

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

David A. Bennett, M.D.

Robert C. Borwell Professor of Neurological Sciences
Director, Rush Alzheimer's Disease Center
Rush University Medical Center
Chicago, IL

*Social Security Administration's
Compassionate Allowance Outreach Hearing on
Early-Onset Alzheimer's and Related Dementias
July 29, 2009*

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

2

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

McKhann et al. *Neurology* 1984;34:939-944.

3

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

McKhann et al. *Neurology* 1984;34:939-944.

4

Memory

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

5

Memory Systems Affected by Alzheimer's Disease

- Episodic Memory
- Semantic Memory
- Working Memory
- Spatial Memory
- Implicit Memory
- Perceptual Speed

6

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

7

Pathological Manifestations of Alzheimer's Disease

- **Atrophy**
 - Hippocampal and generalized
- **Plaques and tangles**
 - Amyloid deposition
 - phosphorylation of tau proteins
- **Amyloid angiopathy**
- **Neuronal loss (neurodegeneration)**

8

Alzheimer's disease

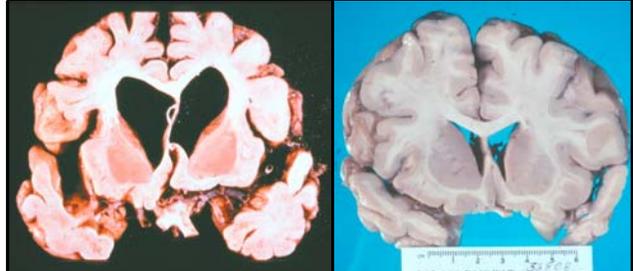
Normal brain



9

Alzheimer's disease

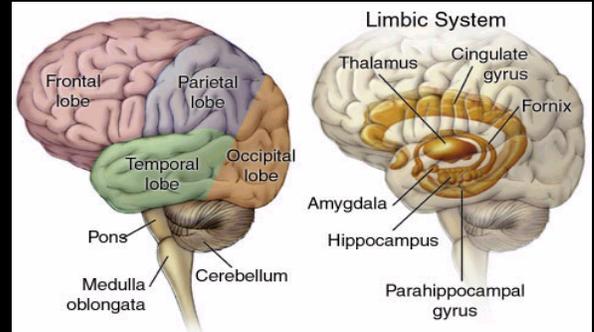
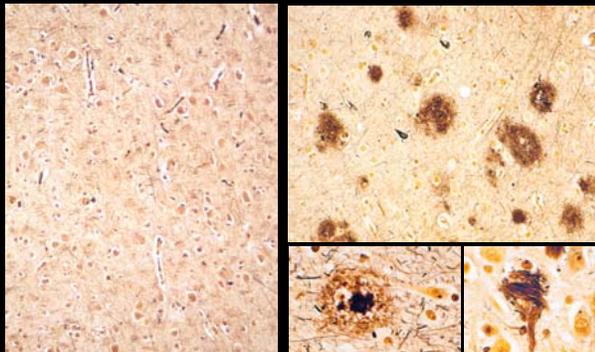
Normal brain



