Journal of Gerontology & Geriatric Research
ISSN: 2167-7182

Tobe, J Gerontol Geriatr Res 2016, 5:2
DOI: 10.4172/2167-7182.1000292

Mini Review Open Access

Geriatric Traumatic Brain Injury: Relationship to Dementia and Neurodegenerative Disease

Edward H Tobe*

Cooper Medical School of Rowan University, New Jersey, USA

***Corresponding author:** Edward H Tobe, Cooper Medical School of Rowan University, 1001 Lincoln Drive West Suite B, Marlton, New Jersey, USA, Tel: 18563612850; E-mail: Edward.tobe@comcast.net

Rec date: Feb 26, 2016; **Acc date:** Mar 09, 2016; **Pub date:** Mar 14, 2016

Abstract

The author explores a hypothesis that the elderly are vulnerable to traumatic brain injury (TBI) precipitating or accelerating dementia or neurodegenerative diseases due to intracellular changes in physiological resilience. Bearing in mind the global human experience, biologic resilience is vulnerable to a vast number of human created and natural conditions. Respectfully, this paper focuses on the role of certain cultural biases, aging, genetic factors, synaptic efficacy, and intracellular enzymatic balance. Clinical vigilance enables diagnosis and treatment leading to improved quality of life.

Keywords: Dementia; Traumatic brain injury; Geriatric; Neurodegenerative disease

Introduction

The USA Centers for Disease Control and Prevention (CDC) has defined traumatic brain injury (TBI) as injury caused by a bump or blow to the head or by a jolt of the head. The severity of a TBI may range from "mild" (i.e. a brief change in mental status or consciousness) to "severe" (i.e., an extended period of unconsciousness or amnesia after injury) [1]. The CDC has collated data about incidence and cause of TBI from 2006 through 2010 [1]. These data reveal that falls are the most common cause of TBI among infants and children aged to 4 years and among adults aged 65 years or older. The statistically significant number of TBI-related events among the geriatric population can prompt a sharpening of diagnostic questions about short- and long-term consequences, including neurodegenerative disease.

There are unnecessary clinical obstacles to identifying the consequences of a TBI. Some clinicians mistakenly conclude that pathology from TBI is ruled out in the context of either brief loss or no loss of consciousness combined with benign results from a computed tomography (CT) scan of brain. Nuances of pathophysiology are not discernable with CT. "TBI is referred to as the invisible epidemic. These disabilities, arising from cognitive, emotional, sensory, and motor impairments, often permanently alter a person's vocational aspirations and have profound effects on social and family relationships" [1].

Certain behaviors of injured individuals may encourage others to ignore the signs and symptoms of a TBI. For example, the youthful individual may want to preserve an illusion of invincibility; the athlete may want to reenter the contest; and an elderly person may want to ward off fears of impermanence.

A TBI challenges the resilience of impacted tissue. Areas of the brain vary in susceptibility to different types of trauma [2]. Whether partial or full recovery develops or deterioration becomes progressive depends upon numerous variables. The author (ET) hypothesizes that TBI results from metabolic stress imposed on intracellular mitochondria. Because of advancing age, the geriatric patient experiences losses in physiological adaptive response and physiologic reserve, as well as elevated vulnerability to the onset of neurodegenerative disease and dementia. To explore this hypothesis, ET provides a brief review of intracellular response to metabolic stress.

Biologic Resilience: Genetic Factors, Synaptic Efficacy and Intracellular Enzymatic Balance

An individual's biologic resilience has genetic roots expressed by nuclear and mitochondrial DNA (mtDNA). Mitochondria are the primary energy sources of the cell, and mtDNA is uniquely inherited from the mother. It is theorized that mtDNA originated evolutionarily as a product of engulfed, circular, haploid genetic material, mostly of bacterial ancestry-a very different origin than the diploid nuclear DNA. There is evidence that specific haploids may determine the outcome of physiological stress by providing a protective "physiologic reserve" [3]. Over the course of hundreds of thousands of years of evolution, the genetic lineage of mitochondrial survivors presumably came to contain the most adaptive haploids, in reference to mtDNA.

