Overview of Alzheimer’s Disease and Mixed-Dementia from a Scientific Perspective

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Overview

- Clinical manifestations of Alzheimer’s disease
- Pathological manifestations of Alzheimer’s disease
- Common conditions that Coexist with Alzheimer’s disease
- Differential diagnosis of Alzheimer’s disease
- Genetic risk factors
- Prognosis of Alzheimer’s disease
- Differences with late onset disease

NINCDS/ADRDA Definition of Dementia

- Acquired intellectual deterioration in an adult
- At least 6 month’s duration
- At least two spheres of mental activity (eg, orientation, attention, memory, language, spatial abilities, etc) compromised
- Impairs the ability to function optimally in the community


NINCDS-ADRDA criteria for Alzheimer’s disease

- Progressive decline of memory and other cognitive abilities
- Cannot be entirely explained by another condition
- Definite AD requires pathologic confirmation by biopsy or autopsy


Memory

- The recording, retention, and retrieval of information
- Memory accounts for all knowledge gained through experience
  - specific events
  - knowledge of facts
  - acquisition of skills

Memory Systems Affected by Alzheimer’s Disease

- Episodic Memory
- Semantic Memory
- Working Memory
- Spatial Memory
- Implicit Memory
- Perceptual Speed
Clinical Manifestations of Alzheimer’s Disease

- **Cognitive impairment**
  - Memory, language, attention, processing speed, spatial ability
- **Behavioral disturbances**
  - Hallucinations, misperceptions, delusions; agitation, aggression
- **Affective disturbances**
  - Depression
- **Motor impairment**
  - Parkinsonian (extra-pyramidal) signs
    - Gait disturbance, bradykinesia, rigidity, tremor
    - Weakness and physical frailty
- **Other signs**
  - Weight loss
  - Sleep disturbance
  - Incontinence

Pathological Manifestations of Alzheimer’s Disease

- **Atrophy**
  - Hippocampal and generalized
- **Plaques and tangles**
  - Amyloid deposition
  - Phosphorylation of tau proteins
- **Amyloid angiopathy**
- **Neuronal loss (neurodegeneration)**
Hippocampal formation: Brain region critical to laying down new episodic memories.

Hippocampus

Cholinergic basal forebrain neurons (Nucleus basalis of Meynert)

Nucleus basalis of Meynert: Source of cholinergic projection neurons to hippocampus and neocortex.

Tangles in the Substantia Nigra

Substantia Nigra: Part of brain affected by Parkinson’s disease and involved in motor function.

Hippocampal Neurons

Many Few

Low Amyloid High Amyloid

Low Tangles High Tangles

cerebral amyloid angiopathy

Low High
Common Conditions that Coexist with Alzheimer’s Disease

- Cerebral infarctions
  - Macroscopic
  - Microscopic
- Parkinson's/Lewy Body Disease
  - Nigral
  - Limbic
  - Neocortical

Cerebral Atherosclerosis

Cerebral Infarctions (Stroke)

Subcortical macroscopic infarct

Cortical Microinfarct

Parkinson’s disease

Normal brain

Substantia Nigra
Nigral Lewy bodies
Hippocampal Lewy bodies
Cortical Lewy bodies

Diagnosis of Alzheimer’s disease
• Progressive decline of memory and other cognitive abilities relative to a previous level of performance
  • History of decline obtained from a knowledgeable surrogate
  • Usually sufficient
  • Repeat neuropsychological testing
  • Needed occasionally
  • Inferred from knowledge of premorbid function
  • Sometimes unavoidable
• Documented by formal mental status testing
  • Cognitive Screening Tests
  • Full Neuropsychological Battery
  • Helpful in early disease when dementia is not clear
• Other tests primarily used to identify coexisting conditions

Differential Diagnosis of Alzheimer’s disease
• Other less common causes of progressive dementia
  • e.g., fronto-temporal lobar degeneration
• Conditions that may mimic dementia
  • Depression and other Psychiatric Conditions
  • Malingerer
• Other tests that may aid in the identification of these conditions
  • Formal neuropsychological testing
    • MRI
    • PET
    • EEG
• There are no good estimates of the number of persons with early onset AD in the US, but it likely about 100,000 or more.
• There is no evidence of differences by gender, race or ethnicity.
• There is no evidence that environmental, experiential, or psychological factors known to be associated with late-onset AD are also associated with early onset AD.
• A variety of genetic factors are associated with risk of early onset AD.

Genetic Risk Factors for Alzheimer’s Disease
Increase Risk
• Genetic mutations
  • Amyloid precursor protein (APP, 21q)
  • Presenlin 1 (PSEN1, 14q)
  • Presenlin 2 (PSEN2, 1q)
• Genetic polymorphisms
  • Apolipoprotein E ε4 allele
Decrease Risk
• Genetic polymorphisms
  • Apolipoprotein E ε2 allele

Prognosis of Alzheimer’s disease
• Cognitive decline inexorably progressive until death
• Plateaus may occur but patients do not improve (in the absence of a reversible coexisting condition)
• Rate of decline variable; factors associated with decline:
  • Younger age
  • Parkinsonian signs
  • Hallucinations
  • Weight loss and frailty
  • More educational attainment
• Disability virtually by definition
  • Clinical Dementia Rating Scale
• Death in 8-10 years, but highly variable
Staging of Dementia—Clinical Dementia Rating

- 0 = no dementia
- 0.5 = questionable dementia
  mild forgetfulness
- 1 = mild dementia
  moderate memory loss, mild disorientation and impairment of social/occupational functioning
- 2 = moderate dementia
  severe memory loss, requires assistance in activities of daily living and personal hygiene
- 3 = severe dementia
  help with care and personal hygiene
- 4 = profound dementia
  speech unintelligible, does not follow simple commands, barely ambulatory with assistance
- 5 = terminal dementia
  no response or recognition

Compared to persons with late onset AD, persons with early onset are more likely to:

- Be gainfully employed and present at an earlier stage of illness
- Progress more rapidly
- Survive to experience terminal disease
- Have a genetic cause
  - Especially those with very early onset (< age 35)
- Have AD without a co-morbid condition.