Rehabilitation Considerations for Traumatic Brain Injury in the Geriatric Population: Epidemiology, Neurobiology, Prognosis, and Management

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Abstract Traumatic brain injury (TBI) is a leading cause of morbidity and mortality in the United States, and the incidence has been increasing within the geriatric age group as the population ages. There are many factors that are unique to this subgroup, including normal aging processes, differences in pathophysiology, and inherent medical comorbidities that affect their outcomes, treatment, and therefore, the allocation of medical and social services. The geriatric population has age-appropriate strength, coordination and balance deficits that make them predisposed to falls and subsequent TBI. The aging brain often has premorbid atrophy and increased susceptibility to the inflammatory, excitatory, and vascular processes that facilitate neurologic damage during the acute phases after injury. The aged also can have premorbid neurodegenerative and medical comorbidities that also affect their rehabilitation course, recovery, and outcomes once a TBI has occurred. Pharmacological strategies to maximize rehabilitation and recovery require specific considerations of the potential for adverse effects and contraindications specific to common comorbidities in the aged population. The management of geriatric TBI requires a coordinated effort between physicians and other healthcare providers with focus on risk factor modification, medical optimization, and successful return to the

community by setting goals that emphasize level of function and quality of life.

Keywords Traumatic brain injury · Elderly · Geriatrics · Etiology · Pathophysiology · Dopamine · Glutamate · Neuroprotection · Neuroendocrine disorders · Hypogonadism · Sex hormones · Estrogen · Progesterone · Neurodegeneration · Alzheimer's disease · Parkinson's disease · Functional outcomes · Neuropharmacology · Anticholinergics · Antihistaminics · Antipsychotics · Antiepileptics · Fall prevention · Neurostimulants · Rehabilitation

Introduction

Traumatic brain injury (TBI) is a leading cause of mortality and long-term disability with an estimated 1.7 million related deaths, hospitalizations, and emergency department visits yearly within the United States [1]. Over 323,000 of these injuries involve persons older than 55 years [1]. It is also estimated that at least 5.3 million Americans have long-term needs for assistance with activities of daily living as a result of TBI [2]. Adults that are 75 years or older, have the highest rates of TBI-related hospitalization and death in the United States [1]. It recently has been demonstrated that elderly patients have a lower Glasgow Coma Score on presentation, an increased incidence of a midline shift on computed tomography (CT) scans, and an increased likelihood of sustaining a fatal injury following TBI [3, 4]. Older patients have higher rates of premorbid functional deficits [4]. They also have more chronic diseases with a decreased physiologic reserve for organ systems other than their brains [4, 5, 6]. It has been demonstrated, however, that age is an independent predictor of worse outcome, even when the data are adjusted for comorbid disease [5, 7, 8].

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Economic Data

It is argued that aggressive treatment of even severe TBI is a cost-effective option for all patient ages, including those older than 80 years [9]. Overall, the post-injury cost of care in the elderly is high, but research in this area is limited. In 2003, the aggregate hospital charges in the US for treating TBI in patients older than 65 years exceeded \$2.2 billion [7]. When comparing subgroups within the older population, the age range of 75–84 years demonstrated significantly higher numbers of rehospitalizations, home health visits, and hours of unpaid care compared to 55-to-74-year-old patients 1 year after a TBI [4•]. Acute care resource consumption per favorable outcome is greater in older patients compared to younger patients after TBI [6].

Trends

In the US from 2002 to 2006, the number of emergency department visits for TBI in the geriatric population increased by 46 %, hospitalization rates increased by 34 %, and deaths increased by 27 % [1]. Not only are TBI rates increasing within this age group, but also it is well established that the geriatric population is getting larger. Thus, the aging population further contributes to the increasing numbers of geriatric patients with TBI, and this trend demonstrates why it is imperative that we understand the complexities and unique issues with regard to rehabilitation in the aged population with TBI.

Etiology

In the U.S. from 2002 to 2006, falls were by far the leading cause of TBI in adults older than 65 years, accounting for about two thirds of geriatric TBI. Motor vehicle accidents were a distant second at 7.9 %, with a slight preference for low-velocity vehicle-on-vehicle accidents (<20 mph) and pedestrian versus vehicle accidents occurring in crosswalks and in parking lots [1].

