are critical to improving child outcomes.

So, there is a way to go yet, and the challenge for the next decade is to begin to translate empirical findings into clinically relevant information that will lead to improved and appropriately targeted care and better outcomes for the child and family. To do this, we need to ask why, despite the commitment of clinicians and researchers alike, we have been unable to achieve more. In considering this question, we can identify a number of very real obstacles, many specific to this particular population. To begin, pediatric TBI has not attracted the public attention received by other childhood disorders. As a result, funding for this population is surprisingly low, and does not reflect the high cost to the community of such injuries in childhood. To some extent, this may reflect the traditional view that children recover well from brain injury and that their needs are few. The observation that the consequences of TBI are “masked” is also of relevance, with most children appearing “normal” after injury, despite suffering from functionally significant impairments. But perhaps we as a field have not been sufficiently proactive in informing the community of the needs of these children and their families, and need to consider an increased focus on advocacy and public policy.

Even with adequate funding, substantive studies are difficult to conduct. TBI in children has a low base rate, and individual centers struggle to recruit sufficient numbers of children...
to conduct studies that can help answer the outstanding questions regarding management, treatment, and prognosis. At a practical level, contemporary health systems worldwide are not set up to facilitate this research, instead focusing on acute care and rapid discharge and paying limited attention to the transition home or to community reintegration.

An additional complication is that children who suffer TBI are not representative of the healthy population, and are more likely to have pre-existing behavioral and learning problems as well as social disadvantage (Taylor & Alden, 1997). These factors may impact negatively on recovery, and confound our ability to determine which post-injury difficulties are due to TBI and which might have predated the injury. These unique characteristics also lead to challenges in selecting appropriate comparison groups for determining injury-related consequences, and differentiating them from pre-existing problems. Researchers to date have either ignored these issues by using normal control groups, employed recruitment criteria that exclude children with pre-injury problems, or selected comparison groups deemed similar to TBI cohorts on key characteristics such as social background or behavioral function.

The developmental context creates its own challenges. In contrast to colleagues studying adult TBI, pediatric researchers cannot assume that all children are at the same level of development, or that the same injury will have an equal impact across childhood. In fact, increasing evidence indicates that age and skill attainment at the time of injury are important considerations in assessing likely recovery. Further, some argue that, in contrast to the recovery patterns described in adults, children may in fact “grow into their difficulties” as they progress through childhood, as environmental demands increase but age-appropriate developmental milestones fail to be mastered. This view is supported by an emerging literature that describes adult survivors of pediatric TBI as experiencing educational failure, restricted vocational options, psychological adjustment difficulties, and poor quality of life (Anderson et al., 2009; Cattelani et al., 1998; McKinlay et al., 2002). The child’s need to acquire new skills and knowledge and meet educational demands, in the context of increased risk of physical, cognitive, and behavioral impairment, generates unique challenges for rehabilitation and reintegration following pediatric TBI.

Associated with developmental issues is the problem of identifying acceptable “gold standards” to measure outcomes that are relevant from infancy to adolescence (Fletcher et al., 1995). This dilemma impacts on acute outcome measurement, because most widely used measures of levels of consciousness and post-traumatic amnesia are inappropriate for infants and young children. Radiological measures, in particular functional neuroimaging, are also problematic with children, because of practical issues around brain scanning, as well as given the lack of normative comparisons. However, perhaps the greatest challenge is in the area of cognitive and behavioral outcomes, where few if any measures are available which are applicable across the desired age range. As a result, studies utilize a wide range of outcome measures and findings are difficult to compare.

‘Pediatric Traumatic Brain Injury: New Frontiers in Clinical and Translational Research’ emerged from an international research conference held in San Diego, California, USA, in 2007, with financial support from the National Institutes of Health, the Centers for Disease Control, the Murdoch Children’s Research Institute, the Research Institute at Nationwide Children’s Hospital, and the Australian Society for the Study of Brain Impairment. The conference was attended by over 200 delegates, representing many disciplines, cultures, and levels of training and experience. The program for the meeting comprised keynote addresses from a panel of international experts across a range of specialties relevant to...
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pediatric TBI, ranging from bench scientists to clinical researchers. Our intent was to bring together people with similar goals and interests to facilitate communication across disciplines and to encourage those in the field to begin to work together.

In designing the program, we placed an emphasis on research and evidence-based practice, and its potential to contribute to clinical practice and better child outcomes. The meeting was designed not so much to present specific research findings as to illustrate multi-level, integrative, and translational research and to consider how best to promote such research in the future, as well as to encourage both new and established investigators to undertake research consistent with this goal. Our aim with the conference, as well as with this book, was to highlight the need to move away from simple comparisons of children with and without TBI to investigations of factors across a range of levels that account for variations in outcomes, and to translate this information into evidence-based models for intervention with these children.

