Traumatic Brain Injury and Neurodegenerative Disorders: Brief review of recent research connecting TBI and the development of dementia and neurodegenerative disease

About the Presenter

• Dr. Joseph Murphy is a research clinical psychologist who has worked at the National Institutes of Health and National Institute on Aging in Bethesda, MD., as Scientific Review Administrator in support of Neurodegenerative disease research across the lifespan.
• He worked with the US Army’s Medical Research and Materiel Command, Military Operational Medicine Research Program, Ft. Detrick, MD. as Deputy Program Manager for Psychological Health and was a Senior Policy Analyst at the Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury, Silver Spring, MD.
• Dr. Murphy partnered with the Pennsylvania Behavioral Health and Aging Coalition in developing an Older Adult Behavioral Health Literacy and Peer Training program as part of PABHAC research project funded by the National Libraries of Medicine and the Pennsylvania Department of Public Welfare.

Traumatic Brain Injury (TBI) can cause epilepsy and increase the risk for conditions such as Alzheimer’s disease, Parkinson’s disease, and other brain disorders that become more prevalent with age. 1

Introduction:

- In September 2014, the Pennsylvania Alzheimer's Disease Planning Committee presented the First Annual Pennsylvania Alzheimer's Disease and Related Disorder Forum.
- According to State Plan presented at the forum, there are over 400,000 Pennsylvanians living with Alzheimer's Disease or a related Neurodegenerative Disorder.
- Many of these individuals are provided care by family members and other informal caregivers affecting at least one in every twelve Pennsylvania families.
- The State Plan(*) presents recommendations for responding to the current Alzheimer's Disease crisis in the Commonwealth, and the anticipated growing crisis in future years.
- The number one recommendation of the PA state plan is to improve awareness, knowledge, and a sense of urgency about the medical, social, and financial implications of this “epidemic” across the Commonwealth.
- This webinar is designed to improve awareness of the connection of traumatic brain injuries over the lifespan to the potential development of progressive neurodegenerative disorders like Alzheimer's disease even decades after the trauma.

(*)The Plan is available on the Department of Aging's web site, at www.aging.pa.gov

MONDAY, Oct. 27, 2014 (HealthDay News) – A mild concussion after age 65 might boost your risk of developing dementia, a new study suggests. Head injuries seem to pose special hazards for seniors compared to those in upper middle age, the researchers said.

"This was surprising and suggests that the older brain may be especially vulnerable to traumatic brain injury, regardless of the traumatic brain injury severity," said study lead author Dr. Raquel Gardner, a clinical research fellow with San Francisco Veterans Affairs Medical Center. "Or to spin it more positively, the younger brain may be more resilient to mild traumatic brain injury or may take longer to show symptoms of dementia," she added. Whatever the case, she believes the findings should spur efforts to prevent head injuries among older adults.


Traumatic Brain Injury and Neurodegenerative Disorders

Traumatic Brain Injury (TBI)
Dementia
And Mild Cognitive Impairment (MCI)
Neurodegenerative disease
Linkage between TBI and Neurodegenerative Disease
Traumatic Brain Injury and Neurodegenerative Disorders

**Traumatic Brain Injury:**
- Mild Traumatic Brain Injury (TBI) are also called “concussions.”
- Concussion – is defined as a short loss of normal brain function in response to a head injury.
- Common among athletes who suffer sport injuries, concussions are also common in older adults who, as a result of a fall, have hit or injured their head.
- Approximately 82% of all TBIs are mild. With mild TBI (mTBI) generally speaking, effects are seen in attention, processing speed or short term memory. Recovery is usually complete within days.
- In seniors, 75% of mild TBIs are a result of a fall. Other risk factors include accidents or injuries.
- In 2010 2.5 million TBIs occurred either as an isolated injury or along with other injuries.
- 52,000 of these result in death.
- 1.161 million are treated and released from Emergency Departments.
- Adults over 75 have the highest rate of TBI related hospitalization and TBI related deaths.

2. National Hospital Discharge Survey (NHDS), 2010; National Hospital Ambulatory Medical Care Survey (NHAMCS), 2010; CDC.