It is estimated that 30–40 % of community-dwelling older adults fall at least once a year, with 10 % resulting in significant injuries such as TBI [10, 11]. Many factors come into play when evaluating fall risk in these patients. Generally, these factors can be divided into normal aging processes versus medical comorbidities and polypharmacy.

The strongest risk factors for falling appear to be a prior history of falls, muscle strength deficits, balance and gait impairments, and the use of specific medications. Other risk factors for fall commonly documented in the elderly include urinary incontinence, anemia, arthritis and cognitive decline. Adult women more frequently sustain

fractures with their falls, and this phenomenon is likely associated with their increased risk of osteoporosis and lower body mass compared to aging men [11, 12]. Visual deficits are also common in this population. Visual impairments, including a reduced ability to detect low-contrast hazards, judge distance, and perceive spatial relationships, can increase fall propensity [13].

Depression is common in the elderly population, and depression is known to be an independent risk factor for falls [14•]. The relationship between depression and fall risk is complex. Depression negatively affects attention, executive functioning, and processing speed, all of which contribute to impaired gait performance [14•]. Side effects of medications commonly used to treat depression likely also play a role in the association between depression and increased fall risk. These include selective serotonin reuptake inhibitors (SSRIs) and tricyclic medications, which can have the side effects of orthostatic hypotension and impairment of postural control, especially within the first few weeks of initiating therapies [14]. Depression also negatively affects sleep patterns and can decrease appetite, contributing to nutritional deficiencies, both of which can increase the risk for falls [14•].

Medical comorbidities also increase fall risk in the elderly. Diabetes in the setting of peripheral neuropathy affects proprioception and increases the tendency for falls. Tight glycemic control, especially with insulin, has been cited as increasing the incidence of hypoglycemia-related falls, whereas a more liberal control using oral hypoglycemics seems to actually decrease fall risk. Syncope is another understudied etiology of geriatric falls and TBI. Non-cardiovascular causes account for the largest proportion of syncopal episodes, when a cause could be determined, and include orthostatic hypotension, vasovagal response, and drug-induced syncope [12]. Cardiovascular causes accounted for almost a quarter of syncopal episodes, with arrhythmias and heart block being the most common mechanisms [12].

While hypertension, heart failure, arrhythmias, and depression increase fall risk in the elderly, so do the medications commonly used to treat these diseases. Psychoactive medications, such as antipsychotics, antidepressants, and sedatives, as well as antihypertensive medications, and antiarrhythmics are most frequently linked to increased fall risk [11]. Anticoagulant use before a fall has been linked to traumatic intracerebral hemorrhage, need for admission to intensive care units, and mortality [15, 16]. While anticoagulants increase the likelihood of sustaining an intracerebral hemorrhage, they also may have a modest neuroprotective quality, by countering the hypercoagulable state that follows trauma [17, 18]. However, newer anticoagulant medications are increasingly being used in the elderly population with atrial fibrillation. Lower-dose direct thrombin

inhibitors like dabigatran, and the selective inhibitors of factor Xa, an enzyme within the coagulation cascade, such as rivaroxaban and apixaban, are considered equally effective in stroke prevention and to have an improved safety profile with less risk for hemorrhage when compared to warfarin, regardless of the average time spent in therapeutic range on warfarin [19–21]. The effects that these medications have on TBI incidence and outcomes, compared to other anticoagulants as well as controls, has yet to be studied. After TBI, anticoagulants are often considered a necessary part of their medical care to reduce risk of other complications and comorbidities, and lower risk agents like the ones described above may be an effective treatment alternative for rehabilitation practitioners to reduce risk for recurrent TBI in the aging population.

Acute Pathophysiology

Geriatric patients will experience the same general injury patterns as the younger population following TBI. It is clear, however, that there are key differences in the pathophysiology, and much is still to be learned about how age affects these complex processes. Older brains typically have atrophy that advances with age. With a smaller sized brain, bridging veins must traverse a greater distance, and the brittle nature of these veins with age makes this population more susceptible to venous tears and the development of subdural hematomas following head trauma. Brain tissue undergoes long-term progressive atrophy following a TBI [22–24], which further accelerates brain atrophy associated with aging.

