Genetics of Dementias

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Objectives

At the conclusion of this session participants will be able to:

- Describe the role of genetic factors in the development of dementias.
- Differentiate genetic and non-genetic causes of dementia.
- Specify symptoms associated with varying types of dementia.
- Compare and contrast age at onset and disease progression in dementias.
Four Alzheimer’s genes have been identified.

- **APP (Amyloid Precursor Protein) gene** is located on chromosome 21. Twenty-five different mutations of this gene have been discovered in 71 families.
- **Presenilin 1 (PSEN1)** is located on chromosome 14. Over 150 mutations affecting 315 families have been identified. The Presenilin 1 gene is responsible for the majority of cases of autosomal dominant early onset AD. Onset is in the late 40s and 50s.
- **Presenilin 2** is located on chromosome 1. Ten mutations affecting 18 families have been identified. Age of onset is variable.
- Families in which AD is evident may also carry an **APO** gene. This is identified as a susceptibility gene. There are 3 variants: **APOE2, APOE3, and APOE4**.
  - The APOE gene is located on Chromosome 19.
  - Risk of AD is greatest in individuals who are **homozygous for APOE4**.
  - Onset is generally in the 60s.
Cognitive Decline Related to Alzheimer’s Associated Brain Damage
The primary types of non-genetically based dementia are:
- Vascular
- Dementia with Lewy Bodies (DLB)
- Parkinsonian
- Frontotemporal
- Creutzfeldt-Jakob
- Normal Pressure Hydrocephalus
- Huntington’s
- Wernicke-Korsakoff Syndrome
Vascular Dementias

- These are also known as multi-infarct or post-stroke dementia.
- Can also develop as a result of poor management of hypertension over several decades.
- Other relevant factors are blood vessel blockage and microscopic bleeding.
- Symptoms differ from Alzheimer’s Disease in that memory loss is not an early symptom.
- Rather, the hallmark sign of vascular dementia is impaired judgment, inability to make decisions and inability to plan and organize.
- Brain imaging can readily detect blood vessel problems that are producing classic vascular dementia symptoms.
Dementia with Lewy Bodies (DLB)

- Clients with Lewy Body Dementia demonstrate memory loss and thinking problem typical of clients with Alzheimer’s.
- However, they also typically demonstrate a constellation of symptoms atypical in Alzheimer’s. These include: sleep disturbance, visual hallucinations, and muscle rigidity.
- The behavioral changes seen are caused by lewy bodies which are clumps of a specific protein called alpha-synuclein.
- Some clients exhibit Alzheimer’s type behaviors as well as Lewy Body symptoms. They are said to have **mixed dementia**.
Parkinsonian Dementia

- As Parkinson’s Disease progresses, clients are also at risk for a progressive form of dementia.
- Alpha nuclein also causes Parkinsonian Dementia. It creates a toxic environment in a specific area of the brain called the substantia nigra.
- The result is degeneration of nerve cells that produce dopamine.
Frontotemporal Dementia

- Clients with this diagnosis show primary progressive aphasia. Language becomes a problem for them.
- They also exhibit personality changes caused by damage to the frontal lobe of the brain.
- Frontotemporal Dementia was previously called Pick’s Disease.
- In frontotemporal dementia, portions of these lobes atrophy or shrink. Signs and symptoms vary, depending upon the portion of the brain affected.
Some people with frontotemporal dementia undergo dramatic changes in their personality and become socially inappropriate, impulsive or emotionally indifferent, while others lose the ability to use language.

Frontotemporal dementia is often misdiagnosed as a psychiatric problem or as Alzheimer's disease. But frontotemporal dementia tends to occur at a younger age than does Alzheimer's disease, generally between the ages of 40 and 75.
Normal Pressure Hydrocephalus

- Here we see symptoms such as difficulty in walking, memory loss, and urinary incontinence.
- The cause is a build up of fluid in the brain which is creating elevated cerebral pressure.
- Careful history taking is essential. The most common scenario is that the client had a recent fall or a motor vehicle accident.
- This is highly treatable and involved placement of a shunt to drain excess fluid from the brain.
Wernicke-Korsakoff Syndrome

- In Wernicke’s clients, severe memory loss and changes in behavior are due to severe deficiency of Vitamin B, particularly thiamine (Vitamin B-1).
- Thiamine is needed by brain cells to produce energy. When deficiency exists, brain cells cannot generate enough energy to function properly.
- The most common cause of Wernicke’s is chronic, severe, alcoholism.
Creutzfeldt Jacob Disease

