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Traumatic Brain Injury Induced Hypopituitarism: The Need and Hope of Rehabilitation

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Abstract. **Traumatic brain injury is a leading cause of death and disability in developed countries. Damage caused by focal and diffuse lesions produces symptoms involving most major medical systems as well as symptoms of neurological and psychological origin. The severity of a traumatic brain injury is difficult to assess, and therefore, an initial accurate prognosis is difficult as well. Present treatments focus on relieving symptoms without adequately addressing the underlying cause of those symptoms. Recent studies have shown anterior pituitary deficiencies to be common amongst survivors of TBI. As many symptoms ascribed to a TBI are similar to the symptoms of hypopituitarism, it is possible that treatment of these deficiencies will improve functioning and the quality of life for survivors of traumatic brain injuries.**

Key words. **traumatic brain injury, rehabilitation, hypopituitarism**

Introduction

Traumatic brain injury is not an event. It is a life-long disease, occurring throughout the world in epidemic proportions. This disease causes a marked change in the individual's life, a profound disruption of the family, and certainly, an enormous expense of resources and finances.

Every year in the United States alone, almost 1.5 million individuals sustain a traumatic brain injury (TBI). Although most recover, over 200,000 survivors will have persistent cognitive, physical and/or emotional deficits that prevent them from functioning at their pre-injury level. And of that number, approximately 80,000 individuals will have a very significant loss of function. TBI is the leading killer and disabler of young adults under the age of 35. The overall annual cost of acute care and rehabilitation in the U.S. is estimated to be 10 billion dollars [1]. As anticipated, most of the financial resources are utilized in the acute hospital setting. Due to the advances in care, more individuals are surviving their brain injury; however, once the patient leaves the acute care hospital, health care providers have woefully little to offer. There have been very few significant scientific advances to improve the cognitive and physical problems that keep these individuals from returning to an active and independent life.

The highest incidence of TBI is amongst individuals from 15–24 years of age and, due to the risk of TBI from falls, in those 75 years or older. There is a smaller peak in children five years and younger. In the 15–24 years age group, males are more than twice as likely as females to sustain a TBI [1]. Risk taking behaviors, alcohol and drugs are likely to be involved. In the United States, approximately 50% of TBIs are due to motor vehicle accidents, bicycle or pedestrian-vehicle accidents. Violence-related incidents account for approximately 20% of TBIs. Sports and recreation related injuries account for 3% of hospitalized TBIs; however, as the majority of sports related TBIs are mild, they may go unreported, therefore underestimating the actual incidence of this cause of brain injury [1].

Pathology of Traumatic Brain Injury

Primary injuries to the brain, suffered immediately after the injury, are of two major types: contusions/hemorrhages and axonal stretch/shearing. The contusions may be multiple, small, and even microscopic. They are usually immediately below the cortical surface. As the energy of the impact increases, the size and number of such lesions may grow, coalesce and ultimately form an intracerebral hematoma. Vascular injury also may occur at the junction of structures with different mechanical-elastic properties [2]. These types of lesions will give rise to more focal neurologic signs and symptoms.

Diffuse axonal injury (DAI) is due to stretching and shearing of the axons. It is a common lesion of the white matter particularly in acceleration/deceleration injuries associated with rotation of the brain on its axis. Although radiographic findings may be limited to small punctate hemorrhages, white matter lesions and diffuse edema, DAI is one of the major causes of severe cognitive and motor deficits following a TBI [3]. DAI within the mesencephalic region is frequently the cause of coma following a TBI.

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In addition to the primary lesions, secondary processes will produce further damage to the brain. At the cellular level, there will be changes to the basic molecules of metabolism, mechanisms of the cellular response to injury, and to the quantities of certain molecules, such as oxygen free radicals and nitric oxide that may be injurious when in excess. The levels of neurotransmitters may also be changed. Excitatory amino acids such as glutamate and aspartate may occur in huge amounts after a brain injury, leading to over excitation and ultimately the death of neurons. Altered levels of acetylcholine, dopamine and serotonin can affect cognition and behavior [1]. Cerebral edema, ischemic neuronal loss due to vascular occlusion or hypoxemia, and compression from mass lesions all contribute to secondary cerebral damage. Unfortunately, although the pathophysiology of TBI is being studied extensively, the exact relationship of these neurobiological deficits to functional recovery as well as physical and cognitive sequelae remains very poorly defined.