As will be illustrated in the following chapters, the past few decades have seen an explosion of interest in this field that has led to advances in acute medical treatments for childhood TBI. Researchers have begun to study the biomechanics of TBI using non-human models, including animals and simulations, such as “crash dummies.” This work has provided important insights into the mechanisms of TBI and its unique impact on the developing brain. Within the human domain, a major research focus in recent years has been the reduction of more preventable secondary brain insult, via implementation of more rapid medical response, investigation of potentially predictive biomarkers for early detection of injury, and interventions such as hypothermia.

Advances in brain imaging have assisted in early diagnosis and guiding appropriate treatment, with current high-resolution imaging enabling the identification of even subtle brain damage in the context of mild TBI. Growing evidence, from both structural and functional imaging technologies, indicates common patterns of brain pathology resulting from childhood TBI, both macroscopic and microscopic, and changes that occur over time in response to damage to the developing brain.

Further, research has established that the mechanisms of injury often vary with developmental stage. For example, inflicted injuries due to child abuse are almost exclusive to infants, whereas in preschool children, the majority of injuries occur as a result of falls from furniture or play equipment. These early injuries are likely to be linked closely to environmental factors, such as family dysfunction and social disadvantage. In contrast, in older children, injuries are more likely to be due to sporting or motor vehicle accidents, and can be more directly associated with the child’s own actions and behavior. These epidemiological data have implications for prevention and community education, and small steps are beginning to be made in this direction. For example, mandatory helmet usage for bicycle riders and for certain contact sports has been introduced in some countries.

Other research findings, from a range of mostly discipline-specific research endeavors, describe an increased risk for a multitude of residual impairments following childhood TBI, both acutely and in the long term. Persisting neurological symptoms, motor dysfunction, communication difficulties, poor attention and information processing, reduced memory, executive dysfunction, and social and emotional disorders have been consistently reported for many children with serious TBI. In association with these impairments, functional outcomes are also impacted, with solid evidence of low school attainment, reduced vocational opportunities, poor adaptive skills, and lowered quality of life. Unfortunately,
although these problems are now accepted as frequent consequences of serious TBI, findings have yet to be successfully translated into more precise prognoses or acceptable evidence-based treatments for victims and their families.

Of crucial importance is growing evidence for a developmentally specific response to injury, demonstrating that adult knowledge and theories cannot be simply translated to the child population. The relative vulnerability of the young brain to the impact of TBI and the increased behavioral consequences in terms of reduced skill and knowledge acquisition is a relatively new concept, but is now supported by animal research, neuroimaging data, and behavioral findings. Again, these findings are yet to be incorporated into clinical practice or reflected in availability of appropriate medical and rehabilitative resources.

In an effort to improve the precision of prognoses, and to facilitate the development of treatment and management models, attempts have been made to link child outcomes with a variety of injury-related, environmental, family, and developmental factors, with only modest success. We believe that this stalling of progress may be due to a variety of factors. In particular, prior research has often occurred in separate silos, with little integration across domains or disciplines. The scientific advances that have occurred within domains (e.g. genomics and proteomics of neural recovery, neuroimaging, neuropsychology) are unlikely to result in significant progress in the clinical management of children with TBI until they become the topic of collaborative research that cuts across levels and specialties. In comparison to the field of TBI, we can learn much from the study of other childhood disorders, such as childhood cancer, where international collaborative consortia have been in existence for many years and have led the way in developing and implementing evidence-based, life-saving treatment protocols that have reduced mortality rates from 70% in the 1970s to closer to 10% in the past decade.

The time appears ripe for an interdisciplinary and collaborative approach to pediatric TBI that promotes integrative and translational research efforts. We believe that ‘New Frontiers in Pediatric TBI’ will help advance the state-of-the-art of research in the field and promote networking and collaboration among investigators. The chapters that constitute the book describe the state of the art in research across a variety of disciplines, all of which contribute to developing knowledge about pediatric TBI. This body of work makes it clear that the challenges and obstacles we face are similar, regardless of discipline, and that the solutions for progress will require a concerted effort by investigators that cuts across disciplines and other artificial boundaries.

References


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Journal of Rehabilitation Medicine, suppl. 43, 28–60.
Traumatic brain injury (TBI) is a leading cause of death and disability among children and young adults in the United States (NCIPC, 2000). Each year TBI results in approximately 3000 childhood deaths, 29,000 hospitalizations, and 400,000 emergency department visits. The predominant causes of TBI in young children are motor vehicle accidents, firearm incidents, falls, and child abuse.

