The Challenge

Traumatic damage to the brain is seen by the industry as “an event”

Traumatic damage to the brain is seen by the industry as “an event”
A broken brain is the equivalent of a broken bone—the final outcome to an injury of an isolated body system.
Once in was “fixed” and given some therapy, no further treatment would be needed in the near or distant future—and CERTAINLY, there would be no effect on other organs of the body.
Brain injury is not an event
It is a disease
It never ever ever goes away

Event: “The final outcome”
Disease: “A condition of ill-health or malfunctioning in a living organism.”

Funk and Wagnalls

Purpose of this presentation

• To encourage the classification of a TBI
• NOT as an event
• NOT as the final outcome
• BUT as the beginning of a disease process

• Show that neither an acute or chronic TBI is a static process
• It impacts organ systems
• It is disease causative and disease accelerative
• SHOULD be managed and paid for on a par with other diseases
WHO Definition of Chronic Disease

One or more:
- Permanent
- Leave residual disability
- Caused by non-reversible pathological alteration of an organ or system
- Require special training of the patient for rehabilitation
- May be expected to require a long period of supervision, observation or care.

World Health Organization, 2002

Mortality

MODERATE TO SEVERE TBI
Individuals with TBI 2.23X more likely to die as cohort
Life expectancy reduction of 9 years

MILD TBI
Have a small but statistically significant reduction in long term survival

Mortality

767 subjects with mild-moderate-severe TBI followed over 13 years:
Severity of injury not associated with survival beyond 1st yr of injury
Those surviving 1st yr post TBI—Overall death rate 2.5X higher than controls
Death rate for mild TBI in was 2X greater than controls.

McMillan et al, JNMP, 2010

Causes of death

Individuals more than one year post TBI:
• 50X more likely to die from seizures
• 9.5X more likely to die from septicemia
• 6.4X more likely to die from aspiration pneumonia
• 4X more likely to die from other respiratory conditions

Harrison-Felix JHTR, 2015

Neurologic Disorders

Post traumatic epilepsy
TBI is leading cause of epilepsy in young adult population
Patients with a TBI are 1.5-17X more likely to develop seizures than the general population
The risk of sudden death in epileptics 20X greater than general population: risk increases with increasing seizure frequency
Latency to first seizure as long as 17 years
Of 67 children with mod-severe TBI, 40% developed post traumatic epilepsy
Patients with epilepsy 3X more likely to have strokes

Annegers, NEJM, 1998
Shorvon, Lancet 2011
Chaga, Sience J. Epilepsy, 2014
Liesemer, J. Neurotrauma 2011
Strokes

1.25 MILLION trauma subjects in California (37% with TBI) followed for as long as 4 years:
Increased risk of stroke in TBI compared to non-TBI: 1.1% of TBIs v. 0.9% non-TBI

Same risk factor for stroke as hypertension

Burke, Neurology, 2013

Strokes

Data base from Taiwan over 4 yrs:
30,000 new TBIs vs. 120,000 non-TBIs

TBI cohort had almost twice the incidence of subsequent stroke
--- severity of TBI correlated with stroke incidence AND post-stroke mortality

Liao, Mayo Clinic Proc, Feb 2014

Brain Tumors

• 5,000 patients with TBI compared to 25,000 randomly selected non TBI
• Followed for 3 years post-TBI
• Patients with TBI 5 times more likely to develop malignant brain tumor
• The more severe the TBI, the more likely to have tumor development

Chen, J Neurotrauma 2012
Multiple Sclerosis

- Same data base as Stroke study—6 year follow-up
- TBI: .055% (72,765 individuals)
- Non-TBI: .037% (218,215 individuals)

Kang, J. Neurotrauma, 2012

Sleep Disturbances

- Subjective sleep complaints in 70% of chronic TBI outpatients
- Objective sleep disturbances in 30-45% of chronic TBI: OSA, PLMS, Narcolepsy, PTH
- Cog issues associated with sleepiness
- (56,000 auto crashes annually in U.S. attributed to drowsiness)

