Dementia: An Overview

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“Memory Changes with Age”

1. Age associated memory change
2. Mild cognitive impairment
3. Dementia
Age Associated cognitive Change


- Memory loss - 40% of people aged 65 or older (16 million people) have ML
- Not associated with functional impairment
- Only 1% will develop Alzheimer’s Disease
1. Age Associated Memory Change

- Usually self aware of memory change
- Often with time, forgotten item is recalled
- Types of memory loss
  - Recent events
  - Names of persons more than faces
  - “Tip of tongue”
  - Words in middle of sentence
- Retention of other cognitive skills
2. Mild Cognitive Impairment

- Not demented
  - changes in cognition from baseline
  - lower than expected performance
  - ADLs may be slightly affected
- Seen in 10% of people aged 65 or older
- As many as 50% will develop dementia in 3 years

- Window of opportunity for reversing brain pathology through effects of medications
  Hence newly proposed concept of “preclinical AD”
Learning Objectives:

- Recognize key features of dementia
- Get an overview of latest advances in diagnosis and treatment of dementia
- Learn about appropriate pharmacologic and non-pharmacologic approaches to dementia treatment
Dementia

- **Most common form** of dementia - Alzheimer disease (AD) was first described more than 100 years ago.

- Alzheimer disease (AD) is a progressive neurodegenerative disorder affecting more than **37 million** people worldwide and is increasing in incidence based on its primary risk factor, which is **advancing age**.
Dementia - disease burden

- Aggregate healthcare expense on Dementia in 2011 was estimated at: $183 Billion

- On present trajectory by 2050 this cost is projected to rise to 1.1 Trillion $.

- In 2011 Congress ==->->>President signed NAPA - the “national AD project act”
Defining Pathological Features - synaptic & neuronal loss causing atrophy

Due to accumulation of plaques & tangles - major targets for drug discovery today

Normal | AD

AP | NFT
Current hypothesis:

*Amyloid cascade to amyloid – B deposition (plaques) ➔ drive tau phosphorylation, tangle formation and neuronal death*

- Tangles represent aggregation of hyperphosphorylated form of the microtubule-associated protein *tau*
- AD pathology starts as pretangles in proximal axons of the noradrenergic locus ceruleus that spreads by neuron-to-neuron & transsynaptic transport of tau aggregates to the entorhinal cortex, hippocampus & neocortex like prions (also seen in FTD; CBD; PSP)
NFTs begins accumulating in the entorhinal cortex, subsequently spreading to hippocampus amygdala and neocortex.

There is cells loss in nucleus basalis of Meynert & the basal forebrain - structures responsible for most cortical cholinergic projections, thus resulting in cortical acetylcholine depletion, the most notable change in AD.

Neurochemical dopamine, norepinephrine, and serotonin deficiencies have also been detected – smaller foot print
Autopsies have shown profound layer-2 loss of entorhinal cortex neurons **even in very mild AD or MCI** with MMSC scores of >24.

**Atrophy begins years before diagnosis of AD** & is non-specific.
Biomarkers are being incorporated in dx

Radiotracers label fibrillar forms of amyloid

Imaging accurately defines focal atrophy

CSF and even plasma markers identified

Challenges remain for biomarkers to become widely applied in clinical practice
Two broad categories of biomarkers
(scans and tissue – CSF; biopsy)

**AMYLOID-B1-42 ACCUMULATION**

- Paradoxical decrease in CSF amyloid-1B thought to represent that it is polymerizing and depositing in the brain
- Recent amyloid PET is likely equivalent to plaque pathology at autopsy
  - (** amyloid positivity does not reliably distinguish clinical diagnosis)**

**MARKER OF NEURONAL INJURY**

(NEURODEGENERATION)

- MRI volumetry
- CSF phosphorylated tau (p-tau) 181 and total tau are markers of neuronal injury; (increased levels seen in advanced disease)

⇒ Combination of low csf AB1-42 & elevated csf P-tau & total tau is thought to indicate a biomarker signature of AD
Are “biomarkers” prime time? – nearly!!

- There may be potential utility in aiding diagnosis in young patients
- In those with unusual presentation
- Or in MCI where MCI + biomarkers = mild AD
Are “biomarkers” prime time? – nearly!!

- One ¹⁸F PET FDA approved
- Routinely tested for drug trial (changes may also serve as surrogate markers for success)
- Available markers need “standardization”

“not for regular clinical practice”
Why some do, others do not get AD: Nature v/s Nurture?

- A Genetic factors may account for most of this variability but only about 5% of genetic cases are associated with identified genes.

- Only 1% in an autosomal dominant inheritance pattern. → RARE BUT HIGHLY PENITRANT!

- APOE "4 allelic variation is the currently identified genetic factor that contributes most significantly to the development of AD.

- But it's neither necessary nor sufficient to cause it!
population studies are identifying novel risk genes

Trials to prevent familial Alzheimer by administering experimental medications to asymptomatic mutation carriers are likely to commence in 2013

- DIAN dominantly inherited AD network NIH U01 AG016570
While memory concerns predominate, patients with AD often experience language and visuospatial dysfunction in addition to neuropsychiatric symptoms such as anxiety, “d” - depression, apathy, and agitation – in reality a continuum.
AD – definition:
Gradually progressive cognitive and behavioral disturbance that represents Decline from prior level in 2 or > areas of cognitive function not due to other medical or psychiatric illness

1. Insidious episodic memory impairment → chronic progression
2. Multiple cognitive defects
3. Significant impairment in social or occupational function
4. Ultimate irreversibility
Diagnosis:
informant corroboration of progressive episodic memory impairment is critical for diagnosis

- **Early phase**
  - Sphere of psychological dysfunction
    - *Confusion* with psychiatric disorders