Secondary injury occurring after TBI involves cerebral edema, disruption of cerebral blood flow and metabolism, inflammation, excitotoxicity, oxidative damage, and general disruption of ion homeostasis leading to cellular injury and death. Cerebral edema results in elevated intracranial pressure and decreased cerebral perfusion pressure. At the cellular level, excitotoxicity can result in neuronal and astrocyte swelling secondary to an influx of sodium and chloride and the overabundance of excitatory amino acids (EAA's) such as glutamate [25–27]. Excess EAA's also result in increased intracellular calcium, leading to the production of free radicals, and subsequent oxidative damage to DNA and cell membranes that ultimately result in cell death [28]. A significant inflammatory response can facilitate blood–brain barrier disruption, cerebral edema, and cell death by contributing to many secondary injury mechanisms, including excitotoxicity [29].

Susceptibility to glutamate-mediated oxidative damage to DNA and cell membranes increases with advanced age [30, 31]. This phenomenon likely results in a greater amount of cell death for elderly persons following a TBI. Excitatory amino acid receptors are distributed more densely in certain

brain regions, such as the hippocampus, which therefore, has an increased vulnerability to excitotoxic damage following traumatic injury [32, 33]. The hippocampus is heavily involved in learning and memory, and it has been demonstrated that selective hippocampal damage is also more severe with advanced age [33]. Free radical damage to neuronal DNA and cell membranes also results from mitochondrial dysfunction that develops following a TBI. Baseline mitochondrial function is decreased in the older population, and reduced function is likely to negatively affect the secondary injury response observed in older patients [34]. When aged brains are compared to their younger counterparts following experimental TBI, there are decreased levels of antioxidant enzymes, increased free radical production, increased lipid peroxidation, and decreased neuronal survival near damaged areas [35•]. Elevations in systemic inflammation have been linked to cognitive deficits, independent of other risk factors within the elderly population [35•, 36], and it is likely that both systemic and the central nervous system (CNS) inflammatory responses following TBI also have greater effects in older patients, though this needs to be studied further.

Endocrine

Neuroendocrine disorders are quite common after TBI, typically occurring secondary to hypothalamic and pituitary gland dysfunction [37, 38]. These disorders are complex and negatively impact patient cognition and other related outcomes. Many TBI patients will develop chronic growth hormone deficiency, hypothyroidism, and hypogonadism, each of which can occur with aging, but are also particularly common within the elderly population post-TBI. It is therefore important to check these laboratory values routinely in the elderly TBI patient [39] and provide appropriate hormone replacement to optimize their recovery.

The role of sex hormones and sex in TBI neurologic protection is complex. The experimental literature suggests that the provision of female sex hormones can attenuate oxidative damage [40] and lessen the evolution of other secondary injury cascades that occur early after TBI [41]. Also, increasing evidence shows that progesterone can improve mortality and outcomes following a TBI, via effects on vascular remodeling, restoration of the blood–brain barrier, and attenuating edema, inflammation, and cell death [42–44]. Estrogen therapy can provide these neurologic protective effects in both men and women [43, 44], but specific effects in the aging patient with TBI are unclear. However, recent data in experimental stroke models using aged animals show that progesterone can attenuate damage, suggesting that hormone treatments may be

beneficial specifically in the aging population with TBI. Despite the known neuroprotective effects of sex hormones on TBI pathophysiology, endogenous gonadal hormone production is severely reduced in the clinical population after severe TBI. Peripheral hormone production from extragonadal sources, particularly estradiol production, is increased with older age, and this phenomenon is linked to poorer outcomes [45•]. Thus, the effects of hormone therapies clinically on post-injury hormone profiles and specific markers of secondary injury should be monitored carefully, and the influence of aging on hormone therapy effectiveness monitored. Chronic hypogonadism occurs frequently and negatively impacts both cognition and outcome [46•]. Given the prevalence of hypogonadism with the aged, the effects of post-traumatic hypogonadism on recovery in the older population with TBI merits further study [47].

Neurodegeneration

Chronic neurodegenerative changes occur after both clinical and experimental TBI, including ongoing cerebral atrophy and accelerated development of histopathological markers associated with aging and dementia [22]. Further, a progressive cognitive decline has frequently been described, especially within the geriatric population [22].

