Genetics of Dementias

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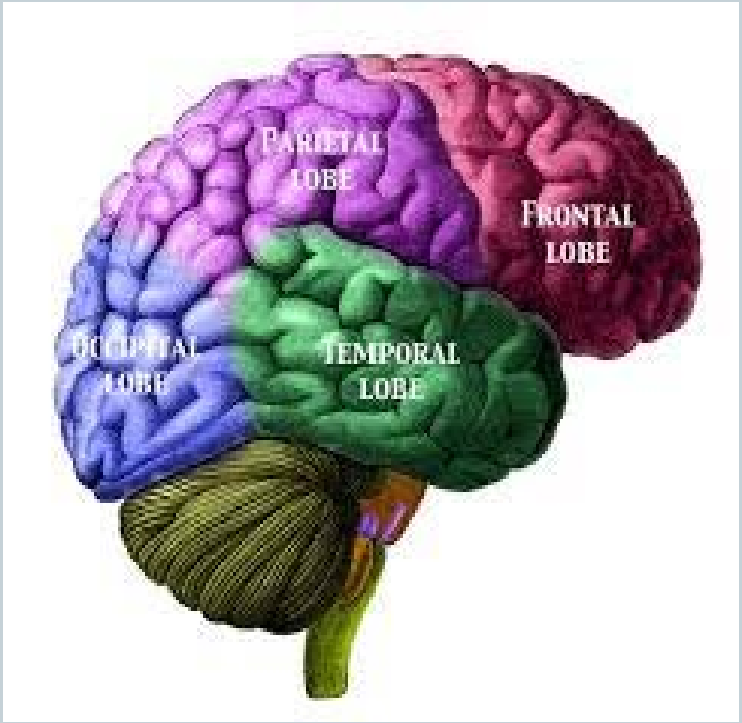
Objectives

- 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.

Genetic Basis of Alzheimer's Disease

- Four Alzheimer's genes have been identified.
  - The **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



Genetic and Non-Genetic Dementias

- The primary types of non-genetically based dementia are:
  - Vascular
  - Dementia with Lewy Bodies (DLB)
  - Parkinsonian
  - Frontotemporal
  - Creutzfeldt-Jakob
  - Normal Pressure Hydrocephalous
  - 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.

Frontotemporal Dementia

- 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 Hydrocephalous

- 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 studies 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.

Patterns of Inheritance in Alzheimer's Disease

- 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.