
Introduction: Biomedical Challenges and Socioeconomic Burden

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1. Introduction

Modern socioeconomic developments have generally resulted in a greatly improved quality of life for most, but these advances have been accompanied by the introduction of numerous health challenges arising from new diseases and casualties associated with environmental, industrial, and economical disasters, social and armed military clashes, occupational exposures, daily high-speed traffic accidents, and so on. Among the diseases of growing public and military health concern is traumatic brain injury (TBI), which has been recently recognized as a “silent epidemic” emerging globally at the transition of the twentieth and twenty-first centuries [1–8].

2. Traumatic brain injury (TBI): definition, assessment and classification

Traumatic brain injury (TBI) can be defined as alteration in brain functions due to head collision with a stationary or a moving object (e.g., a projectile) or upon coupling of an external mechanical force (e.g., g-force, blast shock wave (SW)) with the head [9–12]. The traumatic effects of these insults emerge as either open or closed head wounds yielding penetrating or closed TBI [11–14]. Clinical classification of TBI severity is widely achieved using the *Glasgow Coma Scale* (GCS)—a neurological scale designed to tally medical conditions of individuals in the disease sequelae. The severity of TBI can be classified as mild, moderate, severe, as well as vegetative state and brain death—estimated upon clinical presentation of a patient’s neurologic signs and symptoms varying from case to case. Translational and clinical observations indicate that many symptoms resolve completely upon recovery, while others, especially

those resulting from “secondary injury” due to neurological complications and reactive traumatic responses to “primary trauma,” can persist as chronic illnesses resulting in partial or permanent disability [2, 3, 13, 15–18]. Consequently, TBI should not be regarded as a single clinical entity with a defined outcome but rather represents “a spectrum of brain injuries,” where each TBI subtype can lead to a distinct clinical condition which requires case-specific medical treatment [3]. From these considerations efficient personalized therapy would need implementation of advanced diagnostic techniques (such as contrast-enhanced computed tomography, diffusion tensor MRI, TBI biomarkers) for assessment of injury and monitoring of recovery (discussed in Chapters 1.5, 2.1, 2.2 of this book).

3. TBI: Etiology, pathobiology and translational research

Statistically, the vast majority of TBI is associated with vehicle collisions, damaging assaults, falls, collision/contact sports, and combat operations [4–11, 13]. These events initiate the primary mechanisms of blunt, ballistic, and blast-associated neurotrauma that may or may not be accompanied by skull fracture. Penetrating TBI is readily apparent and generates damage localized along the projectile path through the brain that includes a site of fractured or perforated skull, ruptured meninges, and lesions of the brain tissue [13, 19]. The absence of such conspicuous hallmarks in closed TBI can result in an initial underestimation of injury severity, particularly when a TBI score is “mild” [12]. In situations producing blunt closed TBI, the damaging forces to the head induce an intracranial inertial force due to linear acceleration/deceleration or rotational momentum to the brain, so it collides inside with the skull resulting in focal “coup or contrecoup or rotational shearing injuries” [12, 20, 21]. Moreover, the same external forces to the skull can generate an array of tensor stress forces (e.g., normal and shear, tensile) through the brain tissue that cause cell compression/stretching, disorder axonal trafficking (i.e., axoplasmic transport of mitochondria, synaptic vesicles, proteins, etc., from neuron’s body through the axoplasm), and yet shear and fraction neuronal fibers and disrupt the microvasculature and meningeal structures, thus leading to different forms of intracranial hemorrhage [13, 18, 20, 22–28]. The disruption and dismantling of brain circuitry by these mechanical forces are the principal effectors of injury [20, 25]. Primary brain contusions can elicit concussions, diffuse axonal injury (DAI) and encephalopathy, dysregulation of intracranial pressure and the flow of cerebrospinal fluid (CSF), and the impairment of visceral organs and systems complicated by a variety of neurochemical and metabolic effects [12, 20, 21, 26, 27]. From an etiological perspective, the secondary injury factors can feature brain ischemia and hypoxia, hypercapnia, neuroinflammation, impairment of blood-brain barrier, cerebral edema, meningitis, seizures, and so on [12–17, 21, 25].

A devastating form of TBI is produced by shock waves generated by detonation of explosive devices [7, 11, 12]. At the center of the explosion, gaseous products instantaneously expand from a small volume at a very high-pressure state through the surrounding ambient pressure environment. The compressed gases expand outwards at a supersonic speed in a form of air shock wave (SW). When encountering the head, the SW can impart energy to skull bones, dura and arachnoid mater, CSF, and neuronal tissue through which energy is delivered and dissipated via different mechanisms, namely inertia, spalling, shearing, compression, and

cerebral air embolism. A combination of DAI, meningitis, brain edema, ischemia, and neurocognitive disorders accompanied by systemic organ system complications are the described features of blast TBI and reflect the multifactorial nature of SW effects [12, 21, 23, 28].

