Neurodegenerative Diseases
October 7th, 2016
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Outline

- Global costs & impact

- Alzheimer’s Disease (AD)
  - Symptoms, Pathology, Cellular Mechanisms

- Parkinson’s Disease (PD)
  - Symptoms, Pathology, Cellular Mechanisms

- Traumatic Brain Injury (TBI)
  - Symptoms, Pathology, Cellular Mechanisms
5.3 million Americans diagnosed with Alzheimer’s disease

1 in 9 individuals over the age of 65
1 in 3 individuals over the age of 85
These diseases have an impact around the world.

Global health crisis

GDP ($ Billions)

Mexico ---------- 1,082
Indonesia ------- 936
Netherlands ----- 762
Turkey ------------ 751
Switzerland ------ 651

If global dementia care were a country, it would be the 18th largest economy in the world exceeding the market values of companies such as Apple and Google.
Aging population

Age is the biggest risk factor for most neurodegenerative diseases

1) Increased life expectancy

2) Older individuals make up larger percentage of global population
Incidence rate for most neurodegenerative diseases increases with age

United States birth rate (births per 1,000 population)

Baby Boomers

Born between 1946 and 1964

In 2016: Currently age 52-70
Symptoms of Alzheimer’s Disease (AD)

AD is the most common form of dementia

- Cognitive impairment
  - Confusion
  - Memory deficits
    - (1) Trouble forming new memories
    - (2) Long-term memories affected later
    - (3) Childhood memories are among the last to be lost

- Behavioral Changes
  - Irritability
  - Personality changes
  - Wandering → Getting lost

- Psychological
  - Loneliness
  - Depression

www.alzdiscovery.org
Alzheimer’s disease

Healthy brain

Cerebral cortex:
Responsible for language and information processing

Hippocampus:
Critical to the formation of new memories

Alzheimer’s disease brain

The cortex shrivels up, damaging areas involved in thinking, planning and remembering

Ventricles filled with cerebrospinal fluid grow larger

Hippocampus shrinks severely

Source: Alzheimer’s Association

Plaques

Amyloid-β

Neurofibrillary Tangles

Tau
The hippocampus

“seahorse” in Greek

Involved in the **formation** of new memories, and **consolidation** into long-term memories
Role of Amyloid-β in Alzheimer’s Disease

Normal cleavage product = Aβ-40 (soluble)
Abnormal cleavage product = Aβ-42 (insoluble) → Aggregates → Plaques
Role of Tau in Alzheimer’s Disease

Tau (microtubule-associated protein)

Microtubule

Cell body

Axon

Hyper-phosphorylation of Tau

Destabilized microtubules (impaired axonal transport)

Neurofibrillary Tangles

Paired helical filaments

Hyperphosphorylated tau proteins

(Querfurth & LaFerla, 2010)
Misfolded proteins that stick together to form aggregates can induce normal proteins nearby to misfold as well.

Proteins can break off from aggregates and start these events over again in a process called **Seeding**.

These aggregates can then spread between neurons and throughout the brain.
Parkinson’s Disease
Clinical symptoms of Parkinson’s Disease

2nd most common neurodegenerative disease (~1 million Americans currently diagnosed)

Locomotor Impairment

- Difficulty moving when you want to
- Uncontrolled movement when you don’t want to
- Bradykinesia - slow movement

2-minute neuroscience
Substantia Nigra

(INDIRECT) control of movement

Coordination of motor programs
(both excitatory & inhibitory)
Aggregates of alpha-synuclein are the primary component of Lewy Bodies.
Alpha-synuclein localizes to synaptic terminals

1) Recycling of synaptic vesicles

2) Trafficking of synaptic vesicles from reserve pool to readily releasable pool
Aggregates of alpha-synuclein block lysosomal degradation

**Autophagy** = “self eating”
Breaking down and recycling cellular material (proteins, organelles, etc.)
Traumatic Brain Injury

Chronic Traumatic Encephalopathy (CTE)
Comparison of Tau pathology

Case 1
- Alzheimer’s Disease
- Age: 85

Case 2
- Chronic Traumatic Encephalopathy (CTE)
- Age: 40’s

McKee et al., 2013
The History of CTE

Dementia Pugilistica
“Punch-drunk” (1928)
The History of CTE

Mike Webster (1952 – 2002)
4 Super Bowl Championships

Amnesia
Dementia
Depression

Died from heart attack at age 50
The History of CTE

Mike Webster

Terry Long

Justin Strzelczyk

Tom McHale
Growing prevalence of CTE

Boston University: As of September 2015, **87 of 91** deceased former NFL players tested positive for CTE

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*Every case of diagnosed CTE has had one thing in common: a history of repetitive hits to the head.*

—Robert Stern, director of clinical research for Boston University's CTE center
JUDGE APPROVES $1 BILLION SETTLEMENT FOR THOUSANDS OF NFL CONCUSSION SUITS

By Polly Mosendz on 4/22/15 at 7:01 PM

For first time ever, NFL admits there's a link between CTE and football

The NFL made a surprising admission about CTE on Monday.

by John Breech  @johnbreech  Mar 15, 2016  •  3 min read
Damage to the brain in a closed head injury

The brain is not stationary inside the skull.

**Bathed in CerebroSpinal Fluid (CSF)**

Brain can be damaged from impact, but also from acceleration or deceleration secondary to the force of impact.
Damage to the brain in a closed head injury

The force from the impact causes the brain to hit the inner surface of the skull and rebound against the opposite side.

Padding on the outside of the head can only do so much. Helmets have been very effective at preventing skull fractures, but not concussions and other types of closed head injuries.
Diffuse Axonal Injury

When the brain moves around inside the skull after impact, the tissue can stretch and tear.

1) Neuronal loss

2) Release of toxic proteins
Many sources of traumatic brain injury

Over 115,000 troops have suffered traumatic brain injury over the last 10 years.
Treatments for TBI

• Current focus on monitoring individuals after injury
  • Avoiding repetitive injuries

• Identify biomarkers
  • Read-out in living patients to study pathology
  • Current diagnosis is in autopsy

• Why are neurofibrillary tangles (tau aggregates) widespread in cases of CTE?
  • Will any treatments to clear these tangles help with CTE?
  • “You pop a pill before you play, a medicine that prevents the buildup of tau. Like you take an aspirin to prevent heart disease.” - Bennet Omalu
Summary

1. Aging is the biggest risk factor for diseases like Alzheimer’s & Parkinson’s Disease.

2. Particular areas of the brain are vulnerable in each disease.
   - The symptoms reflect the functions of those brain areas (Hippocampus & Substantia Nigra)

3. Key Players in these diseases:
   - (AD) Tau, Amyloid-Beta
   - (PD) alpha-synuclein

   Aggregates

4. The relationship between the brain and the skull is large part of why the brain is susceptible to injury after impact.