CHAPTER 1

The clinical problem of traumatic head injury

Ramon Diaz-Arrastia¹ and Pieter E. Vos²
¹Center for Neuroscience and Regenerative Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD, USA
²Department of Neurology, Slingeland Hospital, Doetinchem, the Netherlands

Introduction

Traumatic brain injury (TBI) is among the oldest and most common medical afflictions affecting humankind. A South African australopithecine skull estimated to be 3 million years old shows evidence of a lethal skull fracture administered by another early hominid [1], and injuries to the cranium are commonly found in skeletal remains of prehistoric humans. Between 10 and 50% of skulls of prehistoric humans show evidence of cranial trauma [2, 3]. Most of these injuries were a consequence of warfare, but it is also likely that many of these TBIs were accidental and occurred during hunting or otherwise interacting with a harsh environment. The advance of civilization has resulted in a dramatic decrease in interpersonal violence, as recently pointed out in an influential book by Steven Pinker of Harvard University [4], but TBI remains a common and frequently disabling feature of modern life in industrialized as well as industrializing societies.

This book is organized so that the information is maximally useful to practicing clinicians as they encounter patients with TBIs. This often starts at the site of injury, where the decision of regarding transport to an emergency department (ED) for higher-level evaluation and management is made. In cases of severe TBI, some interventions must be started in the field in order to minimize secondary injury. In the ED, the diagnostic and management algorithm is determined by the patient’s level of consciousness, the extent of cranial and extracranial injuries, and findings on neuroimaging studies, usually cranial computerized tomography (CT). A subset of patients require emergent surgical treatment, and care by a neurosurgeon is often lifesaving at this stage. Subsequent to the ED (or operating theater), patients are usually cared for in the intensive care unit, where careful monitoring and interventions are aimed at lowering intracranial pressure and maximizing cerebral perfusion pressure.
to minimize secondary brain injury. Neurocritical care medicine is a new and rapidly growing subspecialty of neurology and represents a fertile area of research in neurotrauma. Some patients with milder injuries are discharged from the ED with instructions to seek follow-up care in the community, while others with moderate injuries may be admitted to the general hospital ward for close observation. Upon discharge from the hospital, many patients, particularly those with moderate and severe injuries, require inpatient rehabilitation therapy, while others are sent home for outpatient rehabilitation services. The availability of rehabilitation services and specialists varies widely even in wealthy countries, and while it is generally accepted that rehabilitation treatments are valuable, research to identify optimal rehabilitative strategies is still in its infancy. Ultimately, most TBI patients attempt to reintegrate into their communities and resume their normal lives. While many can do so successfully, a substantial fraction experience disabilities that limit their ability to resume their preinjury lifestyle. During the chronic stage after injury, many patients experience long-term and sometimes delayed complications that require continued medical attention.

TBI patients encounter different physicians at each stage of the continuum of care, and while specialists from different disciplines (including emergency medicine, neurosurgery, neurology, neuroradiology, critical care medicine, rehabilitation medicine, psychiatry, and psychology) are involved at each stage, the best care is provided by medical systems that integrate and coordinate care at each stage along the continuum. Unfortunately, such integrated systems of care are rare, even in wealthy countries. This book is a small attempt to bridge that gap by introducing physicians involved at each level with the challenges that face their colleagues at other stages and to point out the needs to those involved in developing integrated systems of care for one of the most common human maladies.

