Cannabis and Health

Module 11: Neurocognitive/Brain Disorders Part I

Lecture 3: Etiology of MS, Epilepsy, Traumatic Brain Injury

Causes of MS

- Not a lot is known about causes of MS – multifactorial with complex interactions between genetics and environment
- It is an autoimmune disease – virus, bacterium, or other immune insult may be important precipitant
- Immune system factors appear to be important, T cells, B cells, and disruption in other mechanisms appear to be important
- Prevalence very different across global environments and genetic groups

Common Causes of Epilepsy

- Some forms of epilepsy have no known cause
- Genetics important for some types of epilepsy
- Some children may be born with structural change in an area of the brain that gives rise to seizures
- Infections of the brain are common cause of epilepsy
- Head injuries are a very common cause of epilepsy
- Common causes vary depending on age
  - In people over 65, stroke is most common cause of new onset seizures

Etiology of Epilepsy: Autoimmune Mechanisms

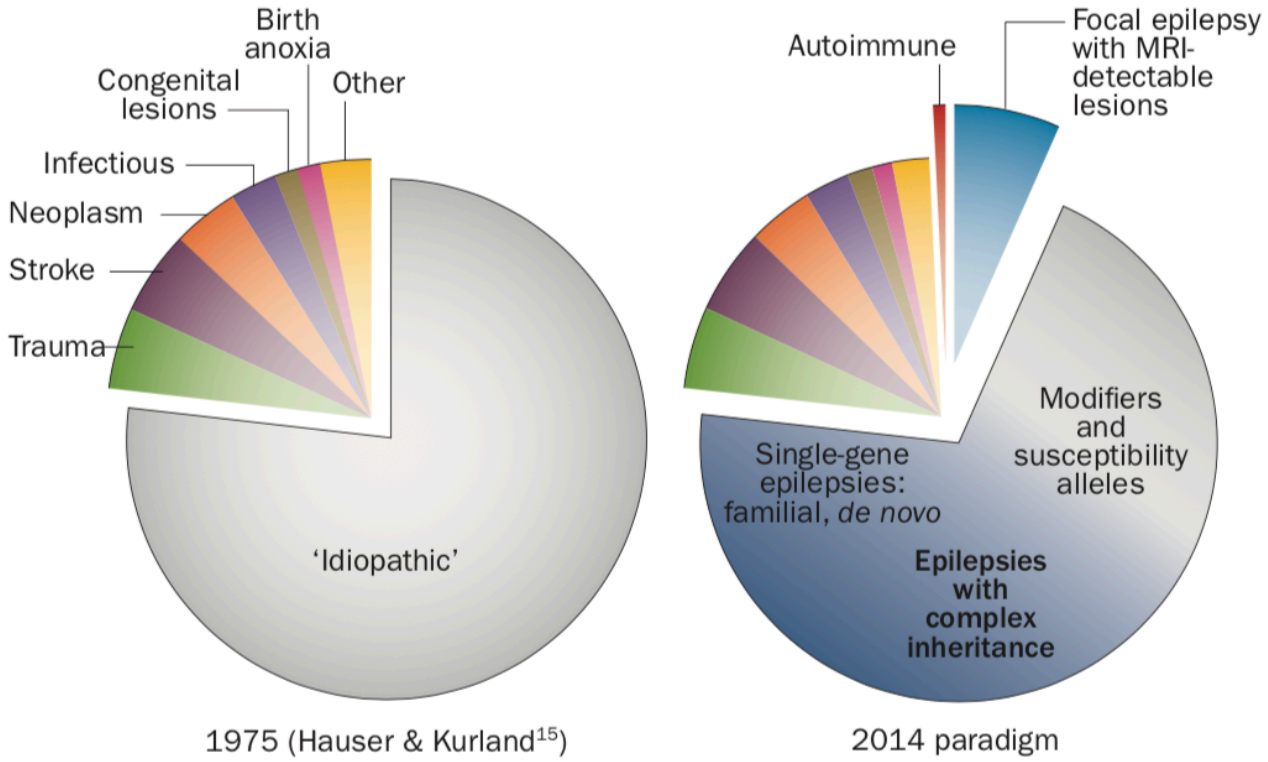
- A recent population-based study looked at claims from a nationwide employer-provided health insurance plan in the United States between 1999 and 2006 (N = 2 518 034)
- Examined relationship between epilepsy and 12 autoimmune diseases:
  - type 1 diabetes mellitus
  - psoriasis
  - rheumatoid arthritis
  - Graves disease
  - Hashimoto thyroiditis
  - Crohn disease
  - ulcerative colitis
  - systemic lupus erythematosus
  - antiphospholipid syndrome
  - Sjögren syndrome
  - myasthenia gravis
  - celiac disease.