- This is a rare, fatal, rapidly progressing form of dementia.
- Life expectancy after diagnosis is about 1 year.
- It is an infectious illness with a very long incubation period.
- For this reason it is very difficult to trace back to its source which is typically infected cattle.
- The cause of death is the production of incorrectly structured proteins, they are genetically incorrect, which produce abnormal products.
- You will recall that DNA makes RNA, and RNA makes protein.
- Protein throughout the brain malfunctions.
Alzheimer’s Disease

- This is the most common type of dementia.
- Accounts for 60 to 80 percent of cases.
- The most recent set of diagnostic guidelines was published in 2011.
- The neurology and neuropsychology communities agreed that the Alzheimer’s Disease process begins well before symptoms emerge.
- Hallmark abnormalities are: 1) deposits of the protein beta-amyloid which produce plaques; 2) twisted strands of protein tau causing tangles, 3) progressive, irreversible neuron damage and death.
Risk Factors

- Age
- Family History
- Gender- Women > Men; women also live longer than men increasing risk.
- History of cardiac and vascular health problems.
- Traumatic brain injury including concussions.
- History of neurodegenerative disease.
- Alteration in the sleep cycle.
  - Normal aging is characterized by changes in the sleep cycle.
  - When the sleep cycle becomes erratic cognitive decline accelerates.
Pathophysiology of Alzheimer’s Disease

- Brain cell death caused by a stroke, a head injury, or activation of specific genes leads to the production of an abnormal product.
- Genetic factors are present, i.e. specific genes.
- This is called amyloid precursor protein (APP).
- This breaks into 2 types of fragments:
  - **neuroprotective** fragments which reduce damage and death of neurons
  - **Neurotoxic** fragments called Abeta which destroy neurons.
- The pathology of Alzheimer’s is caused by a vicious cycle of Abeta accumulation, tangle formation, and inflammation.
- Abeta accumulation leads to inflammation which leads to more Abeta production.
Advances in Treatment

- Researchers have developed a synthetic sPPA.
- Given post-head injury, synthetic sPPA results in greatly improved clinical outcomes and decreased potential for later development of head trauma.
- In 2014, Drs. Kim and Tanzi received $100,000 for the development of two new Alzheimer’s drugs that work by decreasing the toxic effects of Abeta specifically plaques and tau pathology.
Intervention Strategies

- Develop new medications to either inhibit the production of Abeta and/or a means of clearing it from the brain.
- Inhibit formation of Tau tangles and develop strategies to protect nerve cells.
- Fight inflammation of reduce damage to the brain thereby slowing down or stopping the disease process.
Prevention

- Exercise: stimulates blood flow to memory centers- 3 hours weekly are suggested.
- Diet has a negligible impact on reducing risk.
- Red wine- 1 glass daily
- Brain fitness- learning something new builds new connections between nerve cells to back up the ones currently active.
- Social stimulation.
Diagnosis

- Brain scan (CT or MRI)- this gives a good estimate of brain weight and volume and is useful in ruling out tumors or normal pressure hydrocephalous.
- Review of medical history.
- Cerebral spinal fluid studies (CSF)- lumbar puncture is used to obtain samples of CSF which are studied for the presence of protein Tau.
- Memory tests- counting, recall of words, problem solving. “Shrinkage” of vocabulary is common.
- Information provided by significant others.
- A diagnosis of AD made at a major academic medical center is considered 90% valid as confirmed at autopsy.
What about forgetting?

- Nearly everyone has subtle memory problems as they age.
- However, this really is not your basic forgetfulness.
- Rather, it is difficulty in storing new memories.
Disease Progression

- **Early**- shrinkage of vocabulary, loss of recent memories, difficulty with word finding.
- **Middle**- loss of reading and writing skills, loss of previously intact long-term memory, change in behavior and personality, sundowning.
- **Late**- severe language and memory decline, general apathy and inactivity. However, a subset of clients are aggressive and hospital.
- **Terminal**- Client has erratic autonomic nervous system function leading to inability to maintain body temperature and to breathe adequately.
What is Protein Tau?

- Tau is an essential normal part of every nerve cell (neuron).
- It runs through every nerve cell like train tracks.
- In Alzheimer’s Disease, the tau being produced is damaged.
- It loses its train track structure and begins folding into a “twisted mess” that is unable to transmit nerve impulses.
- It transport function is disrupted; nerve impulses cannot be generated, and the nerve cell dies.
A 2 to 3-fold increase in risk has been observed in first degree relatives of individuals with Alzheimer’s Disease.

Some families demonstrate an autosomal dominant pattern of inheritance.

This means that individuals with Alzheimer’s are evident in multiple generations of the family.

Early onset Alzheimer’s, occurring in individuals prior to age 60, is associated with positive family history and autosomal dominant inheritance.

The quality of family histories is dependent upon longevity of family members.