All human cellular functions require energy generated mostly through mitochondrial oxidative phosphorylation, which creates adenosine triphosphate (ATP) from adenosine diphosphate (ADP). ATP is generated through the respiratory process and an electron transport chain, with ADP being converted to ATP through oxidative phosphorylation within the mtDNA. The electron transport chain's last electron acceptor is molecular oxygen (O_2), creating superoxide (O_2-) that is metabolized to hydroxyl (–OH) and hydrogen peroxide (H_2O_2). If certain metals bind with superoxide, the result is an aggressive oxidation. Reactive oxidative species (ROS) are free radicals (molecules with one unpaired electron). In its lowest energy state, O_2 has two unpaired electrons with similar spin orientation in its outer electron orbit. If one of the unpaired electrons is excited, the electron orbit changes so that the O_2 becomes destabilized [4]. Excessive ROS potentially oxidizes intracellular proteins, lipids, mtDNA, and nuclear DNA, opening the mitochondrial permeability transition pore and

causing mitochondrial swelling and release of apoptotic effectors. The capacity for modulation of enzymes is crucial for cell survival, with potentially helpful molecules, under different circumstances, becoming harmful. For example, although ROS can be destructive through oxidation, lower concentrations of ROS may function as an intracellular signal transduction regulator [5,6].

Mitochondria are not fixed in location within the cell. Rather, the energy needs of the intracellular microenvironments determine the location of the mitochondria. The endoplasmic reticulum forms a network of tubules and cisternae throughout the cytoplasm, with an inhomogeneous distribution of calcium uptake and release sites. Cytoplasmic signals converge in the endoplasmic reticulum to form spatiotemporally controlled patterns of calcium release [7]. In brain cells, the endoplasmic reticulum has two release channels for calcium ions: inositol 1,4,5-triphosphate receptor and ryanodine receptor type 3. Mitochondria linked to the inositol 1,4,5-triphosphate receptor and ryanodine receptor channels control local calcium release and cytoplasmic calcium regulation [8]. Essentially, each cell has multiple microenvironments. Failure of one environment may precipitate a cascade of metabolic changes that alter cellular morphology and synaptic efficacy.

Mitochondria are involved in numerous metabolic activities, including the urea cycle, lipid metabolism, porphyrin synthesis, and homeostasis of steroid hormones. Calcium ions stimulate oxidative phosphorylation, upregulate the creation of ATP, and affect the metabolism of other molecules. Calcium ions enter the mitochondria via a regulated outer and inner mitochondrial membrane process. The efflux of calcium ions is dependent on sodium exchange. Glutamate stimulates plasma membrane influx of calcium ions, and glutamate synapses are tripartite, including the presynaptic neuron, postsynaptic neuron, and glial cell. There is evidence that the overstimulation of N-methyl-D-aspartate receptors by glutamate may cause excessive calcium ion influx, which compromises mitochondrial membrane polarity. Glutamate overstimulation may increase ROS oxygen species, leading to cellular compromise [9].

Among the enzymes that regulate the intracellular microenvironments are the two isoenzymes monoamine oxidase A and B (MAO-A and MAO-B) and superoxide dismutase (SOD). Enzymes are catalysts that lower the threshold of energy needed to enable a reaction. Through oxidation, the MAO enzymes deaminate biogenic amines, including neurotransmitters. The function of MAO, which is attached to the outer membrane of the mitochondrion, is influenced by its immediate microenvironmental pH level, ion concentration, and heat [10]. SOD is an enzyme that partitions the unstable oxygen molecule (O_2-) to produce hydrogen peroxide (H_2O_2) and/or molecular oxygen (O_2). SOD protects the cell against oxidative stress.

The intracellular stress of TBI requires increased production of ATP. Aging mitochondria have an impaired rate of electron transfer, especially in regard to respiratory complex I and complex IV [11]. As people age, the concentration of MAO-A does not change, but the concentration of MAO-B increases [4] and the concentration of SOD diminishes. The increase of MAO-B enables a corresponding increase of ROS through the deamination of biogenic amines. The lower concentration of SOD creates less ability to partition superoxide.