- Risk of epilepsy was significantly heightened among patients with autoimmune diseases.
- Elevated risk was consistently observed across all 12 autoimmune diseases.

Ong et al., 2014, *JAMA Neurology*

Etiology of Epilepsy—Genetic Vulnerabilities

- Etiology of epilepsy used to be regarded as unknown in 75% of patients
- Many types of epilepsy now thought to have a genetic basis



Thomas & Berkovic, 2014, *Nature Reviews Neurology*

Etiology of Epilepsy—Infection

- FIRES=Febrile Infection–Related Epilepsy Syndrome
  - one of the most severe and irreversible types
  - presumably immune-mediated
  - very rare, so limited clinical data exist
- Clinical Features
  - Age of onset: 2–17 (median 8) years
  - Family history is generally uninformative
  - Occurs without other neurological features
  - Resistance to nearly all drug treatments
  - Outcome is almost always chronic epilepsy
  - Often results in global brain atrophy after a few weeks with mild-to-severe neuropsychologic impairments

Baalen et al., 2017, *Neuropediatrics*

Etiology of Epilepsy—Head Trauma

- TBI is one of the most common causes of acquired epilepsy
  - Risk of epilepsy increases with severity of head trauma (as high as 40-50% in some kinds of TBI)
  - Many patients develop epilepsy in months or years following brain TBI
  - Clinical research hindered by lack of useful biomarkers

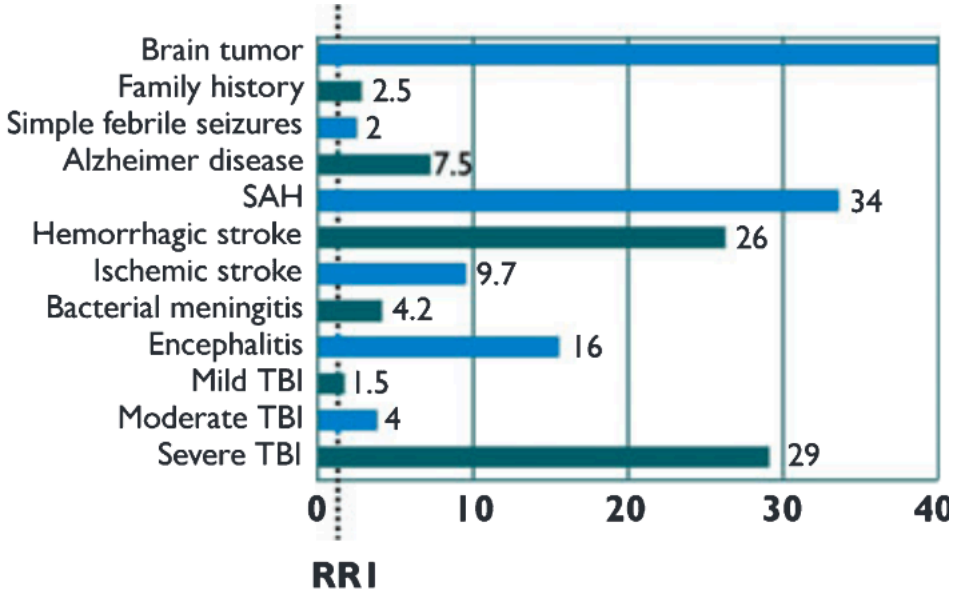


Figure 2.
Relative risks for developing epilepsy (adapted from Herman, 2002).