Social burden of TBI

US estimates

TBI is a major cause of death and disability. In the USA alone, approximately 1.7 million sustain a TBI each year, of which 52,000 people die, and another 275,000 are hospitalized and survive [5]. High-risk age groups are those under 4, 15–19, and greater than 65. These figures do not include injury data from military, federal, and Veterans Administration hospitals. As has been the case since prehistory, military personnel are at particular risk of TBI, which reportedly occurs in approximately 15% of those involved in combat operations [6, 7]. TBI is also a common cause of long-term disability. It is estimated that in the USA, 80,000–90,000 people annually experience permanent disability associated with TBI. Currently, more than 3.2 million Americans (or 1% of the population) live with TBI-related disabilities [8]. This results in an enormous burden on patients, their families, and society. Similar data are available from other developed countries. The social burden in mid- and lower-income countries is likely even higher.
European estimates
In Europe, TBI figures are in general comparable to those in the USA. In a recent survey on the costs of brain disorders in Europe, the best available estimates of the prevalence and cost per person for 19 groups of disorders of the brain were identified via a systematic review of the published literature. An economic model was developed to estimate the mean annual costs of persons sustaining a TBI [9]. Most brain disorders have an insidious onset followed by worsening and often chronic symptoms, and for such conditions, the most reliable epidemiologic data constitute prevalence estimates derived from community-based samples. However, TBI differs from other disorders in that their onset is sudden and followed by an intensive period of care followed by rehabilitation and potentially cure. For TBI, incidence rates are mainly available and the cost of patients during a period following disease onset. In the European study, also estimates on the cost of patients suffering from the long-term consequences of TBI were included as an approximation of the costs for patients with a previous onset of disease. The identified cost of TBI studies presented the mean indirect cost of the whole population, including also the zero estimates of patients not working because of other causes than the disorder (e.g., being underage or retired). The economic model was designed to estimate the number and costs of persons in acute trauma care, in rehabilitation, or suffering from the long-term consequences of a previous TBI. We assumed a time horizon of 20 years divided into three phases: acute (first 6 months following the injury), rehabilitation (the following 18 months), and finally a long-term phase. The cost estimate of TBI based on separate estimates for each severity (mild, moderate, and severe TBI) for 2010 was 33.0 billion €PPP [9].

The problem of mild TBI
TBI is usually classified as mild, moderate, and severe, based on the initial Glasgow Coma Score (GCS) recorded in the ED. Severe TBI is defined by a score between 3 and 8, moderate TBI by GCS between 9 and 12, and mild TBI (mTBI) by GCS 13 and 15 [10]. Although it is recognized that this classification scheme has a lot of limitations [11], it has been universally utilized in clinical practice as well as in clinical research. Although severe TBI has been the primary focus of investigation over the past 30 years [12], mTBI is at least 10-fold more prevalent [13, 14]. While the likelihood of favorable recovery is higher in mTBI compared to moderate and severe TBI, many patients with mTBI are left with disabilities that impair their ability to fulfill their work, school, or family responsibilities. It is likely that the social burden resulting from mTBI is at least equivalent to that resulting from severe TBI, given its much higher prevalence [13]. Using incidence and cost data from 1985, Max et al. [15] concluded that 44% of the total lifetime costs associated with TBI were due to mTBI. Since this study did not consider the costs of lost productivity and reduced quality of life, as well as indirect costs borne by family and others, it is likely to be an underestimate of the true societal burden of mTBI.
Mild TBI has been relatively understudied for several reasons. First, most mTBI patients make a seemingly complete recovery, and early identification of mTBI patients who are most likely to suffer persistent symptoms and develop cognitive and neuropsychological deficits is difficult. Second, since mortality and functional dependence on others are relatively rare in mTBI, the outcome assessments that are traditionally used for severe TBI are insufficiently sensitive for the type of cognitive and behavioral disabilities that most commonly result from mTBI [12]. The cognitive and psychiatric consequences of TBI are often nonspecific and overlap with conditions such as developmental, behavioral, mood and thought disorders, and dementia. Further, many of the long-term consequences of TBI manifest years after the trauma and may not be ascribed to the brain injury from which there was an apparently initial complete recovery. For example, TBI early in the preschool years may alter the developmental potential of the young brain and result in problems that only manifest during adolescence and young adulthood, such as substance abuse disorders, mood disorders, and conduct disorders [16]. Similarly, there is an increased risk of late-life dementia in individuals who suffered a TBI in early to midlife, even after an apparent initial complete recovery [17].

**TBI as a chronic, lifelong condition**

TBI has traditionally been conceptualized as an event, from which there is either complete or incomplete recovery, and that once recovery has plateaued, whatever residual deficits remain have been assumed to be stable. Recently, it has been recognized that TBI is best conceptualized as a lifelong chronic health condition, which begins at the time of the injury but has chronic effects that persist for life and, in many cases, manifest only after a latency of several to many years [18, 19]. These chronic health effects merit careful monitoring and continued therapeutic interventions.

