Alzheimer’s Disease: Causes, Treatments and Ocular Manifestations

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Disclosure Statement:
• Nothing to disclose

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Outline of Presentation

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II. Abnormal neurological changes with age
   A. Vascular Dementia
   B. Alzheimer’s Disease
      i. Causes
      ii. Signs, Symptoms and Diagnosis
      iii. Ocular Manifestations
      iv. Treatments
III. Future of Alzheimer’s Disease

Demographics - Elderly Americans

Life expectancy:

1900: 47 years
   - only 1 in 25 people lived to 60
2012: 79 years
   - 1 of 7 Americans are over 65
   - of Americans who reach 65 today, 75% will live to age 80
      (i.e., another 15+ years)

Demographics - Elderly Americans

• Percent of Americans > age 65
  • 1900  4%
  • 2012  13%
  • 2030  ~23-25%
• During the past 20 years, the number of Americans over age 65 has grown twice as fast as those under age 65.

Demographics - Elderly Americans

During the next 50 years…

• number of people ≥65 years will double
• number of people >75 years will triple
• number of people >85 years will quadruple+
**Demographics - Elderly Americans**

Reasons for increased number of elderly

1) decreased infant mortality
2) preventive health care measures
3) improved clinical medicine
4) advanced life-saving technology

**Health conditions among the elderly**

- of the elderly, 86% have ≥2 chronic conditions (e.g., arthritis, hypertension, Alzheimer's)
- the number of Americans with ocular pathologies will double between 1995-2035

**Abnormal Neurological Changes With Age**

- Definition of a neurological disorder
  - one that affects proper cognitive, physical, and/or behavioral functions and is associated with an acute or chronic Central Nervous System (CNS) disorder
- “Dementia”
  - aka: Senior Dementia
    - Chronic Confusional State
    - Organic Brain Syndrome, etc.

**Types of Dementias/Confusional States**

1) Acute Dementia/ Confusional State
   - Reversible
     - due to short-term illness, medication, sleep deprivation, hunger, dehydration, depression, intoxication, etc.

2) Chronic Dementia/ Confusional State
   - Reversible
   - Irreversible

**Types of Chronic Dementias**

- Reversible Chronic Dementia
  - metabolic disorders
  - nutritional disorders
  - drug reaction or interaction
  - vascular problems
  - space-occupying lesions or tumor
  - diabetes, hypoglycemia
  - renal toxicity
  - infections, illness
  - depression, trauma, stressful events
**Types of Chronic Dementias**

- Irreversible Chronic Dementia
  - Alzheimer's disease
  - vascular dementia
  - Parkinson's disease
  - alcoholism
  - other diseases of the basal ganglia or cerebellum, etc.

**Prevalence of Dementia**

- Alzheimer's: 50-60%
- Vascular dementia: 15-30%
- All Others: 12-20%

**Types of Dementia**

**Vascular Dementia**

- Causes:
  - stroke/cerebrovascular accident
  - hypertension
  - diabetes
  - autoimmune diseases
  - brain injury
  - etc.

**Vascular Dementia - Symptoms**

- Similar to Alzheimer's Disease
- Different than Alzheimer's Disease
  - Sudden onset
  - Step-wise progression
  - History and symptoms/signs of cardiovascular disease
  - Possible severe headache

**Definition of Alzheimer's Disease**

Alzheimer's Disease:

- the progressive neuropsychiatric disease of aging which affects brain matter, and
- is characterized by:
  1. loss of cognitive function
  2. appearance of affective and behavioral disturbances
Prevalence of Alzheimer's Disease

- 2011: 6 million Americans have Alzheimer’s
- 2025: 8 million will have Alzheimer’s
- 2050: 14 million will have Alzheimer’s

Etiology of Alzheimer’s Disease

1) Family history
   - inheritance patterns differ between the early-onset and late-onset types of Alzheimer’s
   - life style (family patterns)

2) Genetic Markers
   - Six genes have been identified:
     - early-onset Alzheimer’s disease: three genes (1, 14 & 21)
     - late-onset Alzheimer’s disease: three genes (9, 12 & 19)