Neurologic complications are usually quite evident—most within the first days and months following the injury. Cranial nerve deficits, visual field loss, dysphagia, hearing loss, motor paresis and paralysis are common. The risk of seizures following a TBI ranges from 2% in mild injuries to 50% in open brain injuries [4].

Certainly, neurologic complications predominate in a brain injury; however, these individuals have problems that cover the spectrum of medical subspecialties. GI problems occur in approximately 50% of individuals with a TBI. Hepatic dysfunction, bowel incontinence, gastroparesis and dysphagia are common [5]. Some individuals require lifelong enteral feedings or supplementation. Genitourinary problems are common due to loss of cortical and sometimes spinal control. Chronic neurogenic bladders are seen in approximately 8%. Cardiovascular problems develop in 32% of individuals with a TBI Deep venous thrombosis occurs in approximately 40% of severe TBIs. Anticoagulation then adds to the expense and morbidity associated with TBI [6].

Decubitus ulcers are frequent complications in bedfast individuals, as well as individuals who require casting for orthopedic procedures. Seborrheic dermatitis (7%) and acne vulgaris (8%) are also seen [5]—very often in individuals without antecedent skin problems. Fractures occur in approximately 30% of moderate to severe TBIs [7]. Spasticity is common in severe injuries. Oral medications for this problem have a high side effect profile, and therefore individuals may require botulism toxin with serial casting and temporary or permanent motor blocks. Spasticity unresponsive to more conservative measures may benefit from continuous infusion of Baclofen through an intraspinal catheter. Heterotrophic ossification is the formation of cartilaginous-like bone usually at the joints of the long bones, requiring aggressive physical therapy, anti-inflammatories, and sometimes surgery and radiation to restore function.

Neuroendocrine problems occur chronically in approximately 40% of individuals after a TBI [8]. Diabetes insipidus and inappropriate anti-diuretic hormone syndrome occur acutely, although the incidence chronically is relatively low [9]. Recent studies have shown thyroid deficiencies in as many as 22% of cases studied, pituitary-adrenal axis abnormalities in up to 22.5%, secondary hypogonadism in up to 22%, and chronic growth hormone deficiencies in up to 20% of those studied [9–13].

TBI Symptoms

Although the objective medical complications of a traumatic brain injury are quite daunting, it is very often the subjective problems that keep individuals from fully re-entering society after a TBI. Patients may develop emotional, cognitive and psychosocial problems. Some of the most persistent problems include short term memory, attention and concentration. As a result of frontal lobe injury (common in vehicular accidents) individuals may display subtle and not so subtle deficits in "executive function." The loss of skills in attention, planning, organizing, abstract reasoning, judgment and self regulation can have profound effects on an individual's ability to function in society. Altered sexual functioning, impulsivity, mood disorders and poor self awareness are also common after a TBI.

As seen in Figure 1 [14], these types of symptoms are common, and often disabling. Fatigue is not just the physical component, as one would assume, but individuals often complain of mental fatigue as well. Sleep disturbances and daytime hypersomnia were identified in 45% of individuals with a TBI. There was no correlation of that problem to time post injury, type or severity of injury. There was also no correlation of the subjects' symptoms and what was found objectively [15]. In essence, the sleepy patients were unaware of their sleepiness.

The social consequences of TBI are enormous, and many are quite serious, including the increased risk of suicide, divorce, substance abuse, chronic unemployment, and resultant economic strain on the individual and family. Family members report depression, social isolation and anger with disruption of family relationships [1]. All this increases the burden on social service and governmental agencies to provide support.

