Brain Injury: Chronic Health Condition and Management for Farmers

Brent E. Masel, MD
Executive Vice President for Medical Affairs CNS
Clinical Professor of Neurology, UTMB
Medical Director Brain Injury Assoc. of America

Maureen Cunningham
Executive Director
Brain Injury Association of Missouri
Missouri AgrAbility Co-PI

Karen Funkenbusch
Project Director/PI, Missouri AgrAbility Project
Extension Instructor and State Specialist
University of Missouri Extension and Occupational Therapy Program

Nicholas Mehrnoosh, MS, MHP
Executive Committee
Washington State Traumatic Brain Injury
Strategic Partnership Advisory Council

David Minor, MIPM
TBI Council and Fund Coordinator
Traumatic Brain Injury Strategic Partnership Advisory Council
Washington State Department of Social and Health Services

BRAIN INJURY ASSOCIATION OF MISSOURI

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Brain Injury As A Disease

Brent E. Masel, MD
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The Challenge

- 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 it 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."

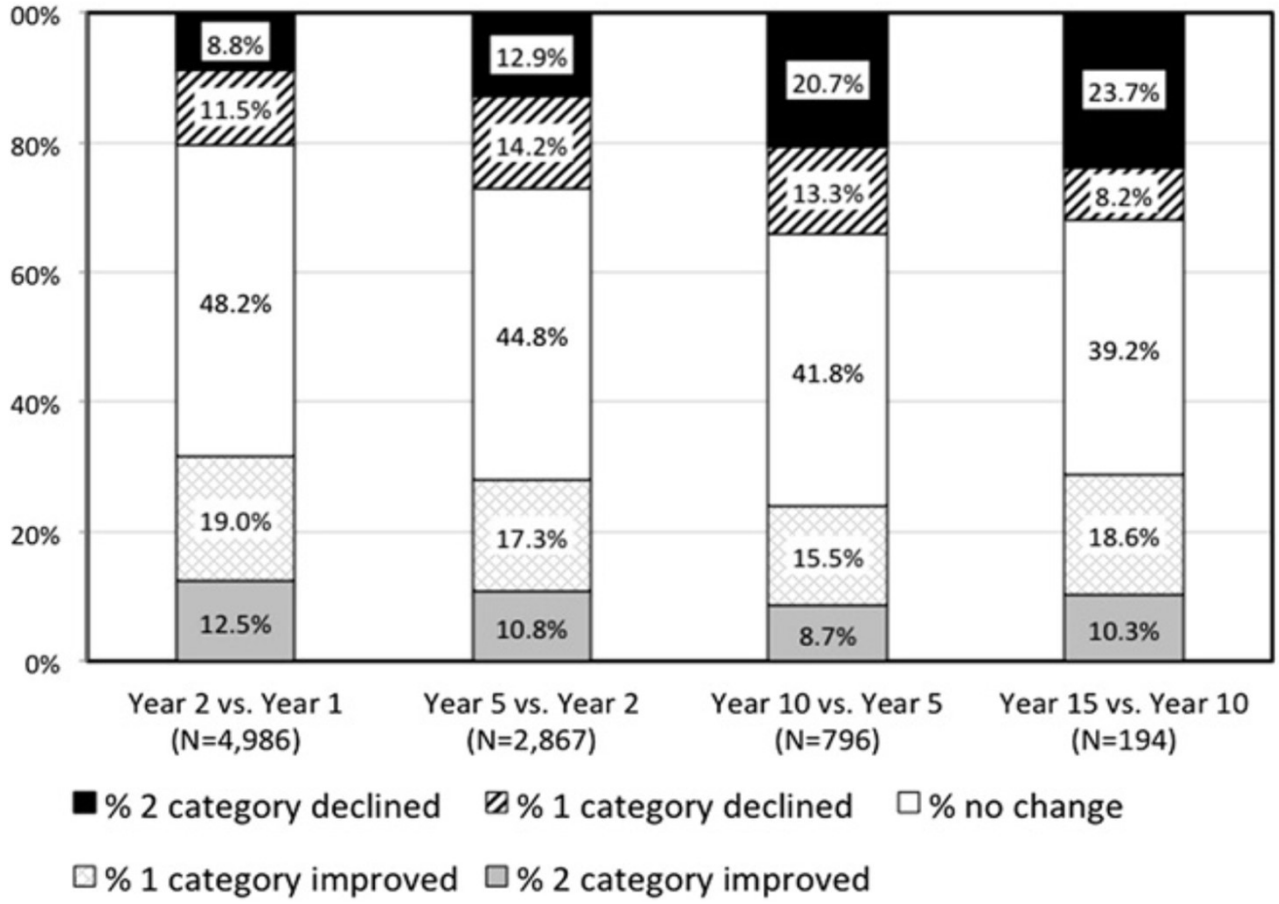
Funk and Wagnalls

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

Purpose of this presentation

- 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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10.8%
20.7%
13.3%
41.8%
15.5%
8.7%
23.7%
8.2%
39.2%
18.6%
10.3%
Year 2 vs. Year 1 (N=4,986)
Year 5 vs. Year 2 (N=2,867)
Year 10 vs. Year 5 (N=796)
Year 15 vs. Year 10 (N=194)
% 2 category declined
% 1 category declined
% no change
% 1 category improved
% 2 category improved

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

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

Hausted, Brain Injury, 2020
Annegars, NEJM, 1998
Shorvon, Lancet 2011
Chang, Eastern J. Epilepsy, 2014
Liesemer, J. Neurotrauma 2011

Post Traumatic Epilepsy

The more severe the injury, the more likely the patient will develop PTE

PTE is linked to poorer outcomes even in patients will less severe injuries (GCS 13-15)

Of 67 children with mod-severe TBI, 40% developed post traumatic epilepsy

Patients with epilepsy 3X more likely to have strokes

Burke, J; presentation to AAN; Oct 2020
Chang, Eastern 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
- Incidence of sleep complaints in VA study of 200,000 vets:

  23.4% of those with TBIs. 15.8% in non-TBIs
- Objective sleep disturbances in 30-45% of chronic TBI: OSA, PLMS, Narcolepsy, PTH
- Cog issues associated with sleepiness

Masel B, Scheibel R, APMR, 2001

Leng Y, Neurology, 2021

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 2**X** greater than controls