3) Physical factors and associations
4) Environmental factors
5) Unknown or idiopathic
Symptoms of Alzheimer's Disease

- Onset is uncertain
- Progression is gradual
- May or may not have history of cardiovascular disease

Symptoms of Alzheimer's Disease

Impairment in areas of higher function, including:
- short-term memory
- attention span
- judgment and orientation
- speech
- interpretation of sensory input

Behavioral manifestations:
- agitation, anxiety, depression, apathy, affect, irritability, or superficial euphoria

Personal habits or interests:
- may change or disappear

Ten Warning Signs of Alzheimer's

(as described by the Alzheimer's Association)

1. Memory loss that affects job skills
2. Difficulty performing familiar tasks
3. Misplacing things
4. Disorientation to time and place
5. Problems with language
6. Poor or decreased judgment
7. Problems with abstract thinking
8. Changes in mood or behavior
9. Changes in personality
10. Loss of initiative

Stages of Alzheimer's

Stage 1  very early Alzheimer's little/mild cognitive decline
Stage 2  early Alzheimer's mild cognitive decline
Stage 3  mid-stage Alzheimer's moderate cognitive decline
Stage 4  end-stage Alzheimer's severe cognitive decline

Diagnosis of Alzheimer's

- Case history
  - history of cognitive symptoms with slow onset and gradual progression
  - family history
- mental tests
- physical and lab evaluations
- MRI, CT, PET and fMRI scans
- autopsy

Laboratory Signs - Scans

MRI  Pet Scan  CTs  fMRI
**Brain Involvement in Alzheimer's**

- Deeper structures of the brain
  - Hippocampus: short-term memory
  - Amygdala: emotional drives
- Cerebral cortex
  - Temporal lobe: controlling memory, hearing, language
  - Frontal lobe: reasoning, judgment, personality, speech, behavior, emotions
  - Parietal lobe: language; senses of touch, pain, space, and temperature

**Hippocampus Damage**

Alzheimer's begins in hippocampus (essential for formation of short-term memories -> long-term memories)
- continues to atrophy as the disease progresses
- these changes in the brain probably start 10-20 years before visible signs and symptoms appear

**Amygdala Damage**

Amygdala is also involved in early -> late Alzheimer's (essential for the emotional content of new memories)
- atrophy can lead to:
  - episodic memory deficits
  - anxiety, irritability, apathy


**Brain Damage in Alzheimer's**

- Temporal lobe
- Frontal lobe
- Parietal lobe
- Occipital lobe

**Temporal Lobe Damage**

The temporal lobes are essential for memory and language. Episodic memory is the memory for changing events - new memories. The new information is encoded in the brain and then later retrieved.

Damage can lead to lose of new episodic memories, such as with language and spelling.

**Frontal Lobe Damage**

Frontal lobes regulate behavior, so damage can cause a person to say or do things that are threatening, bizarre or inappropriate
- changes in personality
- impacts daily routine
- unable to do simple tasks
**Parietal Lobe Damage**

*important for integrating senses*

- Left side: to read, write, perceive objects, make calculations, and produce language
  - damage may result in decreased ability to comprehend text, add & multiply, balance a checkbook, etc.

- Right side: receives information from the occipital lobe to provide a 'picture' of the surroundings
  - damage may result in visual agnosia (inability to recognize faces, objects or surroundings)

**Occipital Lobe Damage**

- For unknown reasons, occipital lobe seems relatively unaffected in dementia.
- If damage does occur, it may lead to:
  - inability to recognize objects
  - visual hallucinations

**PET Scans**

- Reading words
- Hearing words
- Thinking about words
- Saying words

**Progression Through the Brain**

Deeper structures of the brain
- Hippocampus: short-term memory
- Amygdala: emotional drives

Cerebral cortex
- Temporal lobe: controlling memory, hearing comprehension, language
- Frontal lobe: reasoning, judgment, personality, speech, behavior, emotions
- Parietal lobe: language, senses of touch, pain, space, and temperature
- Occipital lobe: visual perceptions and memories

