INTRODUCTION TO NEUROLOGICAL DISEASE

Learning in Retirement
Session #5
STROKE
Lesson Overview

• Neurocirculation
• Intro to Stroke
• Causes and Results
• TIA's
• Stroke Pathology
  • General
  • Cellular
  • Molecular
• Prognosis and Treatment
• Common Impairments Following Stroke
Neurocirculation

- Brain’s blood supply comes from **common carotid** and **vertebral arteries**

- These arteries form a communication circle at the base of the brain: **Circle of Willis**

- Main arteries of the brain arise from this circle (ACA, MCA, PCA)
  - Note the limited overlap in the regions they perfuse
Intro to Stroke

- 2nd leading cause of death globally
  - Has been for 15 years

- In the U.S., approximately 800,000 people suffer a stroke each year

- In Canada, someone suffers a stroke every 10 minutes (50,000 new strokes each year)

- Leading cause of disability in Canada and the U.S.

World Health Organization, 2017
Intro to Stroke

- **Ischemia** – lack of blood flow to tissue or organ
- **Stroke** – interruption of blood flow to the brain
- Two types:
  - **Ischemic**: blockage in blood vessel (80% of strokes)
  - **Hemorrhagic**: rupture in blood vessel (20% of strokes)
- Ischemic stroke can be further classified as:
  - **Large-vessel thrombosis**: blockage in one of larger blood-supplying arteries (e.g. carotid, MCA)
  - **Small-vessel thrombosis**: blockage in one of smaller, but deeper, arteries
What Causes Stroke?

• Narrowing of the arteries in the neck or brain
  • Usually caused by deposits of cholesterol in the arteries (atherosclerosis), which forms plaques

• Certain genetic mutations (changes in DNA) can:
  • ↑ risk of extreme hypercholesterolemia
  • Damage blood vessel walls
  • Cause clotting disorder

• Environmental/Experiential Factors
  • High BP, smoking, obesity, inactivity, trauma, alcoholism
    • Common link in all of these = ↑ inflammation of vessel walls
What Results from a Stroke?

- **Symptoms and prognosis** depend on where the stroke occurred (severity and duration of blockage also important)
  - Deficits observed will be specific to function of affected region
    - And will be on opposite side
- Cerebellar stroke results in **ataxia**
  - Deficits observed = motor impairment; difficulty walking, balance and coordination problems
- Brain stem stroke
  - Rare, but most often **fatal**.
Hemorrhagic Stroke

- Less common, but accounts for nearly 40% of all stroke deaths

**Intracerebral hemorrhage**
- Most common → blood vessel ruptures
- Blood leaks into surrounding brain tissue (intracerebral hemorrhage)
- Creates swelling (edema) and increased pressure
- Damages cells → Leads to cell death
- Most common causes: high BP and aging blood vessels
- Mortality rate: ~35%

**Subarachnoid hemorrhage**
- Involves bleeding in the subarachnoid space
- Most often, caused by a burst aneurysm
- Aneurysm: blood-filled bulge in weakened blood vessel wall
- Mortality rate: 40-50% (i.e. prognosis not good)
Ischemic Stroke Spectrum

**MILD**
- Transient ischemic attacks
- Brief loss of perfusion
- May affect whole brain, or be region-specific

**MODERATE**

**SEVERE**
- Global ischemia
- Complete loss of perfusion
- Often fatal
Transient Ischemic Attacks (TIAs)

- Also known as ‘mini-strokes’
- Causes and symptoms the same as stroke (but last only mins – hours)
  - Average = 5 mins; MAX = 24 hrs
- They precede a more severe ischemic attack in 15-30% of patients
- TIAs might actually be protective.
  - The brain can adapt to things, if they occur slowly
  - Lack of blood flow \(\rightarrow\) hypoxia (lack of O2)
    - Brain can adapt to this (at least partially)
  - Might be that TIA primes (i.e. prepares) brain to deal with upcoming larger event
  - Ischemic preconditioning is a thing, and it works in animal studies
- Treatment using anti-coagulants (blood thinners) helps prevent clotting and larger stroke – treatment very beneficial at this stage
Effects of ↓ Blood flow