Masel B, Scheibel R, APMR, 2001

Neuroendocrine Dysfunction

- Hypopituitarism in 30% of mod-severe TBIs >1 year post injury
- 5% of normals at 3 months develop hypopituitarism at 1 year

Schneider, JAMA, 2007
Aimaretti, JCEM, 2005
Growth Hormone Dysfunction

- Growth hormone deficiency in 20% of moderate-severe TBIs >1yr post injury
  - Increased osteoporosis
  - Increased cholesterol
  - Increased abdominal fat
  - Increased atherosclerosis: higher mortality from cardiovascular disease
  - Decreased cog functioning

Aimaretti, Clin Endo, 2005

Thyroid Dysfunction

Hypothyroidism in ~5% mod-severe >1yr post TBI

- weight gain
- shortness of breath
- intellectual impairment
- cardiovascular disease

Agha Clin Endo, 2006

Gonadal Hormone Dysfunction

- 10-15% >1 year post mod-severe TBI
- 40-60% of individuals complain of sexual dysfunction post TBI
  - males: decreased libido
  - decreased muscle mass
  - decreased strength
  - correlation between low free testosterone and cognitive function

Pedi: Increased incidence of precocious puberty

Zasler, Brain Injury Medicine, 2007
Agha, Clin Endo, 2006
Tan, Arch Intern Med, 2008
Precocious Puberty

- Pediatric TBI: Precocious puberty induces early bone maturation: short females at risk for sexual abuse
- Greater risk for breast cancer
- Males: aggressiveness

Metabolic Dysfunction: Amino Acids

- Essential (from diet) and Non-essential (can be synthesized) amino acids
- Building blocks of the body, derived from protein
- Required for protein synthesis, and therefore, brain tissue repair
- Form antibodies to fight infection
- Carry oxygen to the tissues
- Can produce energy
- Part of the hormonal and musculoskeletal system
- PRECURSORS TO NEUROTRANSMITTERS

Abnormal Amino Acid Metabolism in TBI

1.5 months post TBI: profound reduction of most NEAA and all EAA in plasma

3.5 months post TBI (PEG or NG): Many EAAs and tyrosine concentrations did not recover.
   ? Could this be due to inadequate nutrition?
Study Design

- 6 male subjects (mean 15 months post TBI)
- All moderate to severe injuries
- All ambulatory—regular diet
- 8 healthy controls
- Basal AA levels measured.
- Given 15g of EEA supplementation—AAs measured again.

Amino Acids in Chronic TBI

Lower level of total EAA and total AA in basal state for TBI v. Control—basically due to 33% lower valine (EAA) level

After supplementation: differences in total AA and total EAA concentrations in the TBIs v. Controls did not change:
- valine still low in TBI
- alanine and glutamine (NEAA) lower in TBI

Borsheim, APMR, Feb 2007
Amino acids showing a significant or marginally significant increase in response to feeding

Group A—controls
- Glutamine
- Valine
- Isoleucine
- Leucine
- Phenylalanine
- Tryptophan
- Ornithine
- Lysine
- Arginine

Group B—TBI
- Alanine
- Tyrosine
- Phenylalanine
- Ornithine
- Arginine
- Proline

Red = essential amino acid
Bold = branched chain amino acid

Inflammatory markers
Blunted response to feeding in long-standing TBI patients from different facilities

Blunted response to feeding is a consistent response in long-standing TBI patients

Psychiatric Disease

- Cost of psychiatric disease as much as 1/3rd of U.S. health care budget
- Chronic TBI:
  - Psychosis 20%
  - Depression 18-61%
  - Mania 1-22%
  - PTSD 3-59%
  - Aggression 20-40%
- TBI is associated with high rates of suicidal ideation, suicide attempts, and completed suicide.

• 60 individuals studied 30 years post TBI
  23% developed a personality disorder after their TBI
  50% developed major mental disorder after their TBI

Koponen S, Am J Psychiatry, 2002

Psychosis

“There is limited/suggestive evidence of an association between moderate or severe TBI and psychosis

However, even if the TBI is severe, the psychosis does not appear during the first post-TBI year, but rather, becomes apparent in the 2nd and 3rd years post TBI”

Inst. of Medicine, Gulf War and Health, 2009

Alzheimer’s-Type Dementia

• Young adults who experience a moderate or severe TBI have more than 2X the risk of developing Alzheimers and other forms of dementia later in life.
  The worse the injury, the higher the risk:
  moderate TBI: 2.3X risk
  severe TBI: 4X the risk.