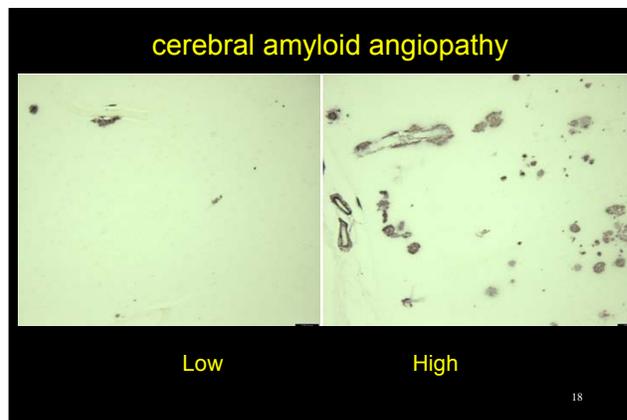
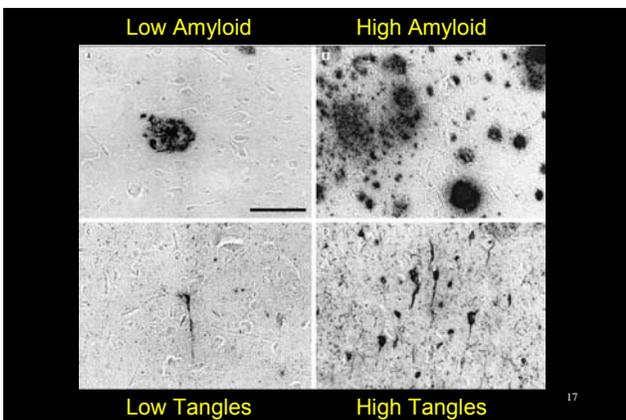
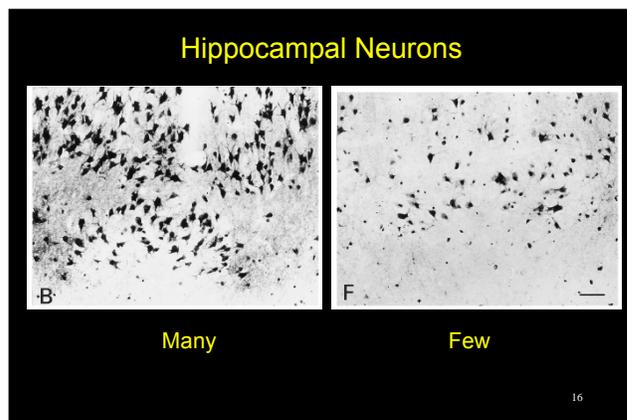
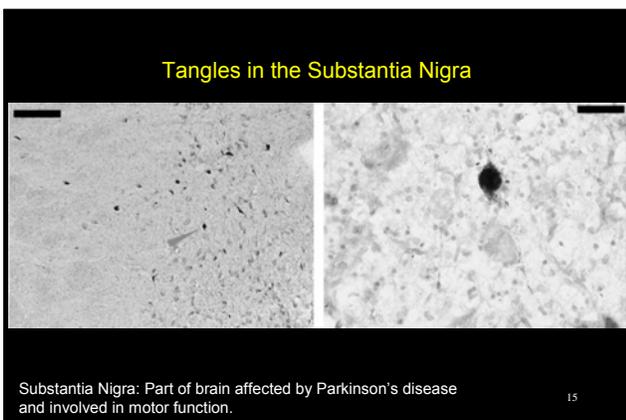
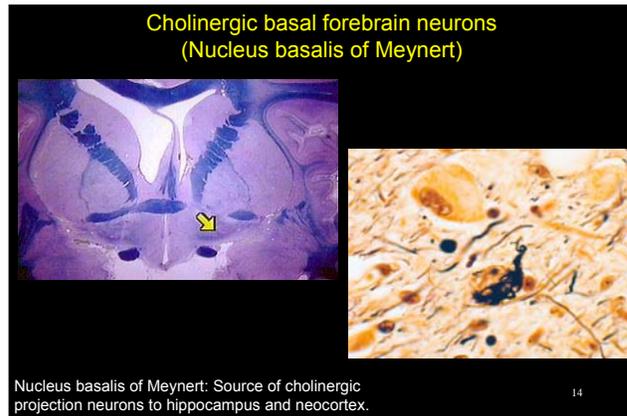
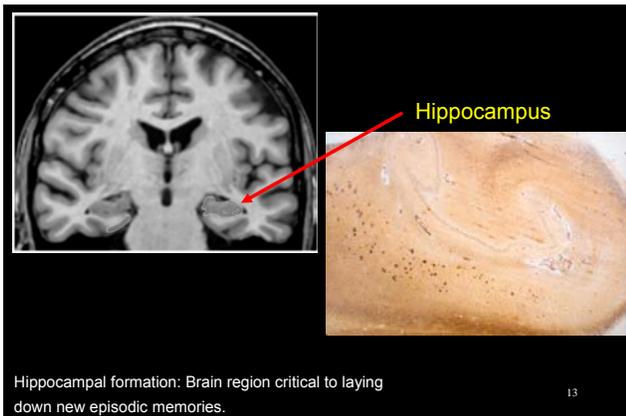
10

