INTRODUCTION TO NEUROLOGICAL DISEASE

Learning in Retirement
Session #6
Alzheimer disease
Lesson Overview

- Normal Aging VS Dementia
- What is Alzheimer disease?
- AD Pathology
  - General
  - Cellular
  - Molecular
- Prognosis and Treatment
Dementia

- **Dementia** refers to a set of symptoms that are caused by disorders that affect the brain.
- Symptoms may include memory loss, problems with thinking and problem-solving, and language problems.
- Changes in mood or behaviour are also common.
- Impairments in these processes are severe enough to affect daily life.
- Dementia is progressive (symptoms worsen as more brain cells die).
- **Dementia is not a specific disease**; many diseases *cause* dementia (e.g. Alzheimer disease, Huntington’s disease, head trauma, Parkinson’s disease, etc).

Alzheimer’s Society of Canada, 2017
Normal Aging VS Dementia

• Memory loss is associated with normal aging; however, these problems are caused by *dysfunctional neurons* rather than *dying neurons*. This represents the main difference in neuronal pathology between normal aging and dementia.

• While both normal aging and dementia target neurons in the *hippocampus*, different patterns of anatomical dysfunction are observed (different cell populations are affected; Small et al., 2011).

• Almost 40% of people over the age of 65 experience some form of memory loss – this is known as ‘age-associated memory impairment’, has no underlying medical cause, and is considered a normal part of the aging process.
Normal Aging VS Dementia

• Age-associated memory impairment is not the same as Alzheimer disease and other forms of dementia

• Some ways to distinguish the two based on functional abilities

<table>
<thead>
<tr>
<th>Normal Aging</th>
<th>Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forgetting details of a conversation or an event that took place last year</td>
<td>Failure to recall details of recent events or conversations</td>
</tr>
<tr>
<td>Forgetting names of acquaintances</td>
<td>Not recognizing or knowing good friends and family members</td>
</tr>
<tr>
<td>Occasionally having a difficult time finding words</td>
<td>Frequently pauses and word substitutions during a conversation</td>
</tr>
<tr>
<td>Individual worries about memory loss, but family members do not</td>
<td>Family worries about memory loss, but individual is not aware of any problems</td>
</tr>
</tbody>
</table>
Alzheimer Disease

• First described by Dr. Alois Alzheimer in 1907
  • He followed a patient in an asylum with symptoms including memory loss, language problems, and unpredictable behaviour
  • After her death, Alzheimer noticed abnormal clumps and tangled fibers in her brain
  • By 1911, doctors were using Alzheimer‘s research to base diagnoses – but abnormal protein forming aggregates not identified until 1990s
AD: The Stats

- AD is the leading cause of dementia
  - Accounts for 60-80% of cases

- It is a neurodegenerative disease, following a specific pattern of degeneration

- Globally, number of people suffering from dementia estimated around 25 million, and expected to double every 20 years until at least 2040

- Of the top 10 leading causes of death in the US, AD is the only disease that cannot be prevented, slowed, or cured
AD: Symptoms

- **Mild cognitive impairment (MCI)** refers to memory problems greater than expected for age, but no daily functional impairments observed.
- Older people with MCI at greater risk for developing AD, but not all do.
- AD progresses in stages – mild, moderate and severe.
  - Memory problems usually appear first, but symptoms vary between individuals.
  - For many, non-memory aspect of cognition are affected first.
    - E.g. word finding, vision/spatial issues, impaired reasoning or judgment.

![Diagram showing stages of Alzheimer's disease](image-url)
AD: Symptoms

- **Mild AD**: Increasing memory loss, other cognitive difficulties
  - Wandering/getting lost, trouble handling money, repeating questions, taking longer to complete tasks, personality and behavioural changes
  - Apathy, depression

- **Moderate AD**: Involvement of language, reasoning, sensory processing, and conscious thought
  - Memory problems worsen, trouble recognizing friends and family
  - Unable to learn new things, difficulty with multi-step tasks (e.g. getting dressed), or cope with new situations
  - At this stage, people may have hallucinations, delusions and paranoia, and may behave impulsively

- **Severe AD**: Massive cell loss leads to dependence
  - Cannot communicate, bed ridden as body shuts down
AD: Symptoms

- Summary of symptoms clustered by category (all are progressive during course of disease)
  - **Cognitive and Functional abilities**
    - Changes in ability to understand, think, remember and communicate
  - **Emotions and Mood**
    - Increased apathy/depressive symptoms (e.g. anhedonia), decreased expression of emotions, withdrawal from social circles/family
  - **Behaviour**
    - Increase in ‘out of character’ behaviours (e.g. hiding possessions, physical outbursts, restlessness, repeating things)
  - **Physical Abilities**
    - Impairments in coordination and mobility influence individual’s ability to perform daily tasks independently (e.g. eating, bathing, dressing)
AD: What Causes it?