Alzheimer's Disease, Dementia, and TBI

TBI is a reported risk factor for the development of Alzheimer's disease (AD) with increasing severity of injury positively correlating with increased risk of developing the disease [48, 49]. There are striking histological similarities between TBI and AD, including the presence of extracellular amyloid beta plaques and neurofibrillary tangles [48, 49•]. Axonal damage, and the accumulation of amyloid beta substrate proteins within the damaged axons, are common to both TBI and AD [49•, 50•]. Several key proteins, including amyloid precursor protein (APP), as well as axonal degeneration and dysfunctional axonal transport can persist after TBI [49•, 50•]. It is well established that carriers of the apolipoprotein epsilon 4 (APOE4) allele have a higher risk of developing AD. Interestingly, some studies suggest that APOE4 carriers who sustain a TBI tend to have more severe cognitive deficits, an increased likelihood of developing dementia, and a slower overall recovery rate than TBI patients without this allele [49•, 50•, 51, 52]. TBI-induced histopathology associated with dementia has significant implications for ongoing dysfunction and slowed recovery in the elderly.

Aging, Parkinson's disease, and Dopamine System Function with TBI

The literature suggests that patients with TBI may be at increased risk for Parkinson's disease (PD). Epidemiological evidence demonstrates that repetitive head trauma can increase the risk for development of PD significantly [53, 54]. Also, patients with PD are at an obvious increased risk for sustaining a TBI secondary to their increased fall risk. These patients also may be at risk for worse outcomes secondary to multiple mechanisms of insult associated with the already depleted dopamine (DA) neurotransmitter systems that occur with PD [55]. Following TBI, there are changes in CNS-DA levels secondary to multiple mechanisms [56, 57]. Long-term changes in DA transporter (DAT) expression, as well as changes in other DA system proteins, are seen within the cortex and striatum [58–60]. This is accompanied by changes in postsynaptic secondary signaling mechanisms and presynaptic DA synthetic enzymes following TBI [61]. The concentration of DAT within the basal ganglia declines as a normal course of aging, and in a more accelerated fashion in PD, while DAT is the most important factor determining concentrations of extra-neural dopamine as well as its duration of action [60]. A reduction in DAT availability expression that occurs following a TBI has some similarities to that observed in PD, but may also be a compensatory response to augment DA transmission [60]. However, evidence supporting that TBI predisposes to the development of PD, and that TBI in the setting of PD can exacerbate the disease course, includes the presence of alpha-synuclein deposits in both conditions [62, 63]. Clinically, it is common to find that the medication dosages for PD patients frequently need to be increased in both the acute and sub-acute periods following TBI. Our experience suggests that elderly TBI patients frequently present with Parkinsonian-type symptoms but did not have symptoms before injury. It is likely that many of these patients already had developed subclinical PD that does not present clinically until after their TBI.

Functional Outcomes

Elderly patients tend to have worse global outcomes, with lower physical and cognitive functional independence measure (FIM) scores following TBI that result in longer lengths of stay in the acute setting and increased percentage of discharges to inpatient rehab or long-term care facilities regardless of TBI severity [64–66]. Inpatient rehabilitation length of stay and costs tend to be higher in the elderly as well [64, 67]. They make similar functional gains as their younger counterparts, although they tend to have greater overall disability at

both admission and discharge from acute inpatient rehabilitation and tend to improve at slower rates [68]. While most elderly TBI-patients are discharged to a community setting, they make up a significantly smaller proportion of the community-discharge population when compared to younger patients [65, 66, 68]. Also, a smaller proportion of the older patients who were working before their TBI will return to work sometime following their injury [65, 66, 68]. These issues with rehabilitation recovery rates are even more pronounced in patients that are older than 75 years [1, 3, 4].