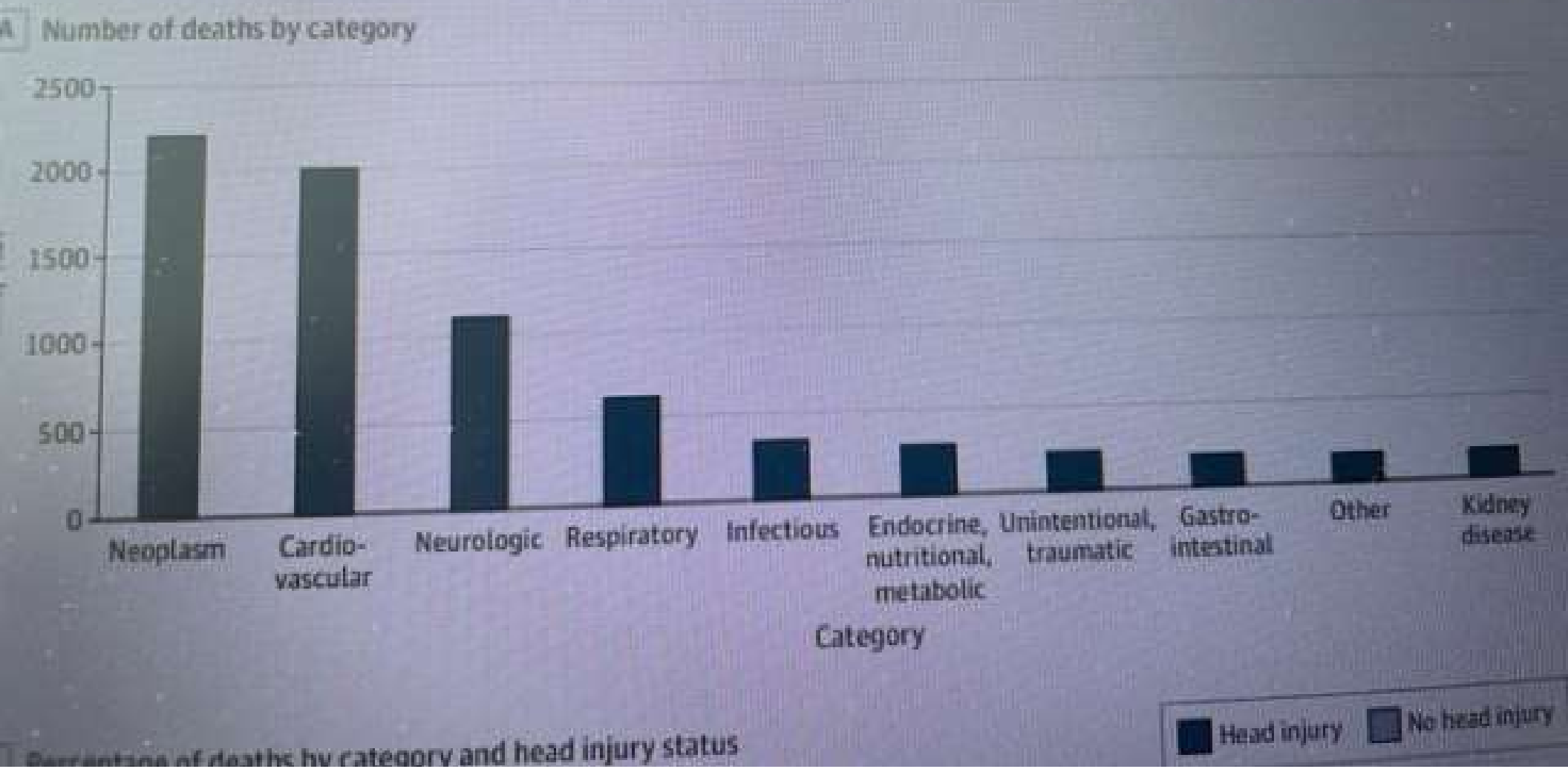
McMillan et al, JNNP, 2010

Mortality

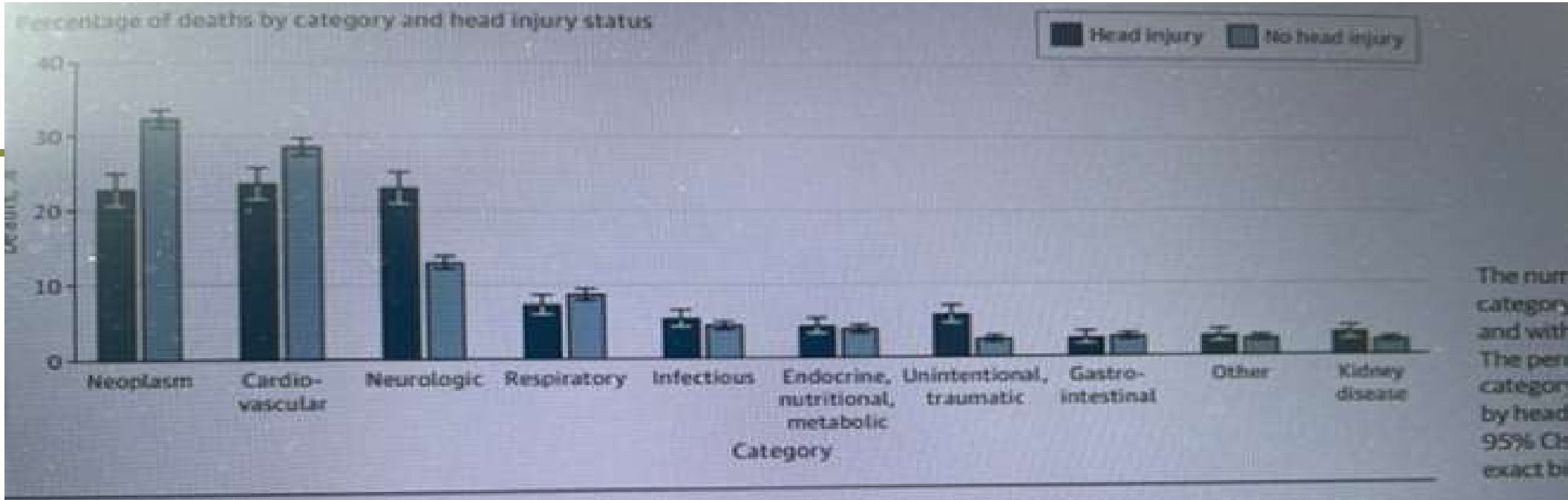
- 13,000 individuals followed over 30 years
- Mild, moderate, severe, multiple TBIs
- Significant increase in mortality in dose dependent manner
- Mild: approx. 2X
- Mod and severe: approx. 2.5X controls