It has long been recognized that neurological disorders such as posttraumatic epilepsy are a consequence of TBI, which may manifest years after the injury [20, 21]. This is a direct evidence for the fact that traumatic insults trigger synaptic plasticity and circuit rewiring that persists for months and years and is likely lifelong. This plasticity is usually beneficial and allows for repair and recovery but, in some cases, results in a maladaptive neural circuit. Other neurological disorders such as Alzheimer’s disease, Parkinson’s disease, and chronic traumatic encephalopathy are also well-recognized long-term sequelae of neurotrauma [22]. Disorders of the hypothalamic–pituitary axis are noted in up to 30% of survivors of moderate and severe TBI [23] and can have protean long-term consequences, including sleep disorders [24]. As a consequence of these and perhaps other chronic health conditions, individuals who experience moderate-to-severe TBIs have a reduction in life expectancy of approximately 4–7 years [25, 26].
Patients who survive more than 1 year after moderate-to-severe TBI are 37 times more likely to die from seizures, 12 times more likely to die from septicemia, and 4 times more likely to die from pneumonia than a matched control group from the general population [27].

**Paucity of specific therapies for TBI**

The high social burden resulting from TBI has led to extensive preclinical studies and numerous clinical trials aimed at developing therapies to improve functional outcome [12]. In animal models, therapeutic interventions aimed at modulating molecular pathways identified to be induced after TBI have been successful in limiting the extent of injury and improving neurologic recovery [28–30]. These experimental observations constitute a convincing proof of the principle that opportunity exists for therapeutic interventions. However, phase III clinical trials of several of these therapies in patients with severe brain injuries have failed to demonstrate efficacy [31]. It is likely that one of the main reasons for this failure to translate therapies from the lab to the bedside is the heterogeneity of TBI [32]. Not all is bleak, however. A retrospective review of neurosurgical databases in the USA found that mortality from severe TBI declined from 39 to 27% from 1984 to 1996 [33]. Most of this remarkable improvement is due to advances in supportive care and the development of specialized neurocritical care units.

Pharmacologic interventions targeting repair, regeneration, and protection after TBI are particularly lacking. Drug development for TBI has traditionally focused on limiting secondary brain injury after the initial traumatic event, based on the belief that the capacity of the central nervous system for repair and regeneration was limited. New evidence now indicates that the adult brain has substantial regenerative capacity, and repair and regeneration processes can be activated or enhanced by pharmacologic and nonpharmacologic treatment. Brain repair mechanisms that are potential therapeutic targets include angiogenesis, axon guidance and remodeling, remyelination, neurogenesis, and synaptogenesis. Pharmacologic interventions supporting regeneration and repair may have a longer therapeutic window than pharmacologic interventions designed to limit injury, and they are also potentially effective in the acute, subacute, postacute, and chronic phases after TBI. Thus, repair and regeneration therapies have the potential advantage of being effective over a prolonged period of time following TBI.

Pharmacologic interventions designed to treat the persistent symptoms associated with the chronic stage of TBI (e.g., memory disturbances, depression, headache) are widely used off-label by clinicians. These usually include pharmacotherapies aimed at modulating the dopaminergic, noradrenergic, serotonergic, glutamatergic, and cholinergic systems. However, strong evidence for their efficacy and safety is lacking. As a result, the selection of drug for individual patients, or drug dose and duration, is empirical and highly variable among
health systems. Clinical trials are needed to assess the efficacy and toxicity of these pharmacologic interventions.

Finally, it is likely that combination therapy will ultimately be required to promote maximal recovery and optimize outcome after TBI. Because TBI damages the brain by multiple mechanisms, combination therapy designed to simultaneously target multiple mechanisms of injury will likely be required. Pharmacotherapy that blocks downstream cellular and molecular mechanisms in the brain combined with pharmacotherapy that targets symptoms resulting from TBI may provide one reasonable strategy. Thus, drug combinations have the potential of having a larger therapeutic efficacy than that of individual drugs. Additionally, nonpharmacologic therapies such as exercise and physical and occupational therapies may also facilitate repair and regeneration. It is likely that the combination of pharmacologic and nonpharmacologic therapies may ultimately prove most successful.