- Why is it so serious? Because the brain is an energy HOG (2% VS 20%)
- Maintaining all those membrane potentials takes a lot of energy – but the brain has nearly no energy stores of its own!
- Brain relies on blood supply to get its glucose and oxygen (i.e. FUEL for all processes)
- As little as FOUR minutes without perfusion can result in permanent cellular damage (and functional deficits)

The cascade of cellular events following stroke are what cause the real damage to the primary site and surrounding regions.
Pathology - General

- There are TWO distinct damaged regions after stroke
  - The **CORE**
    - The area directly fed by occluded vessel
    - <20% of normal blood flow
  - The **PENUMBRA**
    - The outskirts of the lesion
    - Receiving blood flow from other vessels (vessel overlap)
    - Between 20—40% normal blood flow
Cell Death

- **Necrosis**: *Cytolysis*; cells rupture, spilling their contents into the extracellular space
- **Apoptosis**: aka *programmed cell death*; cells are dismantled into membrane-bound vesicles

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Inflammatory Response: ✓

No Inflammatory Response: ✗
Pathology - General

• Infarction: Ischemia-induced cell death
  • Death is most pronounced in the core (region closest to blockage)
• How are the cells dying?
  • Apoptosis
  • Necrosis
Pathology - Cellular

- Two main ways cells can die:
  - **Apoptosis** (not always a pathological process)
    - Recall – maintaining the neuron’s resting potential (at -70mV) is an *active process* (requires energy to fuel ion pumps, in the form of glucose)
    - In stroke, lack of blood = lack of glucose → no fuel for Na/K pump – resting potential cannot be maintained
    - Cells depolarize (many contain glutamate)
    - Flooding of Glu leads cells to initiate self-destruct sequence (called *excitotoxicity*)
  - **Necrosis** (always a pathological process)
    - In stroke, lack of oxygen → switch to anaerobic metabolism
    - Acid build-up → Membrane permeability
    - Ions rush in, followed by water (gradient)
    - Cells swell and rupture
Pathology - Cellular

- So how does the type of cell death differ between infarct regions?
- **CORE**
  - The most dire region
  - See both necrosis and apoptosis
- **PENUMBRA**
  - “Ripple effect”
  - Remember, the core is not at all synaptically separate from the penumbra
    - Toxic signaling cascades can spill into the surrounding region
    - The cells tend to die from apoptosis
    - Cells may be able to survive hours or days after ischemic attack
- So where should researchers focus their attention? Core or penumbra?
Pathology - Cellular

• Another membrane that is compromised due to lactic acid build-up...
• **Damaged blood brain barrier (BBB):** the gateway to the brain, maintained by the glial cells, which act as the “gatekeepers”
• A weakened BBB is no longer ‘air-tight’
  • This means that, during **reperfusion**, peripheral immune cells can leak through and **exacerbate** the immune response and inflammation. And the cycle continues...
**Pathology - Molecular**

- **Inflammatory Response**: A double-edged sword
  - Microglia release pro-inflammatory cytokines
    - Helpful and harmful
  - Reperfusion (return of blood flow) brings peripheral immune cells with it, because BBB weakened
    - Helpful: Reperfusion necessary for return of energy source and clean-up of damaged cells, but...
    - Harmful: Leukocytes (white blood cells) infiltrate via damaged BBB, and release even more inflammatory molecules, further compromising its stability and may impede recovery (due to prolonged inflammatory response)

Lakhan et al., 2009
Pathology - Molecular

- **Increase in Ca\(^{2+}\)** inside cells as a result of neuronal depolarization (calcium signals NT vesicles to approach the membrane)