- **AD** can be sporadic (late onset, >65, 90-95% of cases) or familial (early-onset, <65, 5-10% of cases)

- **Sporadic** – causes not understood, likely a combo of genetic and environmental risk factors
  - Age = biggest risk factor
    - Affects 1% of ppl >65; 50% of ppl >85
  - Genetic risk factor: e4 allele of *apolipoprotein E (APOE)*
    - APOE is polymorphic, with 3 major alleles (variant forms) – e2, e3, e4
    - The protein APOE helps break down a protein called beta-amyloid, which forms aggregates (clumps) in AD
    - e4 allele (frequency of ~14%) seems to be less effective than other forms at breaking down beta-amyloid
    - Inheriting 1 e4 allele ↑ risk of developing AD
    - Inheriting 2 e4 alleles ↑↑ risk

- **Familial** – involvement of dominant gene that speeds up progression of disease
  - Several genes have been identified that are linked to pathology observed in AD (e.g. Trisomy 21; Down Syndrome)
AD Pathology: General

- AD can only be **definitely diagnosed** after death, when patterns of neuronal damage can be clinically assessed within the context of symptoms patient exhibited
  - Plaques and tangles; other causes for dementia must be ruled out

- Degeneration begins in the limbic structures (e.g. hippocampus), and spreads to the cortex over time

- Brain atrophies, gyri get narrower, sulci get wider, ventricles enlarge
Two key pathological features of AD:
- Beta-amyloid plaques (form outside cells)
- Neurofibrillary tangles (form inside cells)

Beta-amyloid plaques can elicit an immune response by glial cells, and can deposit near blood vessels (called amyloid angiopathy) – weakens blood vessel wall and increases risk of hemorrhage.

Tangles lead to dysfunctional axons, and cells initiate apoptosis

(Verkhratsky et al., 2010)
AD Pathology: Molecular

- **Microglia** normally take up beta-amyloid protein (debris-clearing role)
  - However, microglia are also *activated* by plaques
  - They release pro-inflammatory cytokines – causing damage to nearby cells

- **Astrocytes**: Early in disease, atrophy causes disruption of synaptic signalling, NT homeostasis, neuronal death via excitotoxicity; later on, astrocytes become activated and contribute to inflammatory response

- **Reactive Oxygen Species**: Build-up occurs with aging, which renders neurons vulnerable due to oxidative stress on cells

(Verkhratsky et al., 2010)
Treatment

- None of currently available pharmacological treatments slow or stop damage to neurons.

- Six drugs for AD are FDA approved, and temporarily improve symptoms by increasing NTs in the brain - effectiveness of drugs varies person to person.
  - E.g. acetylcholinesterase inhibitors.

- Between 2002-2012, 244 drugs for AD were tested in clinical trials.
  - Only 1 successfully completed clinical trials and became FDA approved.

- Developing effective treatments for AD is challenging for a number of reasons:
  - Cost of drug development.
  - Time required to observe slowing/changing of disease course in response to treatment.
  - Blood brain barrier – getting the drug to the brain.
Prognosis

• AD is fatal, usually within 8-10 years of diagnosis (variable though)

• Cause of death is usually infection

• Can we prevent AD?
  • No, but a nutritious diet, physical activity, and engaging in mentally stimulating activities regularly can help people stay healthy as they age
  • These factors might reduce the risk of AD by preventing cognitive decline in aging individuals
Coping with Memory Loss

- Some tips to help cope with memory loss:
  - Keep a routine
  - Organize information (post-its/notes, calendars, reminders for pills/appointments)
  - Put items in safe/same spot (i.e. car keys, phone, wallet)
  - Repeat information when it is learned (e.g. names), and use associations to help recall
  - Tell stories to others

- When interacting with someone with any form of memory loss, remember to be patient, seek support/community, and remember that your own health (both physical and mental) is required to be in a good state for you to care for another

“Alzheimer’s creates a kind of friction that the family needs to be strong for. You have to hold onto things and know what is true in life.” - Candy Crowley
Take Home Message

• Our ability to develop effective therapies for diseases depends on our ability to understand them