The pathogenesis and recoveries from these varieties of TBI are age- and phenotype-dependent, greatly adding to the complexities and challenges for the development of therapies [29–31]. A recent focus in translational research has been the roles of genetic and epigenetic polymorphism in TBI disease, giving new perspectives on TBI management and identification of potential targets for rehabilitation [30–32]. This translational research has been primarily driven by animal models that have been developed over the past decades to mimic the clinical sequelae of human TBI. As noted earlier, since human TBI is very heterogeneous, no single animal model suffices, and researchers have relied upon the use of distinct yet complementary models to capture the characteristic features of human TBI documented through clinical and postmortem examination. As extensively reviewed [23 34–36], although imperfect, these in vivo and in vitro models together have provided valuable insights into posttraumatic sequelae which can be targeted for therapeutic intervention. Nevertheless, the failure to date to successfully translate a neuroprotective drug through phase 2 and 3 clinical trials highlights the compelling need to improve models to achieve an ecological validity and a greater translational value.

4. Epidemiology and social impact of TBI-related diseases

The epidemiology of TBI is overwhelming worldwide. According to the U.S. Department of Health and Human Services, in the United States, the overall incidence of TBI (either as an isolated injury or in combination with other injuries (i.e., polytrauma)) in 2010 was estimated to be 823.7 per 100,000 population, and the cost for direct TBI medical care in U.S. was estimated at more than \$50 billion per year [4]. A lower TBI rate was reported in Europe (235 per 100,000) in 2006 [5]. It should be noted that the above numbers in U.S. did not account for those persons who received care at the U.S. military or Veterans Affairs hospitals [6]. According to the U.S. Department of Defense report of 2013, the cohort of servicemen diagnosed with a TBI from 2000 through 2011 represented 235,046 persons (or 4.2% of the 5,603,720 who served in the Army, Air Force, Navy, and Marine Corps) (<http://dvbic.dcoe.mil/dod-worldwide-numbers-tbi>) [7, 11, 33]. Overall, among TBI casualties, almost 100% of persons with severe head injury and over 50% of those with moderate head injury acquire permanent disability and will not return to their premorbid level of function, which creates a major socioeconomic burden [4, 5, 9, 33]. In addition, dramatic psychological changes can occur among the TBI survivors who experience “the invisible injuries” of brain trauma (e.g., posttraumatic stress disorder (PTSD)). These occult injuries are particularly challenging, since the changes occur in the absence of any outward manifestation of injury and alterations in patient appearance, making diagnosis, management, and prognosis extremely difficult.

In the global perspective, the recent continuous expansion of military conflicts in the Middle East, Afghanistan, and North Africa occurs with the implementation of enormous amounts of weaponized conventional explosives which when deployed and detonated inevitably affect

civilian populations in the conflict zones. The bTBI civilian casualties due to these proxy wars are poorly determined [8]. Considering massive migration of civilian populations driven by these disasters to Europe, the bTBI epidemiology in these groups requires a particular attention, since their social care is becoming a burden of host countries.

5. Conclusion

TBI disease remains a continually growing public health concern both domestically and globally and has taken on a heightened urgency with the recent recognition of a growing number of chronic traumatic encephalopathy victims among athletes and Warfighters exposed to repetitive sub-concussive insults [37–39]. Although a daunting problem, considerable progress has been made over the past decade with characterizations of TBI etiology, epidemiology, and advances in definitions of age- and genotype-specific pathobiology/pathophysiology, diagnostics, acute medical-surgical treatments (e.g., prevention of secondary injuries and maintenance of brain physiology), as well as on the development of new modalities for long-term targeted therapy, rehabilitative care, and TBI prevention (see Chapters 1.1–2.5 of this book). Despite significantly reduced TBI mortality rates at surgical emergency and acute treatments, improvements in long-term outcomes remain a great challenge, largely because as noted earlier, the disease does not represent one pathological entity but is rather a syndrome represented by a wide range of lesions that can require different patient-specific therapies in order to sustain neurological and physiological recovery. Further resolution of these problems requires a mutual effort of clinicians/surgeons, biomedical scientists, biotechnologists, pharmacologists, and biomedical engineers.

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