Lowenstein 2009, *Epilepsia*

Epilepsy and Autism

- Epilepsy and autism commonly co-occur
- In individuals with an autism spectrum disorder, rate of epilepsy is 6% to 27%
  - single most important risk factor is cognitive function
  - age, sex, language and social function are also risk factors
- In children with epilepsy, rates of autism spectrum disorder or autism spectrum disorder symptoms range from 5% to 37%
  - Strong association with intellectual disability
- Genetic variants may contribute to epilepsy + autism co-occurance

Jeste & Tuchman, 2015, *Journal of Child Neurology*

Common Causes of TBI

- **Falls.**
  - Falls from bed or a ladder, down stairs, in the bath and other falls are the most common cause of traumatic brain injury overall, particularly in older adults and young children.
- **Vehicle-related collisions.**
  - collisions involving cars, motorcycles or bicycles
  - also pedestrians involved in such accidents
- **Violence.**
  - Gunshot wounds, domestic violence, child abuse and other assaults.
  - Shaken baby syndrome is a traumatic brain injury in infants caused by violent shaking.
- **Sports injuries.**
  - soccer, boxing, football, baseball, lacrosse, skateboarding, hockey, and other high-impact or extreme sports.
  - particularly common in youth.
- **Explosive blasts and other combat injuries.**
  - Explosive blasts commonly cause TBI in military personnel
  - TBI also results from penetrating wounds, severe blows to the head with shrapnel or debris, and falls or bodily collisions with objects following a blast

From mayoclinic.org

How TBI Damages the Brain- Concussion

- Concussion associated with cell death, dysfunction and neurodegeneration
- Mechanism(s) not well understood
  - Biomechanical injury leads to glutamate release
  - Biomechanical injury also damages dendrites and axons of neurons
  - Axons especially vulnerable to "biomechanical stretching" which leads to altered neurotransmission and cell death

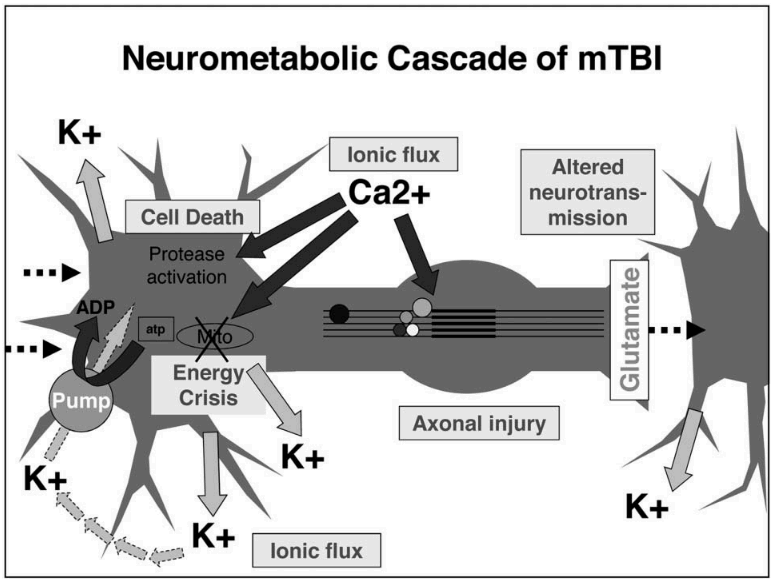
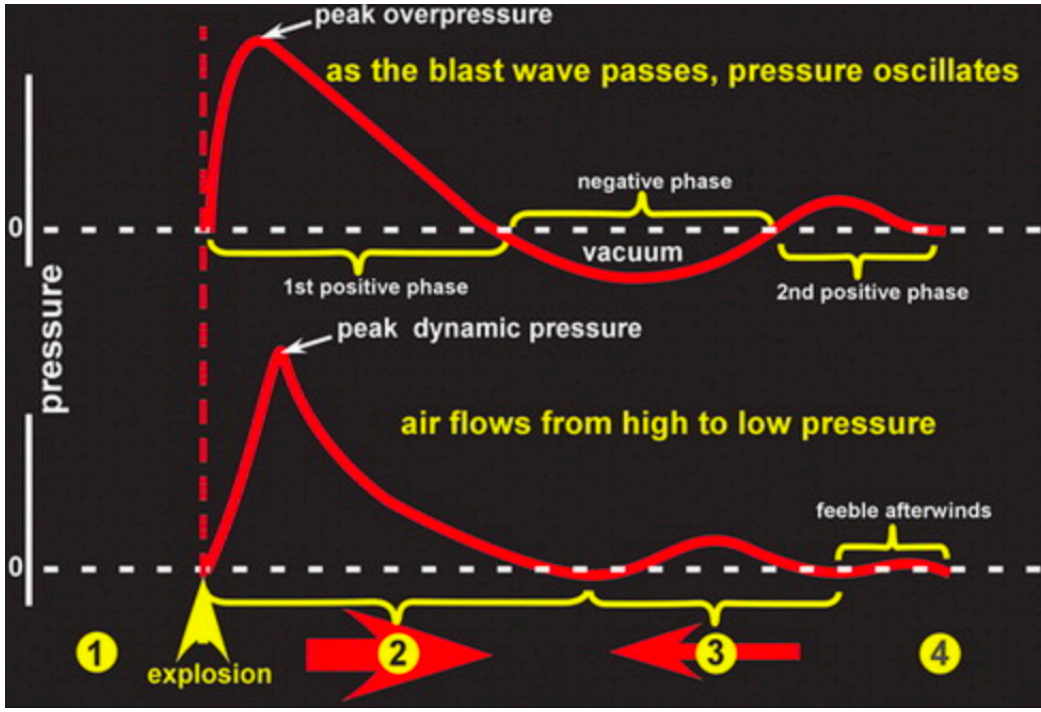