Elser, *JAMA Neurology*, 2023

Figure 2. Cause-Specific Mortality Overall and by Head Injury Status



Percentage of deaths by category and head injury status



.7 years) and younger participants (aged <54 years: edian, 4.8 years; IQR, 1.1-10.7 years).

We evaluated cause-specific mortality among individu- with and without head injury. Overall, the most common uses of death were neoplasm, cardiovascular disease, and urologic disorders (**Figure 2A**). Among individuals with head jury, deaths caused by neurologic disorders and unintenonal injury or trauma occurred more frequently as indited by nonoverlapping 95% CIs (Figure 2B). We further evalu-

among individuals with head injury co out head injury (eFigure 2 in Supple ard ratio (HRs) for the association be mortality for each model specificatio ates included to control for potential and 3), are depicted in **Table 2**. In una 1), the HR of mortality among individu 2.21 (95% CI, 2.09-2.34) compared w injury. The association was attenuate cant with adjustment for sociodemog

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

Mild TBI-mortality

- 964 pts with mTBI vs 5,567 controls:
- 47% increased 5 year mortality
- 17% greater death from Neurodegenerative disease vs. 11% controls

- Cardiovascular, Neurological, and Respiratory co-morbidities associated with mortality in pts with mTBI

- ----mortality in these patients most influenced by pre-existing conditions

Searcy, *Brain Injury*, 2020

Neuroendocrine Dysfunction

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

Emelifeornwu, JNT, 2020

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 stature
  - females at risk for sexual abuse
  - greater risk for breast cancer
  - Males: aggressiveness
  - Increased incidence of ADHD post TBI

Asarnow, JAMA Peds; July 2021

Pediatrics

Children with TBIs (including mild TBIs) are reported to eventually have a higher lifetime incidence of:

- Learning disorders
- ADHD
- Speech/Language problems
- Developmental delay
- Anxiety problems
- Bone/joint/muscle problems
- Seizures

Haarbauer-Krupa, JAMA Pediatrics, 2018
Vaaramo, J Neurol Nsurg Psych, 2014

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

Aquilani, R, et al. Arch Phys Med Rehabil 20000.

3.5 months post TBI (PEG or NG) or NG):

- Many EAAs and tyrosine concentrations did not recover.
- ? Could this be due to inadequate nutrition?

Aquilani, R., et al. Arch Phys Med Rehabil. 2003.

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.