- **Middle phase**
  - Sphere of cognitive dysfunction
    - Usually obvious
    - *Confusion* with functional or psychological disorders

- **Late phase**
  - *Confusion* with Neurological disorder
Clinical Progression of AD and MCI

- MCI
- MMSE 24–30
- Mild subjective/objective memory loss
- Normal function

- Mild AD
- MMSE 20–23
- Forgetfulness
- Repetitive questions
- Daily function impaired

- Moderate AD
- MMSE 10–19
- Progression of cognitive deficits
- Short-term memory loss
- Word-finding difficulties

- Severe AD
- MMSE 0–9
- Agitation
- Altered sleep patterns
- Total dependence: dressing, feeding, bathing

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Reversible Dementias & Delirium (the acute confusional state)

- Depression—“Pseudo D”
- Delirium- the other “D”
- Endocrine Disorders
  - Thyroid disease
  - Vitamin B12 deficiency
Other:
- Sleep disorders: OSA, RBD
- Epilepsy associated
- Occasionally other like HIV
- Normal Pressure Hydrocephalus “NPH” - rare
Laboratory Tests in the Diagnosis of Dementia

(AAN Practice Parameter ’01)

- CBC, electrolytes, glucose, BUN/creat
- LFTs, TFTs, ESR
- B12 level
- Depression screening
- CT or MRI scan
Routine tests not recommended (AAN '01)

- RPR (unless evidence)
- SPECT
- Genetic testing (e.g. APOE)
- EEG
- LP (unless unusual factors- infection, hydrocephalus, etc.)
- Uncertain: PET (Medicare approved), other gene markers such as neuronal thread protein, CSF tau
Treatment Options

I. Cholinesterase inhibitors:
1. Donepezil
2. Galantamine &
3. Rivastigmine (Oral)
4. Rivastigmine (Transdermal)

II. NMDA antagonists:
5. Memantine
   - Regulates glutamate levels in brain ➔ reduce abnormal activity
   - 5. Memantine - NMDA antagonist

Neither stop disease progression:
- Improve global function and cognition
- Reduction in behavioral disturbances
- Temporary stabilization of ADLs
- Delay nursing home placement
- Postpones worsening of symptoms for 6-12 months in 50% of patients
Select AD investigational Treatment Strategies:

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<td>(SSRIs) and nonpharmacologic interventions are often useful in targeting behavioral symptoms of AD.</td>
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<td>Investigational strategies for disease-modifying therapies in AD focus on the neuropathology of A? and tau as well as epidemiologic associations of AD risk. the variant protects people by preventing an enzyme called beta secretase 1, or BACE-1, from helping create the characteristic beta amyloid tangles in the brains of Alzheimer’s patients, according to the study, published today in the journal Nature. Drugs that mimic this action are in development from...</td>
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No therapeutic success to prevent or delay MCI or AD onset so far:

- Approaches targeting amyloid – Unsuccessful

- Tau is the target. Approaches:
  - Enhancement of microtubule stability
  - Blocking/inhibiting tau hyperphosphorylation
  - Clearing aggregates with drugs or antibodies

- Small molecules - serotonin nicotinic receptor sites: some success with in early phase

- Use of biomarkers for diagnosis; prognosis and prediction in drug trials with intervention before onset of cognitive symptoms
Nonpharmacological treatment and Prevention

- **Age & Genetic (most robust data):** may account for most (80%) of the variability in the development of AD; Apo increases risk 3 to 10 fold; only about 5% of genetic cases associated with identified genes in an autosomal dominant inheritance pattern.

- **Cardiovascular risk factors are associated with Dementia:** Hyperlipidemia; HTN; obesity & DM; Metabolic syndrome – trial results for 1st 2 are mixed more needed. Also (more literature emerging) – OSA; obesity; head trauma

- **Epidemiological studies indicate Physical activity may delay cognitive decline** – evidence from early randomized controlled trials is supportive

- **Cognitive and social intervention may buffer against neuropathologic damage associated with dementia** (Late life depression; Social isolation connected with cognitive decline)

- **Tobacco / alcohol:** Current smoking - effect; moderate drinking + effect

- **Nutrition & Diet – deficiencies have been associated with dementia:** single nutrient supplements – have not consistently demonstrated benefit possible omega-3? intervention with vit. B,E,C, Folate or beta-carotene – results inconsistent; estrogen? not yet known whether timing influences hormone effects on cognition.

- **Sleep Disordered breathing associated with dementia**
Prospective cohort sleep study of 208 older adults without dementia at baseline with OSA followed 8 years; Main finding: (Similar to cardiovascular risk)
- Those with presence of OSA by 6 or 7 years were found to be at increased risk of dementia
- Results adjusted for gender & Apo-e 4 allele and age
- Mechanisms not clear and not controlled for body habitués
Insufficient evidence to support use of pharmaceutical agents or dietary supplements to prevent AD or cognitive decline.

Ongoing additional studies including those with antihypertensive medications, omega 3 fatty acids, physical activity and cognitive engagement (the strongest associations) may provide new insights into the prevention or delay of cognitive decline and AD.
Conclusion:

- Advances in genetics, biomarkers for early disease detection and assessment of disease progression, and novel therapeutic strategies to modify the natural history of the disease are compelling.
- There is need of further study before its implementation into routine clinical practice is feasible.

In primary care settings, fewer than 50% of patients with dementia are diagnosed.


Rate of hospitalization for ambulatory care-sensitive conditions is significantly higher among individuals who were diagnosed with dementia (86%) than those that remained dementia free (59%). Phelan EA et al Association of incident dementia with hospitalizations: - JAMA 2012 Jan 11; 307:165.