Jellinger, 2001
Barnes D, Poster Presentation to Alzheimer’s Association, July, 2011
Alzheimer’s Type Dementia

- Retrospective study of 188,000 Veterans > age 55---9 year follow-up:
  10% without TBI developed dementia
  16% with TBI developed dementia
  (60% increased risk)

Barnes et al, Neurology, July 2014

Even individuals with no known cog impairment post TBI have risk of earlier onset of dementia due to Alzheimer’s-type disease

Schoefield, J Neurol Neurosurg Psych 1997

Other neurodegenerative diseases

Parkinsonism

Chronic traumatic encephalopathy (Dementia Pugilistica)
- insidious onset of deterioration in attention, concentration, memory, judgment →motor retardation, ataxia, slurred speech
  - High incidence of neurodegenerative mortality amongst retired NFL players

Lehman, Neurology, 2012
Post-recovery Cognitive Decline

- 33 individuals with mod-severe TBI: 27% showed cognitive decline comparing 12 mo. baseline to 2-5 yrs testing (mean 37mo)
- DTI showed progression of white matter injury when measured 4.5m and 29m post injury in 13 mod-severe TBIs

Till, APMR, 2008
Greenberg, APMR, 2008

Possible etiologies

- Damage to BBB causing plasma protein leakage into the brain
- Liberation of free oxygen radicals
- Loss of brain reserve capacity
- Deposition of beta amyloid plaque (also epileptogenic): Increased risk of AD with high plasma levels in the non-TBI population. Consentino, Arch Neurol, 2010
- Chronic inflammatory process
- Decreased blood flow
- Apoptosis
- Nutritional deficits
- ?????????????????

Lye, Neuropsych Review

Limited/Suggestive Evidence of an Association

(chance, bias, and confounding can not be ruled out with reasonable confidence)
- Mod or severe TBI—Psychosis
- Mild TBI—Ocular and visual motor deterioration
- Mild TBI with LOC—Dementia of Alzheimer’s type
- Mild TBI with LOC—Parkinsonism

Institute of Medicine, Gulf War and Health, 2009
Positive Association
(chance and bias ruled out)
- Severe TBI—Neurocognitive deficits
- Mod or severe TBI—Dementia of Alzheimer’s type
- Mod or severe TBI—Parkinsonism
- Mod or severe TBI—Endocrine dysfunction
- Mod or severe TBI—Premature death
- TBI—Depression, Aggressive Behaviors, Chronic Traumatic Encephalopathy

Institute of Medicine, Gulf War and Health, 2009

Causal Relationship
Penetrating TBI—Unprovoked Seizures
Moderate or Severe TBI—Unprovoked Seizures
Penetrating TBI—Premature Death

Institute of Medicine, Gulf War and Health, 2009

Summary
- Historically, patients with a TBI are referred to as brain injury "survivors"
- Perhaps “staying alive” used, as most with moderate-severe TBI died.
- Perhaps “survivors” implied that the individual outlived their injury, and persevered despite the hardship of trauma
“Survivor” does not address the reality of TBI

- Cancer “survivors” are “survivors” because it is believed they outlived their disease

Many individuals with TBI recover 100%—they have “survived” their injury

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However

- Annually, in the U.S, 90,000 individuals who sustain a TBI become significantly disabled.
- 5.3 million Americans are disabled due to a TBI
- As a result of their trauma, they have

**Brain Injury Disease**

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- Brain injury disease should be taught, reimbursed and managed on a par with other chronic diseases

---only then will be treat the patient with the disease as opposed to the disease in the patient.
---only then will they get the medical surveillance, support and treatment they need and deserve
---only then will TBI research receive the funding it deserves and requires
---only then will we be able to truly speak of a cure.
Is Brain Injury a Chronic Disease?

Thanks to my staff

That's all Folks'