FIGURE 2. *Diagram of the acute cellular biological processes occurring after concussion/mild TBI. mTBI, mild traumatic brain injury.*

Giza & Houvda, 2014 *Neurosurgery*

How TBI Damages the Brain: Primary Blast Injury

- Blast injuries common in war due to increasing use of IEDs
- Changes in atmospheric pressure cause blast injuries
- High-explosive detonation results from nearly instantaneous conversion of a solid or liquid into gasses
- Gasses expand rapidly, cause compression in surrounding air, form a pulse of pressure
- Then pressure drops
- Extreme pressure differences occur as blast wave reaches body leading to concussion, hemorrhage, edema, diffuse axonal injury



Hurley et al., 2006, *Journal of Neuropsychiatry and Clinical Neurosciences*

Effects of Primary Blast Forces on the Brain

- Do primary blast forces injury the brain directly or only indirectly?
  - This is a topic of controversy
- Clinical data are limited
  - In battlefield situation, difficult to identify cases in which *only* primary blast injury is present
- Animal studies provide insights on these questions. In rats:
  - widespread microglial activation after an explosion
  - coordination, balance, and strength significantly impaired following exposure to a larger explosion but not smaller explosion
  - More degenerating neurons seen in cerebral cortex following larger than smaller explosion

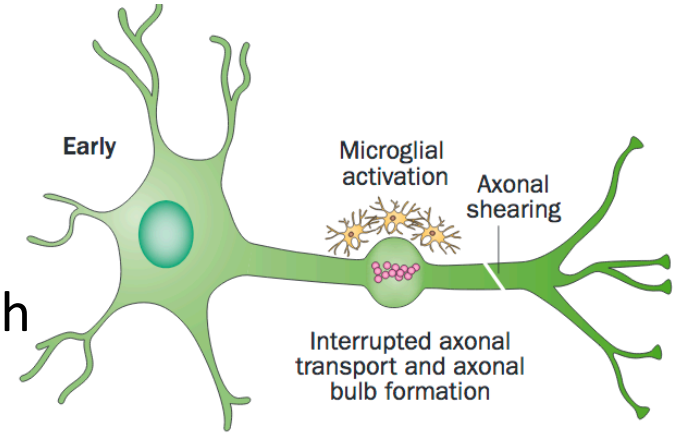
How TBI Damages the Brain- Oxidative Stress