Diminished Biological Reserves

As a result of the oxidative stress that occurs after TBI, the most effected and/or vulnerable areas of brain will manifest signs and symptoms of disease. This process is similar to that of depression, in which areas of the brain vulnerable to oxidative stress predict presentation of mood disorder [4]. The resultant metabolic trauma of TBI may not remain stable [2].

The International Classification of Disease-10 defines 'Mild Cognitive Disorder', F06.7, (comparable with Mild Cognitive Impairment) as presenting with diverse cognitive impairments, differentiated from postencephalitic syndrome (F07.1) and postconcussional syndrome (F07.2) by etiology, usually 'milder symptoms' and 'shorter duration'. This nosology is confusing. Shorter duration assumes significant or complete recovery. If mild is diagnostically differentiated from dementia or delirium by severity, mild becomes a misnomer that might represent a very disabling condition. Repetitive or continuing trauma is associated with a pattern of initial mild cognitive disorder followed by increased risk of early onset of dementia, even in the absence of further brain insult.

Patients with genetic neurodegenerative disease may be at risk for an early onset of the diseases induced by TBI, such as Parkinson disease, Lewy body dementia, amyotrophic lateral sclerosis, and Huntington disease. These diseases are synucleinopathies, one or more of which develop when the protein α-synuclein is mutated. If the pathology affects the substantia nigra, the presentation is Parkinson disease. In this disease, the oxidative stress detaches α-synuclein from the cell membrane, and the synuclein proteins begin to intertwine, forming inclusion bodies. The inclusion bodies may contain tau protein and synuclein within the same cell.

Tau proteins help stabilize microtubules involved in intracellular transportation. There are numerous tauopathies affecting different areas of the brain and different neural cells, and there is a delicate balance between intracellular and extracellular tau protein. The pathological development of tangles, which occurs as proteins coalesce, leads to cellular death. Tauopathy does not only affect the neurons, but "…overexpression of human tau in glial cells results in the formation of hyperphosphorylated and aggregated tau moieties." [12].

Future Options

Because of the suggested co-relationship between TBI and neurodegenerative diseases, advances in diagnosing and treating the early phases of neurodegenerative disease may permit interventions to mitigate its evolution. One example of progress is the documentation of a relationship between the abnormal presence of deposits of amyloid and Alzheimer Disease. The most extensively studied and perhaps best validated tracer has been 11carbon-labelled Pittsburgh Compound-B (11C-PIB) [13]. Rabinovici et al. demonstrated a correlation between 11C-PIB imaging and Mini Mental State Examination scores [13].

A visual evaluation of the FDG-PET can reveal pathologic metabolic changes in patients with TBI. The medical value of FDG-PET is vulnerable to technique and the human factor. Misreads of FDG-PET are due to a variety of factors such as: the reader assumes the test is performed to rule out metastatic cancer; glucose levels at the time of the testing were compromised; a lack of established protocol to specifically document "mild cognitive disorder" (mild cognitive impairment).

Neuropsychological testing is a shotgun approach searching for pathology but always with the suggestion of how much does the examinee's anxiety or depression interfere with the findings. Even in the presence of marked scattering of subtest scores, scattering that has

ranged well over two standard deviations from the examinee's mean, the significance of the scattering is debated by some neuropsychologists, especially in a forensic setting. The initial use of FDG-PET before neuropsychological testing can enable the evaluator to provide the necessary specific psychological testing that would further elucidate abnormal metabolic findings on FDG-PET. Treatment approaches can be significantly affected if for example FDG-PET shows basal ganglia pathology, which would question the use of dopamine blocking agents. FDG-PET may suggest non-motoric seizure disorder. This author has evaluated several patients with FDG-PET and discovered abnormal findings of seizure. Upon inquiry the patients admitted to hearing voices, without the presence of delusions or psychosis, or struggling with disturbing smells. In the incidence of olfactory hallucinosis, one patient was placed on antiepileptic medication that significantly ameliorated symptomatology. FDG-PET can monitor progress or deterioration.

Summary

The author has outlined why the elderly are vulnerable to a TBI:

- Increased incidence of falls
- Response to stress requires increase energy production
- Oxidative phosphorylation of ADP creates ATP and superoxide
- Age related increased concentration of MAO-B
- Age related diminished concentration of SOD
- Aging mitochondria slow the electron transport system to create ATP.