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**Post Traumatic and Chronic Stress:**
- In the case of older veterans the development of Neurodegenerative disease could be related to combat exposure that may have occurred decades in the past. Researchers have shown that within the population of older veterans those diagnosed with PTSD and who had received the Purple Heart (a proxy for combat exposure) had a two-fold higher risk of developing some form of dementia than those who did not experience that level of stress in life, but researchers did not posit a causal relationship.
- A number of longitudinal studies of older adults have suggested a link between chronic life stress, depression and cognitive decline, but not particularly Alzheimer’s Disease.

Stress, PTSD, Dementia-Greenberg, Tanen, Mait, Pitman Alzheimer’s & Dementia 10 (2014) 155-165.

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**TBI:**
- Symptoms of a concussion may not start right away, they may start days or weeks after the injury.
- Symptoms may include: headache or neck pain, nausea, ringing in the ears, dizziness, or tiredness. Sometimes an individual may feel dazed or not quite their normal self for days or weeks after the injury.
- Healthcare provider should be contacted immediately should these symptoms persist, get worse, or the individual develops more serious symptoms such as seizures, trouble walking or sleeping, weakness, depression, any numbness or decreased coordination, repeated vomiting or nausea, confusion, slurred speech.
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**1. HEAD TRAUMA:***
- Head injury can be either closed or open (penetrating).
- A closed head injury means you received a hard blow to the head from striking an object, but the object did not break the skull. These are typically referred to as concussions and about 75% are mild TBIs.
- An open, or penetrating, head injury means you were hit with an object that broke the skull and entered the brain. This is more likely to happen when you move at high speed, such as going through the windshield during a car accident. It can also happen from a gunshot to the head. This typically produces moderate to severe TBI.
- Head injuries include:
  - Concussion, in which the brain is shaken, is the most common type of traumatic brain injury.
  - Skull fractures and excessive bleeding.
  - Bleeding in the brain tissue, or in the layers that surround the brain, produces subarachnoid hemorrhage, subdural hematoma, or epidural hematoma.
- Head trauma accounts for over 1 in 6 injury-related hospital admissions each year.

**2. CONCUSSION:**
- Any loss of memory for events immediately before or after trauma.
- Any alteration in mental state at the time of trauma.
- Loss of consciousness of 30 minutes or less.
- Glasgow Coma Scale (GCS) score of 13–15.
- Post-traumatic amnesia not greater than 24 hours.

**3. MILD TBIs:**
- Mild TBI is most common and typically results from minor accidents.
- Recovery of normal pre-injury cognitive functioning occurs within one month of the injury.
- Multiple mTBIs may result in serious neurodegenerative diseases over time called Chronic Traumatic Encephalopathy (CTE).

**4. MODERATE TBIs:**
- More than 30 minutes, partial amnesia likely.
- Must see a medical treatment specialist, typically within 1 hour of the emergency department post accident.
- GCS below 13 is a moderate injury.

**5. SEVERE TBIs:**
- Severe penetrating injury from projectile such as a gunshot, IED (blast) or auto accidents.
- Skull injury; open head wound; soft tissue damage possible; requires surgery, hospitalization, physical rehabilitation.
- GCS of 8 or less represents a severe brain injury.
- Occurs over a period of about 12 months. Recovery may not result in return of all normal pre-injury cognitive and social functioning.

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2: Mild Traumatic Brain Injury Committee, Head Injury Rehabilitation Special Interest Group, American Congress of Rehabilitation Medicine.
3: "The GCS is scored between 1 and 15. The GCS is a component of some parameters: Best Eye Response, Best Motor Response, Best Verbal Response."
Traumatic Brain Injury and Neurodegenerative Disorders

Dementia:
- We now know that dementia is not a normal part of aging but is caused by a number of underlying medical conditions that can occur in both elderly and younger persons.
- In some cases, dementia can be reversed with proper medical treatment. In most others, it is permanent.
- Primary Dementia, like Alzheimer’s disease, is not caused by any other disease or injury.
- Secondary Dementia is a Neurodegenerative (progressive) disorder that may be caused by an illness or an injury, such as traumatic brain injuries.
- Currently, between 4,000,000 and 5,000,000 people in the United States have some level of dementia.
- The number of persons with dementia will increase significantly over the next few decades with the aging of the population and the increased numbers of OIF/OEF Veterans now seen with TBI and PTSD.