• The less we know about a disease’s mechanisms, the more in vitro and in vivo studies (usually beginning with rodents) are required in order to build our understanding of underlying pathology

• More than 100 years following its initial description, we are almost no further along in our understanding of AD
  • Not entirely true from a research perspective
  • From a patient’s perspective, though…
INTRODUCTION TO NEUROLOGICAL DISEASE

Learning in Retirement
Session #6
Split Brain Patients
Lesson Overview

• Video: Intro
• Left and Right hemispheres
• Lateralization
• Flow of Visual Information
• Callosotomy
• Left Brain: The Interpreter
  • Michael Gazzaniga
• Video: Interpreter Stories
Left Brain: The Interpreter
Left and Right Hemispheres

• Review of the hemispheres...

• Recall, both hemispheres take part in many functions → These are called redundancies
  • Networks of neurons on both sides contribute to many cognitive processes

• Some functions are lateralized
  • One hemisphere almost unilaterally controls certain processes

<table>
<thead>
<tr>
<th>LEFT</th>
<th>RIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Language</td>
<td>Spatial analysis</td>
</tr>
<tr>
<td>Problem-solving</td>
<td>Perception</td>
</tr>
<tr>
<td>Semantic knowledge (richer)</td>
<td>Part-whole relations</td>
</tr>
</tbody>
</table>
Lateralization

- Certain regions unilaterally specialized for specific functions – language is the most lateralized cognitive function, residing almost entirely in the left hemisphere.

- Some language ability exists in the right hemisphere, it’s just much less developed than in the left hemisphere.

**Two important brain areas in the LEFT:**

- **Broca’s area:** Speech production
  - Frontal lobe

- **Wernicke’s area:** Language comprehension
  - Temporal lobe
Flow of Visual Information

- Each EYE sends information to both sides of the brain
- Each eye has two halves to its visual field – a temporal and a nasal ‘side’
- The right visual field (RVF) is located in the left half of each eye
- The left visual field (LVF) is located in the right half of each eye
- This represents a redundancy in our visual system – half of each visual field is located in each eye, so that the loss of one eye does not result in a total loss of vision
Flow of Visual Information

- When looking at an object in our visual field, due to refraction at the cornea, the image gets reversed (flipped) on the retina
- Information from the **temporal** halves of each retina travels **ipsilaterally** to the cortex
- Information from the nasal halves of each retina travels **contralaterally** to the cortex

**The result?**
- Info from the **LVF** is processed in the **right hemisphere**
- Info from **RVF** is processed in the **left hemisphere**
Flow of Visual Information

- If we want to simplify, we can say that:
  - The ‘left half’ of each eye processes visual information from the right visual field (RVF)
  - The ‘right half’ of each eye processes visual information from the left visual field (LVF)
- In this oversimplified diagram, can anyone spot the ‘mistake’?
Flow of Visual Information

• So, if looking straight ahead, an object placed to the LEFT (of the nose) will only be picked up by our LVF (the right half of each eye)

• Why can’t the left half of the left eye see it?
  • It is processing signals from the right visual field

• Most often, we think of our eyes looking out, when in reality, the visual information is coming in – and it does so in a specific, structured way
Callosotomy

- What is a split-brain patient?
  - Callosotomy
    - Epilepsy, primarily
  - Resulting flow of information from visual fields to cortex is unaffected
  - What influence would a lack of hemispheric communication have?
    - None, unless some functions were primarily located in only one hemisphere
Callosotomy

• What would this patient tell you that (s)he sees?
Callosotomy

• What would this patient tell you that (s)he sees?
Callosotomy

• What would this patient tell you that (s)he sees?
Left Brain: The Interpreter

- **Michael Gazzaniga**, a renowned researcher in the area of split-brain patients, has conducted many experiments with patients who have had callosotomies.

- These patients are special, because their two hemispheres cannot communicate with one another.

- Through his experiments, Gazzaniga has discovered that the left hemisphere is **lateralized** for one very important function – making sense of the world (e.g. ourselves, what we see, feel, etc.).

- For this reason, he has labeled the left brain the **interpreter** – let’s look at why!
Left Brain: The Interpreter
Left Brain: The Interpreter

• **Summary**
  
  • Show an image to the LVF (RH)
    • Subject will say they saw **nothing**
    • Left hand can show you, though
  
  • Show an image to the RVF (LH)
    • Subject will tell you what image was
  
  • Left brain feels a need to rationalize, interpret – explain what we do, how we feel, etc
Left Brain: The Interpreter

- Isn’t that NEAT?! So NEURDY 😊