- **Why is this bad?**
  - **1** – Ca\(^{2+}\) influx triggers the release of Glu
    - Aggravates excitotoxic cascade
  - **2** – Excess Ca\(^{2+}\) results in the production of reactive oxygen species (ROS)
    - ROS are normal (in small amounts), and can be balanced out by anti-oxidants
    - Excess ROS place too much stress on the cell
      - Cell releases signals to induce apoptosis
      - Cell suicide
Pathology - Summary

• General
  • Core – necrosis and apoptosis
  • Penumbra – apoptosis (ripple effect)

• Cellular
  • Epithelial cells: hypoxia leads to weakened BBB (lactic acid build-up)
  • Neurons: hypoglycemia leads to neuronal depolarization (Glu excitotoxicity); hypoxia leads to compromised membrane (acid)

• Molecular
  • Inflammatory Response (microglia, leukocytes during reperfusion)
  • Excess calcium in cells (Glu release, ROS production)

Lakhan et al., 2009
Prognosis

- **Collateral circulation** refers to the blood flow through secondary pathways after the obstruction to the principle pathway occurs.

- Survival of the affected region depends on:
  - Degree of vascular obstruction
  - How quickly obstruction occurred
  - Length of time region is ischemic (blocked; no blood flow)
  - The degree of available collateral circulation

The degree of collateral circulation is the **single most important factor** in determining the extent of tissue damage following ischemia.
Treatment: Acute

- Need to restore blood flow
- Tissue plasminogen activator (TpA) – clot buster!
  - Must be given within first few hours after symptoms appear (3-4.5 hours)
  - This is why recognizing the symptoms of stroke is essential!!!
- Neurothrombectomy: surgical removal of the blood clot
- Minimize impact of post-stroke cascade?
  - Many trials going on currently...little success so far 😞
Neuroplasticity

• Neuroplasticity: the ability of the brain to reorganize and form new connections

• Most patients who survive a stroke recover at least a portion of their neurological function

• Following neuronal death and removal of dead tissue/debris, nearby undamaged neurons can migrate to the affected area and take over some lost functions
  • Migration is limited to ~5mm
  • When damage is extensive, recovery of function is less than complete
Endogenous Repair

- Regrowth after stroke:
  - Axonal sprouting
    - New connections from surviving neurons
    - Re-innervation possible – recovery of function 😊
      - Contrast to pathological connections in phantom limb pain
  - Angiogenesis
    - Vascular growth
    - Restores flow of nutrients to the area

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Therapy

• Speech/physical therapy
  • What does this help facilitate?

• Cell replacement therapy
  • None currently approved
  • Many early phase clinical trials ongoing
  • Many questions remain...
    • Best source of cells?
    • When/how/ how many to transplant?
    • How to ensure cells localize (i.e. go where they are supposed to) and integrate (become functional in the network)
    • How to ensure that cells develop into the proper cell type
Common Impairments Following Stroke

- **Motor Symptoms**
  - Impairments in upper limb use
  - Walking (esp. independent ambulation)
  - Inactivity following stroke exacerbates problem

- **Sensory Disturbances**
  - Damage to sensory pathways can lead to tingling, numbness, and chronic neuropathic pain following stroke

- **Cognitive Impairments**
  - Memory, learning, language
  - **Anosognosia**
  - Hemi-spatial neglect
Hemi-Spatial Neglect

- Most common after lesion in right parietal lobe
  - Left side hemi-neglect most common
- Patients are unaware of their condition
- Sensory visual pathways remain intact
- Patients completely ignore (neglect) left hand side of space
- Patients with hemispatial neglect
Stroke: The Big Picture

• Stroke therapy is an intensely researched area – very little success to date

• Although tPA saves lives and represents a major advancement in the therapeutic intervention for ischemic stroke, only ~3% of stroke victims actually receive tPA!
  • Mostly lack of public knowledge RE: stroke, symptoms, importance of taking action fast

• At this point, stroke prevention is actually our best hope
  • Keep BP under control, maintain a healthy diet and bodyweight, quit smoking
INTRODUCTION TO NEUROLOGICAL DISEASE

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Session #5
PARKINSON’S DISEASE
Lesson Overview

• What is Parkinson disease?
• Risk Factors
• Substantia Nigra
• Clinical Features
  • PD Pathology
    • General
    • Cellular
    • Molecular
• Treatment
• Prognosis
What is PD?