Since the 1940s biomechanics has made a significant contribution to understanding the mechanisms and tolerances of adult traumatic brain injury and it continues to play a crucial role in forming guidelines for adult motor vehicle occupancy and sports safety (Goldsmith, 2001; Goldsmith & Monson, 2005). Biomechanical research specific to pediatric traumatic brain injury did not begin until the late 1970s and the paucity of pediatric biomechanical data at the time forced researchers to make assumptions regarding the relationship of infant material properties to adult material properties (Mohan et al., 1979). Since then, biomechanical researchers have measured many pediatric tissue properties directly. Biomechanical studies of the intact skull and brain and the properties of individual tissues have demonstrated that the pediatric brain and skull respond differently to loads than adult tissue, and previous linear extrapolation from adult data does not provide an accurate estimate of pediatric properties (Coats & Margulies, 2006; Prange & Margulies, 2002).

Despite the increased research in the field, not enough key pieces of information are in place to establish realistic injury tolerances for children. The Head Injury Criterion (HIC) was initially established as an estimate of linear acceleration head injury in adults from lateral impact car crashes. Despite ongoing research to create better predictors of head injury in adults (Deck & Willinger, 2008), the HIC is still used as the standard predictor of head injury severity in pediatric biomechanical studies (Bertocci et al., 2003; Kapoor et al., 2005). In a somewhat arbitrary manner, the adult HIC value is reduced for predicting head injury severity in children, but this metric is not based on measurements of the types of forces and accelerations that actually produce injuries in children. Biomechanical data that define an age-specific response of the body to loading and define age-specific tissue thresholds for injury are necessary to improve our understanding of pediatric TBI and to develop more effective prevention, diagnosis, and treatment strategies for kids.

Biomechanics of traumatic brain injury

Large impact forces to the head can cause skull fracture, epidural hemorrhages, and focal contusions to the brain and scalp, but subdural hemorrhages (SDH) and axonal injury are primarily caused during rapid accelerations or decelerations of the head. These rapid accelerations and decelerations can also produce mechanical forces that lead to intracranial hematomas and axonal injury, which can have long-term effects on cognitive and behavioral functioning. Biomechanical studies of the intact skull and brain and the properties of individual tissues have demonstrated that the pediatric brain and skull respond differently to loads than adult tissue, and previous linear extrapolation from adult data does not provide an accurate estimate of pediatric properties (Coats & Margulies, 2006; Prange & Margulies, 2002).

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accelerations may be linear or rotational in nature (Fig. 1.1), but high angular accelerations are more often correlated with SDH and traumatic axonal injury than linear. One early biomechanical study on primates reported that all animals subjected to a primarily angular motion of the head showed immediate onset of unconsciousness that varied for 2–10 minutes, but animals with only a translational (linear) motion of the head never became unconscious (Gennarelli et al., 1971). Subsequent biomechanical experiments focusing on mechanisms of rapid, non-impact head rotation to primates and pigs resulted in widespread axonal injury (Gennarelli et al., 1972; Gennarelli et al., 1982; Gennarelli, 1996; Raghupathi & Margulies, 2002; Smith et al., 2000) and SDH (Gennarelli et al., 1979; Gennarelli & Thibault, 1982; Meaney, 1991).

These rapid angular accelerations can occur without head impact, but they are most commonly associated with an impact to the head (e.g. motor vehicle accident, falls, assault). Assessing the mechanism of injury is challenging in children because there is often no reliable witness to the incident, particularly in the case of abusive head trauma. Additionally, the absence of evidence of a contact injury (i.e. skull fracture, cranial bruising, or scalp swelling) does not establish that there was no impact. A forceful impact of an infant head to a 4-inch thick piece of soft foam dissipates the force to the head possibly eliminating external evidence of impact, but producing a head angular acceleration that is on average three times greater than that of shaking (Prange et al., 2003). Additionally, several clinical studies have reported bruising (Atwal et al., 1998), extracranial swelling (Strouse et al., 1998), and skull fracture (Alexander et al., 1990) that are only found after autopsy and not during clinical examination.

Computational and physical models of angular acceleration mimicking the animal experiments mentioned above have correlated axonal injury with the amount of deformation (strain) in the brain tissue and not the stress (force applied per unit area) of the tissue (Margulies et al., 1990; Miller et al., 1998). Experiments on unmyelinated squid axons support these data (Galbraith, 1988; Galbraith et al., 1993). Specifically, uniaxial tensile strain, not stress, in the axon produced short- and long-term neural dysfunction. In primate models of SDH from non-impact rotational loading, it was also observed that the deformation of the parasagittal bridging veins, and not the stress, correlated with the presence or absence of SDH (Meaney, 1991). Together, these data show that the deformational response
of brain tissue due to angular acceleration/deceleration of the head is tightly linked with primary axonal and vascular damage found in traumatic axonal injury and SDH.

**Biomechanical tools for understanding TBI**

Biomechanics draws from several different engineering approaches to answer questions that are difficult or impossible to answer from clinical and epidemiological studies. The most common biomechanical tools are **material property testing**, **event reconstruction using instrumented surrogates**, **animal studies**, and **computational modeling**. Each of these tools provides valuable information to increase our understanding of pediatric traumatic brain injury.