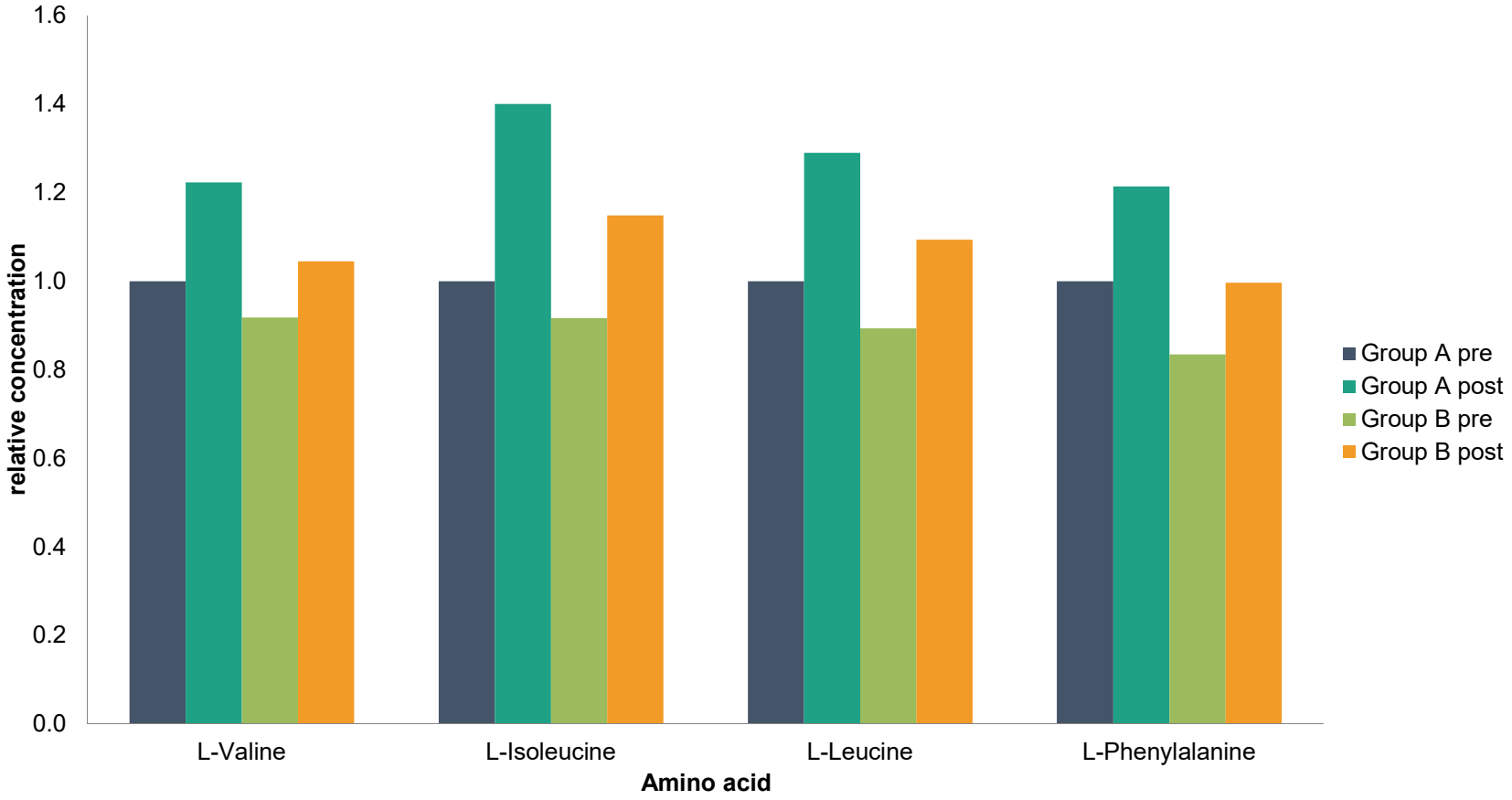
Amino Acids in Chronic TBI

- 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

Relative concentrations of branched chain amino acids and phenylalanine in long-standing TBI patients (B) vs. age-matched healthy controls (A), before and after consumption of a standard breakfast



Amino acids showing a significant or marginally significant increase in response to feeding