- PD is a progressive, neurodegenerative, adult-onset movement disorder
- Originally described by Dr. James Parkinson in 1817 in his work *An Essay on the Shaking Palsy*
- Later renamed Parkinson’s disease by Jean-Martin Charcot, known as the “father of modern neurology” – fun fact, ALS is also called *Charcot disease* (Charcot’s name is used in at least 15 medical conditions)
- PD is the 2nd most common neurodegenerative disorder, after AD, affecting 1% of people over age 60
- Most of the time, PD is sporadic (90-95%); sometimes, genes are involved (5-10%)
  - Most often, likely a combination of risk factors involved in development of PD
Risk Factors

- Genetic, Environmental, and Experiential
  - Family History
  - Mutations in PINK1, Parkin, α-synuclein genes
- Age (adult-onset, typically > 60)
- Sex (men 1.5x more likely to develop)
- Exposure to pesticides (e.g. Paraquat) or heavy metals
- Rural or remote living
Substantia Nigra

- Located in the midbrain (bilateral)
- Can be split into two sub-regions
  - Pars reticulata (SNr)
  - Pars compacta (SNc)
    *SNc is the affected region in PD
- SNc sends signals to the striatum (part of the basal ganglia, role in voluntary movement) using dopamine (DA)
  - This ‘highway’ between these two regions is called the nigrostriatal pathway
  - Ultimately, helps stimulate motor cortex → produces movement
  - When neurons in SNc die, pathway is disrupted, and person becomes hypokinetic (state of decreased movement)

Degeneration of DAergic neurons in the SNc by unilateral administration of the toxin 6-hydroxydopamine
PD: Clinical Features

- SNc not only helps to initiate movements, but also helps fine tune them
  - Loss of SNc neurons results in **motor symptoms** observed in PD

- **Resting tremor**: involuntary shakiness, present at rest, diminishes with intentional movement

- **Rigidity**: stiffness; ‘catches’ during passive movement (also responsible for stooped posture, and ‘expressionless’ face some display)

- **Bradykinesia**: slow movement due to difficulty initiating movement (ex. legs freeze up when walking, shuffling gait)

- **Postural Instability**: problems with balance; can lead to falls

**Despite motor symptoms, PD does not produce weakness** (this can help distinguish it from disorders that affect the motor cortex and corticospinal pathway like ALS, for ex).
PD: Clinical Features

- PD also involves various **non-motor symptoms**
- Depression
- Cognitive Changes
  - Problems with focus, attention, and planning
  - Dementia
- Sleep Disturbances
- Olfactory Problems
- May result from DA signalling problems in other regions (e.g. PFC, leading to cognitive issues)
- May result from dysfunction in other NTs
Diagnosis

- PD difficult to define for several reasons
  - Heterogeneity of clinical presentation
  - Variability of progression rate
  - Different signs and symptoms present in clinical sub-types

- To this date, diagnosis relies on:
  - Presence of primary motor symptoms + response to DA replacement therapy
  - **Definitive diagnosis** can occur only at autopsy
PD Pathology: General

- **MOST prominent feature: selective death of DA neurons in substantia nigra**
  - Loss of DAergic neurons in the substantia nigra pars compacta (SNpc)
  - These neurons project to the striatum
  - Loss of these projections leads to dysfunction of basal ganglia, influencing voluntary movement
  - Motor symptoms arise mostly due to this dysfunctional circuit

- **Involvement/selective loss of other NTs**
  - Serotonin (5-HT) neurons in raphe nucleus
  - Norepinephrine (NE) neurons in the locus coeruleus
  - May contribute to non-motor symptoms of PD
PD Pathology: General