Traumatic Brain Injury and Neurodegenerative Disorders

Dementia:
- The following percentages are estimates and all forms of dementia are considered in these estimates:
  - Dementia affects about 1% of people aged 60 to 64 years.
  - It affects as many as 30% to 50% of people older than 85 years.
- Many people with dementia eventually become totally dependent on others for their care. People with dementia also experience declines in any or all areas of intellectual functioning, for example, use of language and numbers; awareness of what is going on around him or her; judgment; and the ability to reason, solve problems, and think abstractly.
- These losses also take a terrible toll on the quality of their life and the lives of those around them. Dementia is the leading reason for placing elderly people in institutions such as nursing homes.

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Common Neurodegenerative Disorders

- Alzheimer’s disease
- Lewy Body Dementia
- Parkinson’s Disease
- Huntington’s Disease
- Amyotrophic lateral sclerosis (ALS)
- Cognitive impairment without dementia/Mild Cognitive Impairment
Alzheimer's Disease (AD): According to the National Institute on Aging, AD is the most common cause of Primary Dementia, accounting for about one half of all cases of dementia. In this disease, abnormal protein deposits in the brain destroy cells in the areas of the brain that control memory and mental functions.

Alzheimer’s disease is at least partly hereditary in that it tends to run in families. However, just because one family member has Alzheimer’s disease, does not mean that another family member will have the disease.

Up to 5% of those living with Alzheimer’s have an early-onset form of the disease, and are diagnosed in their 40’s or 50’s.

Parkinson’s Disease (PD): PD typically affects body movements which can result in limb stiffness - “bradykinesia” (which causes them to shuffle when they walk or drop when they try and sit down), speech problems, and tremors (shaking at rest). Age of onset typically can be in midlife and can result in some mild cognitive impairment. Secondly, dementia may develop later in the disease, but not everyone with Parkinson’s Disease has dementia.

Reasoning, memory, speech, and judgment are most likely to be affected. Parkinson’s dementia usually develops at a slower rate than other neurodegenerative dementias.
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- **Lewy Body dementia** is caused by abnormal microscopic deposits of protein, called Lewy bodies, which destroy nerve cells. These deposits can cause symptoms typical of Parkinson’s disease, such as tremor and muscle rigidity, as well as dementia similar to that of Alzheimer’s disease. Lewy body dementia affects thinking, attention, and concentration more than memory and language. Like Alzheimer’s disease, Lewy body dementia is not reversible and has no known cure. Lewy Body dementia differs from Alzheimer’s as the patient usually experiences hallucinations which can start early on in the disease and may be managed by an A-typical anti-psychotic drug. In the final stage of Lewy Body, the patient will experience increased psychiatric breaks requiring higher levels of psychiatric care and medication.

The National Institute on Neurological Disorders and Stroke is the most current repository of information on dementia with Lewy body research.

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- **Huntington’s disease** is an inherited disease that causes the wasting away of certain types of brain cells that control movement as well as thinking. Dementia is common and occurs in the later stages of the disease. Personality changes are typical. Reasoning, memory, speech, and judgment may also be affected.
- Huntington’s disease has also been called Huntington’s chorea (chorea from the Greek word for dance). Huntington’s disease is inherited and causes nerve cells to break down in the brain, especially areas involved in thinking and movement.
- It is estimated by the Huntington’s Disease Society of America that over a quarter of a million Americans suffer from Huntington’s disease or have a risk of developing the degenerative disease from a parent. A child of a parent with Huntington’s disease has a 50 percent chance of developing the disease. Symptoms usually appear between the ages of 30 to 50.
- Suspected Huntington’s chorea can be ruled out by genetic diagnosis. People with family members who have Huntington’s disease may be tested in their early 20’s to determine if they are carriers of the Huntington gene. Genetic testing however raises many concerns for young adults and must be incorporated with serious counseling.

The National Institute on Neurological Disorders and Stroke is the most current repository of information on Huntington’s disease.