Group A-controls

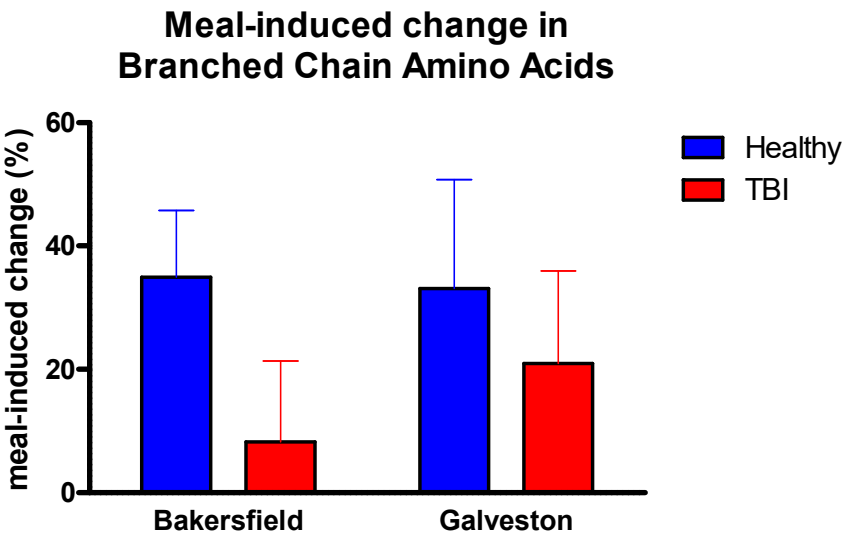
- Glutamine
- **Valine**
- **Isoleucine**
- **Leucine**
- Phenylalanine
- Tryptophan
- Ornithine
- Lysine
- Arginine

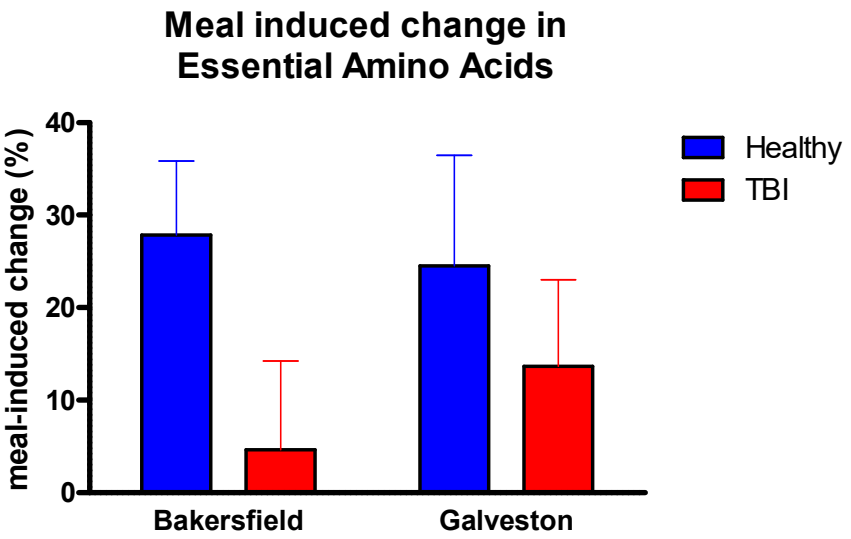
Group B--TBI

- Alanine
- Tyrosine
- Phenylalanine
- Ornithine
- Arginine
- Proline

Red = essential amino acid
Bold = branched chain amino acid

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





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 (including milds) is associated with high rates of suicidal ideation, suicide attempts, and completed suicide.

- Entire population of Denmark (7.4M) studied 1980-2014: 2X risk of suicide if had hx of TBI

Kim E, J Neuropsychiatry Clin Neurosci, 2007
Madsen T, JAMA, 2018
Fralick M, JAMA Neurology, 2018

60 individuals studied 30 years

- 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

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

350,000 Vets with mild TBI—w and w/o LOC

- 2X risk of dementia

Barnes et al, JAMA Neurology, Sept 2018

"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

- 325,000 Vets with TBI: almost 2X risk of PD
- even mTBI had 1.56 risk over non TBIs

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

Gardner, Ann Neurology, 2015
Gardner, Neurology, 2018
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):
- Chronic inflammatory process
- Decreased blood flow
- Apoptosis
- Nutritional deficits
- ??????????????????