Comorbidities

While age is an independent risk factor for poor outcome following TBI, the increased prevalence of medical comorbidities in the older population also plays an important role in outcome [69]. These patients have a higher incidence of diabetes, hypertension/hypotension, pulmonary disease, poor nutrition, cardiovascular disease, and premorbid dementia, all of which can contribute to outcomes following TBI. Diabetes mellitus is an independent risk factor for mortality following TBI, and outcomes are worse with premorbid insulin dependence [70]. Hypoglycemic episodes can exacerbate glutamate-induced excitotoxicity and are associated with increased extracellular cerebral lactate [71–73] and decreased seizure threshold. Hyperglycemia also impairs cerebral perfusion, promotes acidosis, induces oxidative stress, promotes excitotoxicity, and exacerbates blood–brain barrier disruption [71, 74–76]. Diabetic management after an acute TBI is controversial. However, the current consensus is to maintain moderately well-controlled glucose levels, avoiding excessively hyper- and/or hypoglycemic values in the acute setting post-TBI [71, 77].

Elderly persons also tend to have an increased tendency for being malnourished. Early enteral nutrition following TBI can improve outcomes and may exert beneficial effects on early cortisol, TSH/T3/T4, and testosterone following TBI [78, 79]. Therefore, nutritional support is particularly important in the premorbidly malnourished older patient. Monitoring pre-albumin levels is also especially important in this population. With the higher prevalence of osteoporosis, bone fractures are more frequently associated with head injuries in older individuals, and studies suggest that femur fractures, combined with TBI, increase overall humoral inflammation [80]. Systemic levels of proinflammatory cytokines are higher when a TBI occurs in conjunction to additional traumatic injuries compared to isolated head trauma [81]. Elevated peripheral inflammatory levels may be associated with worse outcomes after a TBI.

Pharmacology and Neurologic Recovery with TBI Rehabilitation in the Elderly

During the rehabilitation process, careful attention should be given to commonly prescribed medications that could impact neurological recovery in the elderly TBI patients. All patients with TBI, and elderly patients in particular, are also more likely to experience side effects from anticholinergic medications [82]. These include minimizing the use of anticholinergic, antidopaminergic, and antihistamine drugs, each of which are commonly used as agitation management, urinary, bowel and sleep maintenance medications [83]. Benzodiazepines for anxiety and atypical GABA agonists for sleep disturbances are also very commonly used in the elderly, and their use can negatively impact recovery following TBI [84]. Other options for insomnia, particularly in older patients with TBI, can be considered and include melatonergic (ramelteon) and serotonergic medications (trazodone and mirtazapine) [84].

Several medications that are commonly prescribed to patients following a TBI have increased side effect frequency and severity especially in the elderly. Typical antipsychotics, commonly used to control insomnia and agitation, are often used in geriatric patients, and have been demonstrated to delay motor recovery and spatial learning following TBI [83, 85]. Prolonged use of antiepileptic medications such as phenytoin also negatively impacts neurological recovery, and when possible, the duration should be reduced to the acute period when used for post-traumatic prophylaxis [86, 87]. Recent studies, though, suggest that levetiracetam may have similar efficacy to phenytoin for prophylaxis, and also may have significant neuroprotective qualities when administered daily after TBI [88].

Elderly patients with TBI may require pharmacological treatment for issues that can impede rehabilitation participation and recovery, like post-traumatic depression (PTD) and cognitive deficits. Many of these approaches are similar to the approaches used in treating younger patients with TBI. However, some differences warrant consideration. Dopamine agonists like methylphenidate can increase arousal, rehabilitation participation, and both motor and cognitive processing speed. There are some concerns with these medications regarding increased risk for cardiovascular side effects including hypertension and arrhythmia [89, 90]. Safety studies in TBI suggest that these drugs are generally safe. Though its use has not been heavily researched in the elderly TBI patient, methylphenidate is used in geriatric depression [91]. However, close monitoring is still recommended when using these drugs in the geriatric population, and caution may still be necessary when considering these types of drugs in patients with known significant

arrhythmias and other serious premorbid cardiovascular conditions. DA precursors, like L-dopa, may be considered to enhance cognition, mood, and participation in those with new onset Parkinsonian features after TBI. SSRIs are often used to address PTD. PTD risk may be linked with genetic predilection at the serotonin transporter [92]. Similarly, geriatric depression [91, 93], and associated effects of SSRIs in the geriatric population [91, 94–96], including mirtazapine, may be genetically linked. However, more work is required in this area to understand the clinical treatment impact of these drugs in the geriatric population after TBI. Also, SSRIs carry a number of contraindication and drug interaction warnings, including warfarin and antipsychotic use, that may require special consideration regarding use in the geriatric population with TBI [97]