Normal brain

Alzheimer's disease



12

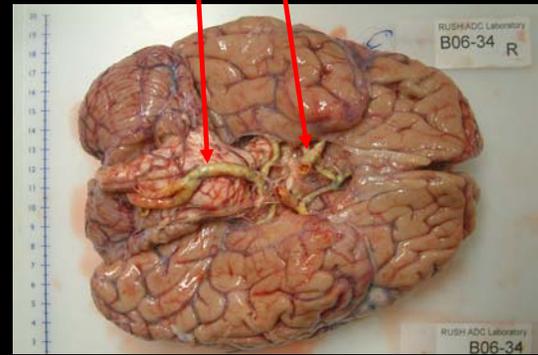


Common Conditions that Coexist with Alzheimer's Disease

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

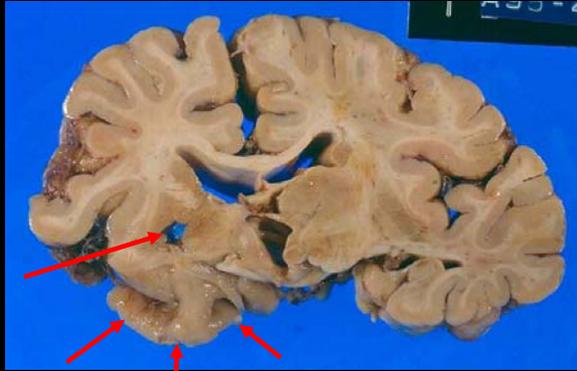
19

Cerebral Atherosclerosis

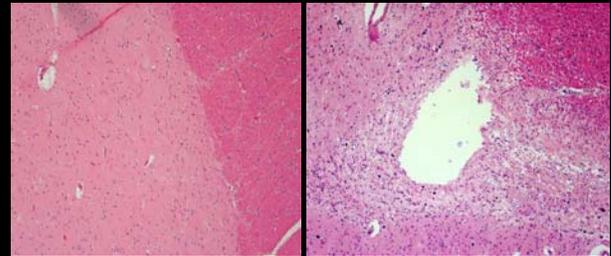


20

Cerebral Infarctions (Stroke)

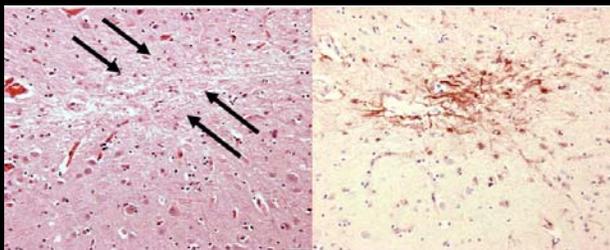


Subcortical macroscopic infarct



22

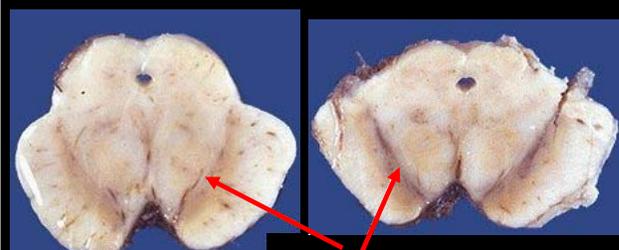
Cortical Microinfarct



23

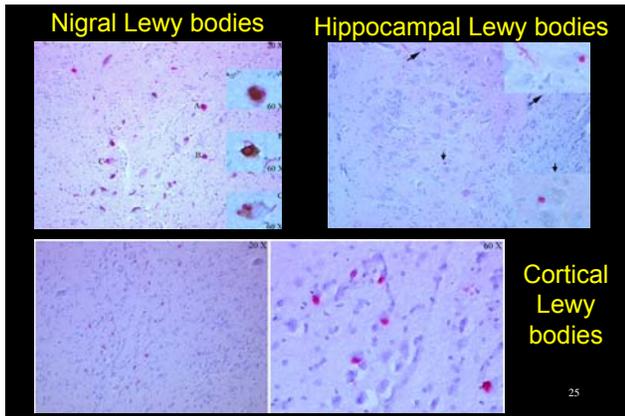
Parkinson's disease

Normal brain



Substantia Nigra

24



- ### 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
- 26

- ### 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
 - Malingering
 - Other tests that may aid in the identification of these conditions
 - Formal neuropsychological testing
 - MRI
 - PET
 - EEG

27

- 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.

28

- ### Genetic Risk Factors for Alzheimer's Disease
- **Increase Risk**
 - Genetic mutations
 - Amyloid precursor protein (*APP*, 21q)
 - Presenilin 1 (*PSEN1*, 14q)
 - Presenilin 2 (*PSEN2*, 1q)
 - Genetic polymorphisms
 - Apolipoprotein E ϵ 4 allele
 - **Decrease Risk**
 - Genetic polymorphisms
 - Apolipoprotein E ϵ 2 allele

29

- ### 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

30

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

31

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.

32