**Material property testing**

Human brain tissue from children is difficult to obtain, and the majority of pediatric brain material property data have been from immature pigs (Prange et al., 2000; Prange & Margulies, 2002) and rodents (Gefen et al., 2003). In both species, the immature brain was reported to be approximately twice as stiff as adult pig and rodent tissue when undergoing large deformation. Similar testing on a single specimen of human temporal cortex gray matter obtained and tested within 3 hours of excision from a 5-year-old patient during a temporal lobectomy procedure was reported to be stiffer than human adult specimens, correlating with the age-dependent findings of the pig and rodent studies (Prange, 2002). This increase in stiffness means that it takes a larger amount of force to deform the pediatric brain compared to the adult. However, it is unknown how much deformation is required to produce injury in the pediatric brain, so an increase in tissue stiffness does not necessarily denote a protective benefit.

The material property differences between the adult and pediatric brain may be due to the degree of myelination. Biomechanical studies have suggested that the axons, rather than the surrounding matrix of astrocytes and oligodendrocytes, contribute more to the effective stiffness of the brain (Arbogast & Margulies, 1999). Thus, the progress of axon myelination during development of the pediatric brain may contribute to the differences reported in material properties of children and adults. Lipids, such as myelin, have a low shear modulus (Yamada, 1970) and may decrease the stiffness of the composite material as the amount of myelin in the brain increases to adult levels.

Because traumatic brain injury events often involve contact to the head, the material properties of the pediatric skull play an important role in defining the underlying brain injury. The developing skull begins as a single layer of mesenchyme in utero, and by birth an infant has several single-layer bony plates approximately 1 mm thick. These bony plates are connected by a membranous material called suture. As a child ages, the bony plates begin to fuse together, eliminating the suture, and becoming a solid encasing for the brain. During childhood the bone begins to differentiate from a single cortical bone layer into a three-layered structure containing a layer of cortical bone on the inner table, followed by a middle layer of spongy diploe, and then another layer of cortical bone on the outer table. The entire thickness of the final composite structure is approximately 5–6 mm. Material property studies on fetal cranial bone have reported that the stiffness (elastic modulus) of the bone significantly increases with donor age (McPherson & Kriewall, 1980a). More recent studies on pediatric cranial bone from infants < 1-year-old also report a significant increase in stiffness with donor age (Coats & Margulies, 2006). The material properties of...
cranial bone in toddlers and adolescents are limited to a single specimen from a 6-year-old child (McPherson & Kriewall, 1980a). While this single specimen is over 7 times stiffer than newborn values, adult values of cranial bone (Hubbard 1971) are still 1.7 times stiffer than the 6-year-old. Overall, these data indicate that the stiffness of cranial bone increases with age, but the relationship is non-linear (Fig. 1.2).

When evaluating infant head injury, however, it is not just the cranial bone stiffness that reflects possible brain deformation upon head impact, but the presence of cranial sutures also contribute to the overall deformation of the skull. Tensile tests on human pediatric cranial suture report that this membranous material can deform over 100% before failure (Coats & Margulies, 2006), further emphasizing that the infant skullcase can undergo significantly larger distortions prior to fracture or rupture compared to the skulls of older children and adults.

**Event reconstruction using instrumented surrogates**

Biomechanics involves understanding the human body’s response to applied forces. Injury severity will vary with the magnitude of the applied force, therefore it is important to quantify and compare the magnitude and types of loads (e.g. linear acceleration, rotational acceleration, impact force, etc.) being applied in events that cause traumatic brain injury. In children, the majority of incidents of TBI are caused by car crashes, accidental falls, and child abuse (CDC, 2005; Kraus et al., 1987; Kraus et al., 1990). Because children are not instrumented during these injurious events, biofidelic surrogates are used to re-enact injurious scenarios. The surrogates are usually instrumented with accelerometers to measure acceleration and/or load cells to measure force. Since the desire of these studies is to mimic the kinematic response of a real child, it is important that the mass, mobility, and deformation characteristics of the surrogate be based on biomechanical measurements in children.

In response to infant TBI from minor frontal car crashes, Klinich et al. (2002) used a commercially available 6-month-old surrogate (CRABI) to measure infant head angular acceleration from a passenger-side airbag impact to the back of a rear-facing child restraint system (CRS). In a car crash resulting in a 11 mph change in vehicle velocity, they report nearly an 8 times increase in infant head linear acceleration when the CRS is impacted with an airbag compared to no impact of the CRS by an airbag. Additionally, they report that even in a more severe car crash (30 mph change in vehicle velocity), a CRS system not impacted by an airbag still results in four times less infant head acceleration than the minor car crash with airbag–CRS impact. The use of anthropomorphic dummies (ATD), such as