• **Lewy Bodies**
  • Protein aggregates found in DA neurons in SN before they die – also observed diffusely in brains of PD patients post-mortem – primarily composed of **α-synuclein** (and other proteins, too)
  • How do LBs contribute to pathology? Much still unclear (including α-synuclein’s role in healthy brain) – but most people with PD have them
PD Pathology: General

• **Lewy Bodies**
  • LBs present in other disorders, too, and even in *healthy* individuals; Buchman et al. (2012) found that out of 744 healthy patients, 17% had LBs without fulfilling PD criteria
  • Interestingly, α-synuclein pathology can develop in previously healthy embryonic DA neurons when transplanted into brains of PD patients (Kordower et al., 2008) – pathological process is present
PD Pathology: Cellular

- Cells in SN appears to be particularly vulnerable to degeneration, in part because of:
  - ↑ numbers of microglia
    - Amplified immune response
  - High concentration of DA neurons
    - Produce reactive oxygen species (ROS) when broken down
    - Creates condition of oxidative stress (ROS>anti-oxidants)
  - ↑ sensitivity to pro-inflammatory cytokines
    - Thought to be linked to oxidative stress
    - Not good though, because these pro-inflammatory cytokines are released in large quantities by the numerous SN microglia during immune response
PD Pathology: Molecular

- **Inflammation**
  - Prolonged microglial activation leads to release of neurotoxic factors; SN has higher density of microglia than other brain regions, making it particularly **vulnerable**
  - Increased sensitivity to cytokines has been linked to oxidative stress

- **Oxidative Stress**
  - Production of ROS (DA metabolism, aberrant cellular processes, microglial activation)
  - ROS can induce pro-inflammatory signalling
  - If too many ROS present, cells can shut down – signals for cell suicide

Inflammation and Oxidative Stress are intimately linked, and one likely exacerbates the other in PD.
PD Pathology: Summary

- General
  - Death of DA-producing neurons in the SNc
  - Lewy bodies

- Cellular
  - Particular vulnerability of cells in the SNc

- Molecular
  - Inflammation
  - Oxidative Stress

FIGURE 3. Illustration showing low levels of dopamine in a neuron affected by Parkinson's disease (right) and normal levels (left).
Treatment

• **L-Dopa**
  • Goal is to **replace DA** that has been lost
  • **Problem**: DA doesn’t cross the BBB
  • **Solution**: L-Dopa, its precursor, does
  • Once in the brain, L-Dopa is converted to DA by an enzyme called **Dopa-Decarboxylase**
  • Most importantly, it specifically acts on the neurons in the SNc to increase amount of DA available in remaining nigral neurons
  • **New Problem**: Dopa-Decarboxylase also exists in the **periphery**.
  • For this reason, L-Dopa is administered with **Carbidopa**, a Dopa-Decarboxylase **inhibitor**
  • **Another Problem**: L-Dopa is only effective temporarily, and after about 5-10 years, **dyskinesias** develop
Treatment

• **Deep-Brain Stimulation**
  • Like a ‘pacemaker’ for the brain
  • Electrodes are able to specifically stimulate regions of the brain
  • Connected to a ‘battery pack’ that is placed under the clavicle
  • We are essentially changing electrical activity within the brain – and relieving motor symptoms of PD in the process

• **Other Treatments**
  • DA agonists: substances that stimulate DA receptors
  • *Antagonists* to enzymes that degrade DA
Prognosis

• PD itself isn’t fatal, but often complications of symptoms can reduce life expectancy – and overall quality of life is definitely affected

• Several treatments are promising (assisting with symptoms only, not pathology)

• No way to slow down/reverse neuronal loss and prevent eventual death

• This is where research like mine comes in!
  • Toxin-based animal models of PD
  • Neurotrophic factors – e.g. EPO
  • Influencing the microenvironment of the SNc in order to promote cell survival