Classifying a multidimensional process

Multiple paradigms exist for classifying TBI, including classification by injury severity, mechanism, pathoanatomy, and pathophysiology. The most widely used classification is by injury severity and is based on factors such as the neurological exam (usually operationalized through the Glasgow Coma Scale) and the duration of loss of consciousness and posttraumatic amnesia [34]. However, it is well recognized that such measures provide only a one-dimensional view and are of limited utility for guiding therapy and prognostic counseling.

A pathoanatomic classification, guided by neuroimaging findings, provides additional valuable information. TBI can result from either focal or diffuse insults, though both patterns may exist in a given patient to varying degrees. Focal injuries result from force directly transmitted to the head upon contact and include skull fractures, extra-axial hemorrhage (epidural or subdural), contusions, lacerations, and focal vascular injuries that produce strokes. Diffuse injuries result from acceleration/deceleration of the head and are characterized by diffuse axonal injury, traumatic subarachnoid hemorrhage, traumatic vascular injury, inflammation, and neuroendocrine dysfunction. Neuroimaging with cranial CT scanning is excellent at detecting focal injuries, but poor at detecting diffuse injuries. Magnetic resonance imaging (MRI) is superior to CT, particularly for identifying diffuse injuries. A single patient, particularly one with injury in the severe end of the spectrum, may manifest both focal and diffuse injuries and multiple pathoanatomic types of each. Recent emphasis has been placed on multidimensional classification, encompassing severity as well as pathoanatomic characteristics that likely have pathophysiologic mechanisms in common. Such schemes, based heavily on patterns seen on neuroimaging studies, hold promise that such an understanding will lead to the development of targeted and more effective therapies [35].
It is also clear that demographic factors such as age, gender, and possibly genetic background play an important role in the response of neural tissue to traumatic injury and will have to be considered when selecting therapeutic strategies. An equivalent mechanical force is likely to result in a more severe and pathoanatomically complex injury in an infant or older person than in an adolescent or young adult, and the long-term consequences of such an injury will also likely differ.

**Understanding the endophenotypes of TBI**

The term endophenotype, initially coined in the field of psychiatric genetics [36, 37], refers to internal phenotypes discoverable by biochemical, physiological, radiological, pathological, or other techniques, which are intermediate between a complex phenotype and the presumptive genetic or environmental contribution to the complex disease. Discovering the genetic and environmental factors contributing to complex human diseases, as well as developing effective therapies for them, often requires understanding the endophenotypes of the disease. For example, the discovery of genetic factors contributing to coronary artery disease [38] and the eventual development of effective therapies based on HMG-CoA reductase inhibition was made possible by understanding the endophenotype of hypercholesterolemia, which is measurable through a simple blood test. It is likely that the development of effective therapies for TBI will require a thorough understanding of endophenotypes discoverable through methods such as MRI, biochemical assays of biomarkers in blood or cerebrospinal fluid, electroencephalography or other physiologic techniques, and neuropathology. Although this work is in its infancy, preliminary observations are starting to point out the broad outlines of the endophenotypes of TBI.

Such TBI endophenotypes may be represented by a vector-based scheme (see Figure 1.1, modified from Saatman et al. [35]). Each measured endophenotype can be represented by a single vector, with the magnitude of the vector representing deviation from normal. Vectors can be arranged radially about a central point representing normal, and the angle between each vector represents the correlation between each measure. For example, endophenotypes that are highly correlated with each other are represented by vectors at small (acute) angles, while those that are not correlated are represented by vectors orthogonal to each other. The surface area mapped out by the vectors represents injury severity, and the shape reflects heterogeneity. Additionally, multivariate statistical analysis can facilitate transformation of univariate statistical relations to multivariate representations, such as path diagrams that convey cause and effect. Improved characterization of data sets via multivariate statistical analysis could also guide the design of testing parameters, thereby enhancing applicability of results and increasing efficiency of bench-to-bedside translation.
Conclusion

TBI is one of the most common medical afflictions affecting mankind, and since it often affects children and young adults and interrupts their education, social, and professional development, its impact on society is disproportionate. Despite much progress over the past decades, much remains to be done. Recent advances in neuroimaging and in understanding the biochemistry and physiology of neurotrauma hold much promise for improved diagnosis, better understanding of endophenotypes, and identification of the most therapies. Success
will ultimately require collaborations between medical and nonmedical specialists from various disciplines and the development of integrated systems of care.

References