Lye, Neuropsych Review, 2000

Limited/Suggestive Evidence of an Association

Bias, chance 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

However

- Annually, in the U.S, over 100,000 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

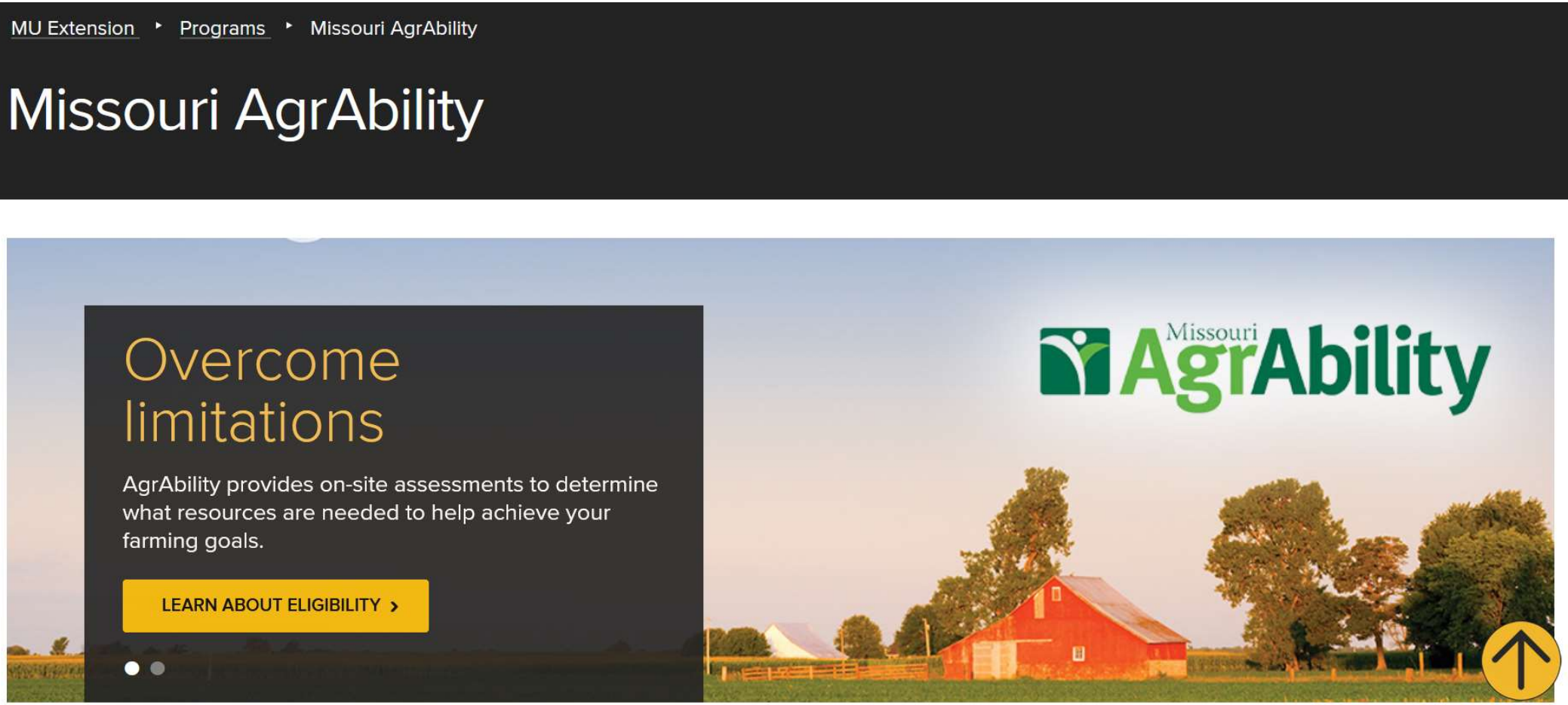
Brain Injury Disease

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.

Thanks to my staff


That's all Folks



Missouri AgrAbility Clients with Brain Injury

- Resources
- Achieving Farming Goals

Brain Injury Recognition and Management

- Highest risk factors for brain injury within agriculture
- Recognizing a potential brain injury
- What to do to improve recovery

Brain Injury Prevention

- Minimize hazards
- Learn first aid specific to brain injury

Acknowledgment

These materials are based in part upon work supported by the National Institute of Food and Agriculture (NIFA), United States Department of Agriculture, under sponsored project number Missouri AgrAbility Award 2022-41590-38128.