**Anatomic Signs in the Brain**

1. Decreased neurotransmitters
2. Decreased number of dendrites
3. Amyloid or senile plaques
4. Neurofibrillary tangles
5. Progressive death of nerve cells
6. Increased size of ventricles
7. Decreased size of the brain

**1. Decreased Neurotransmitters**
2. Changes in Dendrites in the Brain

3. Amyloid/Senile Plaques

4. Neurofibrillary Tangles

5. Progressive Death of Neurons
   - brain tissue shrinks overall
   - the sulcus widens
   - the gyrus shrinks
   - the ventricle enlarges

6. Increased Size of Ventricles

7. Decreased in Brain Size
Diagnosis: PET Scans

Normal Brain

Alzheimer's Brain

Diagnosis: fMRI Scans

hippocampus

Ocular Manifestations in Alzheimer's

Glaucoma

- cellular mechanism underlying neuronal degeneration in the eye parallels that found in Alzheimer’s disease
- found glaucomatous visual field defects or cup-to-disk ratios of ≥0.8 were found in ~25% of patients with Alzheimer’s disease

S. McKinnon, MD. Glaucoma: Ocular Alzheimer’s disease? Front Biosci. 2003 Sep 1;8:s1140-56. University of Texas Health Science Center

Glaucoma (continued)

- study with rats and mice found changes in optic nerves mimic changes found in the brains of Alzheimer’s patients
- optic nerves appear to accumulate the same amyloid-beta protein found in Alzheimer’s


Ocular Manifestations in Alzheimer's

Retinal Changes

- degeneration and loss of neurons
- reduction of retinal nerve fibers
- increase in optic disc cupping
- retinal vascular tortuosity and thinning
- visual function impairment


Ocular Manifestations in Alzheimer's

Glaucoma (continued)

- A recent study found that amyloid-beta is found in the development of retinal ganglion cell apoptosis in glaucoma.
- They suggest that drugs that target these proteins when treating Alzheimer’s patients may be used to treat glaucoma.

Ocular Manifestations in Alzheimer's

Lenticular Changes
- The "Alzheimer's cataract"
  - examined lens & aqueous humor of Alzheimer's patients and patients with other neurodegenerative diseases
  - found the amyloid-beta proteins in the lenses and aqueous humor of all Alzheimer’s patients had concentrations similar to those in the brain tissues and cerebrospinal fluid - but not in the other patients
  - deposits were on the far equatorial region of the lens which are rarely seen in the general population


Visual Agnosia
- a neuropsychological disorder characterized by the inability to recognize common objects or people in the absence of perceptual disability

Preventive Medicine for Dementias
- Nutrition and exercise
- Reducing risk factors for cardiovascular disease
- 'Brain exercises'; use it or lose it theory
- Medications

Treatment for Alzheimer's
- Medications:
  - Cholinergic treatments
    - acetylcholinesterase inhibitors
  - blocks acetylcholinesterase to increase chance that adjacent dendrite will be stimulated
Treatment for Alzheimer’s

Medications:
• may not reduce Alzheimer’s signs/symptoms but may allow progression to plateau for a while
• cholinesterase inhibitors, parasympathomimetic effect
• four medications
  1) tacrine (Cognex)
  2) donepezil (Aricept)
  3) rivastigmine tartrate (Exelon)
  4) galantamine (Razacyne)

Future Treatment for Alzheimer’s

Possible Treatments to Postpone the Onset:

- Anti-inflammatory Drugs:
  • to reduce damage to nerve cells
- Antioxidants:
  • to reduce impact of free radicals
- Secretase inhibitors:
  • to reduce production of amyloid-beta
- Estrogen Replacement Drugs:
  • to protect brain from deterioration

Future Treatment for Alzheimer’s

poly-pharmaceutical approach

Treatment for Alzheimer’s

- Optometric care
- Environmental and visual modifications
- Respite care and adult day services
- Medical care
- Skilled nursing facilities

Future of Alzheimer’s

- Importance of early detection and delaying onset
- Development of medications, medical tests and procedures
- Research in etiology and associations
  • amyloid-beta proteins
  • genetic markers
  • tracer compounds

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