Overall, the intracellular microenvironments can become compromised, causing oxidations of essential biologically active molecules the altered metabolism of proteins, especially the tau and synuclein groups of proteins.

Impairment of a specific tissue provides an explanation for the varied signs and symptoms of dementia or various mood and cognitive disorders. Each neural cell is part of a chain of interacting cells. The disruption of cellular morphology and function without adequate physiologic reserve leads to a deterioration of vulnerable tissues. A physical insult-such as sudden acceleration-deceleration or inhalation of sulfur, carbon monoxide, mercury, or combustible smoke-may impact one brain area more than another. Brain tissue differences in degree of recovery or progressive deterioration based not necessarily on connectivity of brain areas (such as the hippocampus to the parahippocampus) but rather on the vulnerabilities of specific brain areas to a given insult [2]. Thus, some damaged cellular areas will progressively deteriorate, while other damaged areas may remain stable or partially reconstitute.

Regardless of whether this author's hypothesis eventually proves incorrect or too simplistic, this discussion will hopefully encourage clinicians to perform a special evaluation of the elderly to separate what might be labeled the "natural aging process" from a more debilitating disease. The high prevalence of TBI in the elderly should also encourage a longitudinal evaluation for the emergence of mild cognitive disorder, neurodegenerative disease, and dementia. Although there are no definitive treatments for these conditions, physicians should not feel disheartened. Functional imaging may provide improved insights into the pathological mechanisms, which will aid in treatment decisions. For example, a basal ganglia pathology would not be conducive to dopamine-blocking agents. Other pharmacologic approaches might include acetylcholinesterase inhibitors, partial glutamate agonists, direct stimulants, and various antidepressants, especially MAO-B inhibitors. A systematic therapeutic approach to environmental factors as well as to psychopharmacology could best enhance quality of life.

References:

1. http://www.cdc.gov/traumaticbraininjury/data/dist_ed.html
2. Tobe EH (2012) Progressive neuropsychiatric and brain abnormalities after smoke inhalation. BMJ Case Rep.
3. Baudouin SV, Saunders D, Tiangyou W, Elson JL, Poynter J, et al. (2005) Mitochondrial DNA and survival after sepsis: a prospective study. Lancet 366: 2118-2121.
4. Tobe EH (2013) Mitochondrial dysfunction, oxidative stress, and major depressive disorder. Neuropsychiatr Dis Treat 9: 567-573.
5. Brookes PS, Levonen AL, Shiva S, Sarti P, Darley-Usmar VM (2002) Mitochondria: regulators of signal transduction by reactive oxygen and nitrogen species. Free Radic Biol Med 33: 755-764.
6. Brookes PS, Yoon Y, Robotham JL, Anders MW, Sheu SS (2004) Calcium, ATP, and ROS: a mitochondrial love-hate triangle. Am J Physiol Cell Physiol. 287: 817-833.
7. SpAt A, Szanda G, Csordas G, Hajnoczky G (2008) High- and low-calcium-dependent mechanisms of mitochondrial calcium signaling. Cell Calcium. 44: 51-63.
8. Gao X, Xu X, Pang J, Zhang C, Ding JM, et al. (2007) NMDA receptor activation induces mitochondrial dysfunction, oxidative stress and apoptosis in cultured neonatal rat cardiomyocytes. Physiol Res 56: 559-569.
9. Gabay S, Achee FM, Mentes G (1976) Some parameters affecting the activity of monoamine oxidase in purified bovine brain mitochondria. J Neurochem 27: 415-424.
10. Navarro A, Boveris A (2010) Brain mitochondrial dysfunction in aging, neurodegeneration, and Parkinson's disease. Front Aging Neurosci 1: 2-34.
11. Kahlson MA, Colodner KJ (2016) Glial Tau Pathology in Tauopathies: Functional Consequences. J Exp Neurosci 9: 43-50.
12. Rabinovici GD, Jagust WJ (2009) Amyloid imaging in aging and dementia: testing the amyloid hypothesis in vivo. Behav Neurol 21: 117-128.
13. Tobe EH (2014) Functional imaging: A necessary prerequisite to neuropsychological assessment. International Journal of Diagnostic Imaging 1: 2.