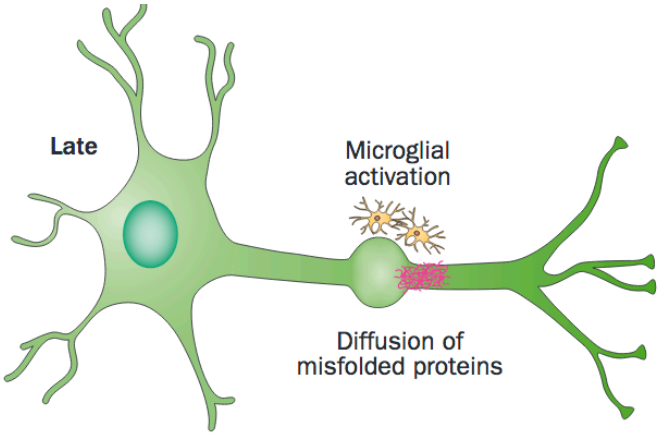
- Close relationship between degree of oxidative stress and severity of brain injury
  - neuronal loss and failure of both inhibitory and excitatory neurotransmission
- Enhanced production of reactive oxygen species plays critical role in TBI
- Oxidative stress occurs very early after TBI
- Oxidative stress negatively impacts synaptic proteins, which affect synaptic functions in the brain's cortex

Ansari et al., 2008, *Journal of Neurotrauma*

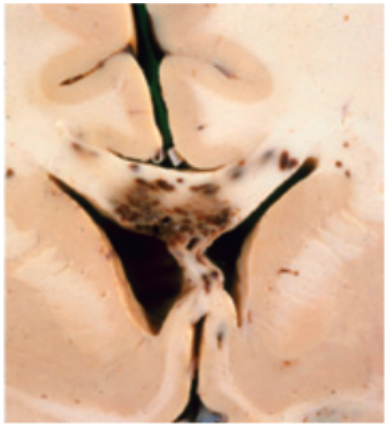
How TBI Damages the Brain—Neural Network Dysfunction

- Diffuse axonal injury interrupts axonal transport and triggers neuroinfla-mmation through microglial activation



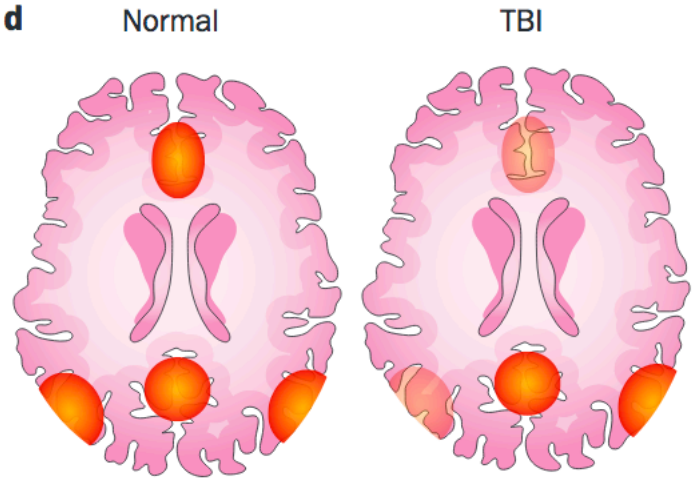


- This leads to damaged white matter tracts…



Disconnection within white matter tract

- …and disconnected brain networks



Large-scale functional network disruption

Sharp et al., 2014, *Nature Reviews Neurology*

How TBI Damages the Brain—Neuroinflammation

- Activation of microglia after TBI is central to the neuro-inflammatory response to injury
  - can persist for months to years after TBI
- Might influence the spread of abnormal proteins
- Could cause neurodegeneration following TBI
- Neurodegeneration is a major determinant of long-term TBI outcome
- Neuroinflammation often located at sites of axonal injury
  - can spread over time to impact the brain more broadly (e.g., disrupt network connections)

Sharp et al., 2014, *Nature Reviews Neurology*

Conclusions

- MS is an autoimmune disease – virus, bacterium, or other immune insult may be important precipitant
- MS prevalence very different across global environments and genetic groups implicating both environment and genetics
- Some children may be born with structural change in an area of the brain that gives rise to seizures
- Infections of the brain and head injuries are common causes of epilepsy
- Falls, collisions, sports, and explosions common causes of TBI
- Oxidative stress and neuroinflammation play important role in effects of TBI