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**Amyotrophic lateral sclerosis (ALS)**

- ALS is a rapidly progressive neurodegenerative disease. It can result in death within 3 years typically from a respiratory failure. Degeneration of motor neurons and non-motor neurons are equally affected. Exposure to neurotoxins and other environmental factors.
- PD, AD and ALS have each been associated with certain chemical and environmental exposures that are increasingly the subject of research, connecting chemical and environmental factors to multiple types of neurodegenerative disorders.
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- Mild cognitive impairment (MCI): Cognitive impairment without dementia (CIND)
  - MCI can be memory loss that is more pronounced than typical age-related forgetfulness. MCI will cause an inability to recall short term memory of recent events, such as what the person did yesterday or last week. However, a strong ability to remember specific events from the more distant past will remain intact.
  - MCI (CIND) is associated with increased risk for disability, increased healthcare costs, and progression to dementia. A study of the prevalence of this condition and estimates of this condition in the United States using a population-weighted sample revealed that, "the incidence of CIND is greater than the incidence of dementia, and those with CIND are at high risk of progressing to dementia, making CIND a potentially valuable target for treatments aimed at slowing cognitive decline."


22. Traumatic Brain Injury and Neurodegenerative Disorders

Linking TBI and potential development of Neurodegenerative Disorders

- Vascular dementia (VaD)
- Depression and Chronic Stress
- Increased levels of Glucocorticoids
- Hippocampal Atrophy
- Post Injury Inflammation in Subcortical Brain systems
- Tau Protein aggregation
- Axon damage and Amyloid Precursor Protein (APP)
- Protein Synthesis disruption
- Chronic Traumatic Encephalopathy

* Depression and inflammation among military veterans (e.g., TBI and in battle)
Traumatic Brain Injury and Neurodegenerative Disorders

Brain Reserves
- Though research is still trying to determine how TBI and future Neurodegenerative disease are associated, many possible links have already been uncovered. One possibility is that head traumas can reduce something referred to be Neuroscientists as "brain reserve," a normal neuro-protective factor against disease.
- Recent findings suggest that chronic impairment of a system of vascular channels in the brain after a TBI reduces "brain reserve" and makes the brain more vulnerable to the kind of tau aggregation seen in dementia.

Depression and Chronic Stress
- High levels of stress, including post traumatic stress, and chronic states of anxiety, particularly resulting in isolation have all been linked to mTBI. Social and physical "engagement" have been studied as major factors in contributing to the concept of "mental reserve" in older adults and reducing the risk of Neurodegenerative disease and Mild Cognitive Impairment.
- White matter brain abnormalities in some patients with depression disorders closely resemble abnormalities found in patients who have experienced a mild traumatic brain injury (mTBI), according to new research presented by University of Pittsburgh School of Medicine researchers at the annual meeting of the Radiological Society of North America (RSNA).

Hormonal Imbalance; Increased levels of Glucocorticoids
Glucocorticoids are secreted by the middle region of the adrenal cortex. The principal glucocorticoid is cortisol, which increases blood glucose levels.
- The HPA axis of the hypothalamus, pituitary gland and the adrenal gland act in a coordinated effort to respond to stressors in the surrounding environment.
- In chronic stressful situations where cortisol is overproduced, the HPA axis eventually becomes desensitized to feedback from the brain telling it to "shut down," leading to increased levels of glucocorticoids.
- Elevated levels of glucocorticoids enhance memory for emotionally arousing events and lead to poor memory for material unrelated to the source of stress.
- Long-term exposure to glucocorticoid medications, such as asthma and anti-inflammatory medication, has been shown to create deficits in memory and attention, both during and after treatment, a condition known as "steroid dementia."
- Chronic exposure to stress-related hormones has a direct impact on brain structure, cognition, memory and mental reserve over a lifetime.