Although it is generally believed that they tend to have better outcomes than adults, children also have some unique consequences from their TBI. Because TBI frequently affects memory, concentration, vision, hearing, and impulse control, children frequently can not sustain their previous rate and levels of achievement. Educational systems are poorly prepared to meet the needs of these young individuals. Unless the school has a TBI-specific program, the child may even

be assigned to a group with severe emotional or psychiatric problems. Children with a TBI frequently have difficulties with their peers due to behavioral problems or difficulty comprehending social cues [1]. Parents face significant parenting challenges as they confront changed academic aspirations and goals. Parental denial has been identified up to 10 years after injury [16], and certainly may be a significant impediment to rehabilitation and recovery.

Prognosis for Recovery

Although death or profound disability can be predicted for most patients within hours to days after injury, the estimation of the eventual functional outcome for those less severely injured is much more difficult. In the early phase of coma, the prognosis for patients cannot routinely be reliably distinguished between those who will never regain consciousness or recover with catastrophic neurologic deficits and those who will recover with minimal deficits. Penetrating injuries, increasing age above 50, abnormal pupil response, low post-resuscitation Glasgow Coma Scale Score, increased intracranial pressure, low cerebral blood flow, and pre-hospitalization hypoxia and hypotension all suggest a poorer outcome [17]. Duration and length of coma as well as duration of post traumatic amnesia (the period of time during which the patient can not store new memory) has a clear predictive value in individuals with DAI [18]. Due to the marked variability in type, location and degree of pathological changes following a TBI, as well the equally ubiquitous variability in pre-morbid organic and psychological functioning, the prediction of outcomes and residual deficits following a TBI will always remain an educated guess.

What is Available for Rehabilitation?

Rehabilitation of individuals with moderate-severe TBI is a long term multifaceted process. The goal of restoration of sensory, motor and communicative skills is combined with the goal of improving cognitive, social and behavioral functioning. It therefore involves the management of ongoing and developing medical conditions, as well as ongoing and developing cognitive, psychological and social issues. Experienced clinicians in multiple disciplines must work together in coordinated teams. Although *formal* rehabilitation is eventually time limited due to financial restraints, in actuality, rehabilitation is a life-long process.

There are innumerable approaches to TBI rehabilitation, especially at the post-acute phase. Community reentry programs, out-patient programs, comprehensive day programs, residential programs, neurobehavioral programs and home-based rehabilitation programs are all being utilized. Unfortunately, due to the numerous confounding variables previously cited, rigid conclusions regarding the effectiveness of each type of program are difficult.

Restorative training focuses on improving specific cognitive functions. Compensatory training focuses on enhancing the capability of the individual to adapt to the presence of a cognitive deficit. Comprehensive programs will blend both approaches. Cognitive exercises, including computer based treatments have been utilized with isolated successes. Psychotherapy is used to treat depression and loss of self esteem.

Pharmacological agents have been used for behavioral disorders. Antidepressants, anticonvulsants, major tranquilizers, anxiolytics and stimulants have all been utilized. Unfortunately, there are very few well controlled studies of these medications in TBI. It is also felt that individuals with a TBI are more likely to experience medication side effects that the non-injured population. The choice of medications for the symptoms from a TBI therefore has remained to the great extent, empirical.

Previously cited studies now have identified hypopituitarism in a significant number of individuals who have sustained a TBI. Until recently, the commonality of symptoms of a TBI and the symptoms of hypopituitarism has not been appreciated. Hypothyroidism can cause: fatigue, weakness, somatic complaints, poor concentration and memory. Similar symptoms are seen in adrenal cortical insufficiency [19]. Testosterone replacement in hypogonadal men has resulted in decreased anger and irritability, and increased libido and energy [20]. Symptomatic post menopausal females receiving hormone replacement have shown improved verbal memory, reasoning, vigilance and motor speed [21]. Studies of the effects of replacement in growth hormone deficient adults have shown improved psychological well being, energy levels and lean body mass [22], as well as improved memory and concentration [23].

Although treatment studies are now in progress, the effects of replacement therapy for post traumatic hypopituitarism are presently unknown. What is known, however, is that the majority of treatments for TBI are merely symptomatic. It is the hope of TBI survivors, their care givers and health care providers that we may soon be able to treat the primary underlying cause of those symptoms, restoring what was lost due to the injury, and thus produce a better outcome and improved quality of life.

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