Fall Prevention in the Elderly with TBI

Head trauma prevention plays a key role in improving and maintaining the overall health of the elderly population. With falls being the leading cause of TBI in the elderly, efforts to prevent falls should be taken whether it is while they are in the hospital, long-term care facility, or the community setting. Even after TBI, risk for recurrent fall and TBI is significant, and approaches to prevent recurrent injury are a high priority. Older patients are highly susceptible to delirium-associated falls in the hospital setting [98]. Steps to prevent and/or treat delirium outlined by the Hospital Elder Life Program include frequent orientation, therapeutic activities, early mobilization, the use of proper glasses and hearing aids, volume repletion, and proper sleep hygiene [99, 100]. There is limited research on physical and environmental modifications/enrichment, but hospitals, inpatient rehabilitation units, and other inpatient sub-acute settings are using these types of strategies as part of their fall prevention programs. Ensuring adequate room lighting and reducing unnecessary lines, tubes, and physical restraints, along with incorporating the use of low beds, padded floors, and bed alarms, are common approaches instituted by programs working with the elderly in this regard.

Once elderly patients return to the community setting after rehabilitation, these safety initiatives should be extended to their home environment, starting with a comprehensive home assessment geared towards minimizing fall risk [101]. Observing patients in their homes helps the rehabilitation team formulate and implement individualized therapy goals, with emphasis on energy conservation and negotiating physical barriers. Once the patients have mastered their home environment, their safety and prevention goals can be expanded into community reintegration and directed toward improved cardiovascular endurance,

improved dynamic balance, and the ability to negotiate obstacles such as curbs, ramps, and uneven terrain. Instituting exercise and physical therapy programs into outpatient rehabilitation and wellness programs for older patients with TBI significantly reduces fall risk, especially when balance retraining is incorporated [102]. These balance-training programs also improve confidence by reducing fear of falling, therefore improving overall quality of life and improving community integration [102, 103]. A 15-week course of tai chi also has been shown to significantly reduce fall risk [104].

As previously discussed, numerous medications that are commonly prescribed in the elderly population can increase fall risk. After TBI, elderly patients are often placed on medications that could further increase fall risk in this vulnerable population. The rehabilitation period after TBI is often a good time to review medications and remove unnecessary medications that may increase falls and risk for recurrent TBI. Psychotropic medications are associated with increased fall risk [105], and careful review and withdrawal of those medications can reduce falls in the elderly [102, 105, 106]. Aggressive blood pressure management increases the chance for developing orthostatic hypotension in older adults, which can contribute to fall risk. This situation warrants extra caution and frequent monitoring of blood pressures by the patient's primary care physician.

Multidisciplinary Team Approaches to Rehabilitation in the Elderly

Maximizing rehabilitation potential in the elderly patient with TBI can be challenging from both a medical and psychosocial perspective. As such, a multidisciplinary team approach that includes psychiatrists, primary care physicians, nurses, therapists, psychologists, social workers, and home care providers offered through inpatient rehabilitation programs can be extremely helpful in managing the medical and discharge planning complexities that are required for optimal outcomes. Medical complications often occur in association with poor transitions of care from their acute hospitalization to inpatient rehabilitation and also during transition back into the community. The utmost importance should be placed on high quality multidisciplinary communication to and from multiple providers as patients negotiate these transitions. When the elderly patient with TBI returns to the community setting, it is crucial that their recent medical course, newly acquired medical conditions, and their new management strategies are properly communicated to their primary care physicians. It is also highly important to provide proper communication and teaching to the patients' families so they can take an active role in their care once discharged from the acute or sub-acute setting.

Coordination of community care through home health services, follow-up appointments with physician-based primary and specialty care, and establishing plans for ongoing therapies can ensure the safest possible transition back to the community setting.

Conclusions

The incidence, risk factors, pathophysiology, complications, and rehabilitation course for elderly patients with TBI is unique. However, understanding how each of these elements plays into recovery and potential for community reintegration is essential for optimizing outcome. Further, understanding the unique neurobiology and medical management issues for this population also may shed light on new therapeutic targets, venues for research, and best practices for optimizing rehabilitation outcomes for the TBI population in general.

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