References:
Traumatic Brain Injury and Neurodegenerative Disorders

**Hippocampal Atrophy**

- Animal models of a chronic stress response cycle have provided much of the evidence for the cortisol-hippocampal connection to dementia and suggest that high-stress conditions producing exogenous glucocorticoids can cause hippocampal neuron damage and memory impairment resulting in hippocampal atrophy.
- Current research suggests that a similar cycle may exist in humans in whom there is a high correlation between exposure to stressful events and depressive episodes. The HPA axis is hyperactive in depression. Hippocampal atrophy is a hallmark of Alzheimer’s disease and frequent finding in post-mortem studies of persons with long-term depression. *Kim JJ, Song EY, Kosten TA. Stress effects in the hippocampus: synaptic plasticity and memory. Stress 2006;9:1-11 28

**Inflammation**

- Acute inflammation response over time triggered by TBI, particularly in subcortical regions of the brain, may persist and further evolve over time. This persistent inflammation may be an initial trigger of a larger cascade ultimately leading to a TBI-related dementia, neurodegenerative, or cerebrovascular disease.
- The presence of inflammation is foreboding, given findings that elevated inflammatory markers are predictive of cognitive decline decades later.*

**Tau Protein aggregation**

- A common connection seems to be that TBIs promote the development of neurofibrillary tangles (NFTs) in the brain, comprised of aggregates of the protein tau which is commonly observed in all dementias. Accumulated tau protein has been observed after mTBI in animals and human studies creating neurofibrillary tangles (NFTs).
- NFTs are composed of abnormally phosphorylated Tau protein. This Tau accumulation is neurotoxic and has been hypothesized to cause neuron death.
- Multiple mTBIs have been causally linked to tau protein pathology with the increased risk of dementia and neuron death.*


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**Axonal damage**
- In response to a TBI, increased Amyloid Precursor Protein (APP) is expressed in neuron cell and axons. This accumulation of APP is a key factor in subsequent amyloid (beta) plaques which are a hallmark of Alzheimer's disease.
- Axon damage from the accumulating amyloid precursor protein after repetitive mTBIs has been observed in both human and animal studies.
- Studies have linked the accumulation of this key protein component with injured axons after TBI events.*


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**Protein Synthesis disruption**

*From Medical News Today: 22 December 2014*
- UCLA researchers claim that encouraging the nervous system to regenerate damaged connections between brain cells could restore lost memories in humans. The research team led by David Glanzman, Departments of Integrative Biology and Physiology and Neurobiology at the University of California Los Angeles, says their findings from animal studies may lead to new treatments for patients in the early stages of Alzheimer's disease.
- According to Glanzman, while long-term memories are being created, the brain makes new proteins that play a part in creating new synapses. But disruption of this process - through concussion, or more serious traumatic brain injuries can prevent this protein synthesis. This would have the effect of preventing long-term memories from being created or stored.

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**Chronic Traumatic Encephalopathy** Chronic Traumatic Encephalopathy (CTE) is a progressive degenerative disease of the brain found in athletes (and others) with a history of repetitive brain trauma. This trauma, which includes multiple concussions, triggers progressive degeneration of the brain tissue, including the build-up of an abnormal protein called tau. These changes in the brain can begin months, years, or even decades after the last concussion or end of active athletic involvement.
- Repeated TBI has been linked to symptoms such as slowed movement, tremors, confusion, and speech problems. Once described as the "punch drunk" condition of boxers, Chronic Traumatic Encephalopathy (CTE) also included depression, loss of cognitive function, impulsivity, aggression, and heightened risk of suicidality.
- Post mortem research on two former NFL football players who had a history of demonstrated Neuro-behavioral disorders, found evidence linking chronic encephalopathy to traumatic brain damage resulting most likely from repeated concussions during their playing careers.*

**Traumatic Brain Injury and Neurodegenerative Disorders**

**Future Directions:**
- Research into connection between TBI and neurodegenerative disorders must rely on improved genetic testing, research into the effects of environmental and chemical interactions, continued search for biomarkers from imaging techniques and cerebrospinal fluid, for use in the immediate post-trauma period.
- In older adults routine assessment using increasingly sensitive instrumentation and improved technologies for monitoring health factors and cognitive metrics will continue to be targets of future research.
- Connectivity between TBI and a number of co-occurring disorders underscores the need for much more research into brain trauma and its lingering comorbidities over the course of the lifetime, including large scale studies of preclinical bio-markers of neurocognitive decline.

For more information please visit National Institute of Neurological Disorders and Stroke, National Institute on Aging. Visit us at [www.olderpa.org](http://www.olderpa.org)