Senile dementia: can we do anything significant?

Prof Ahmed Hossain
Professor of Medicine
Sir Salimullah Medical College

Dementia is defined as :

- an acquired deterioration in cognitive abilities that impairs the successful performance of activities of daily living

- Episodic memory, the ability to recall events specific in time and place, is most commonly lost

- Clinically identifiable memory loss present in
  - 10% of persons aged >70 years
  - 20–40% of individuals aged >85 years

- In addition to memory,
  - dementia may erode other mental faculties, including language, visuospatial, praxis, calculation, judgment, and problem-solving abilities

- Neuropsychiatric and social deficits also arise :
    - Depression, apathy, anxiety,
    - Hallucinations, delusions, agitation,
    - Sleep disturbances, compulsions, or disinhibition

CAUSES OF DEMENTIA

- *Alzheimer's Disease (AD)* is the most common cause in Western countries
  - More than half of all patients

- *Vascular disease* is considered the second most frequent cause

CAUSES OF DEMENTIA

- Dementias associated with Parkinson's disease may develop,
  - *PD-related dementia (PDD)* – years after onset of a parkinsonism, or
  - *Dementia with Lewy bodies (DLB)* – concurrently with the motor syndrome

CAUSES OF DEMENTIA

Fronto-temporal dementia

- A number of different syndromes characterised by behaviour abnormalities and impairment of language
- Abnormal accumulation of tau and other proteins in brain tissue
- Cytoplasmic inclusion bodies on histological examination

CAUSES OF DEMENTIA

- Chronic intoxications from alcohol and drugs, often treatable cause of dementia

CAUSES OF DEMENTIA

- Other disorders may be caused by some neoplastic, endocrine, inflammatory, traumatic, nutritional deficiency and infective conditions, or hydrocephalus
- These are uncommon but many are reversible
- Be actively sought especially in younger patients with short histories

CAUSES OF DEMENTIA

In a study of 1000 persons attending a memory disorders clinic,

- 19% had a potentially reversible cause
- 23% had a potentially reversible concomitant condition

Clinical course may be :

- *Slowly progressive*- in Alzheimer's disease (AD)
- *Static*- in anoxic encephalopathy
- *May fluctuate* from day to day - in dementia with Lewy bodies (DLB)

- Early prominent gait disturbance suggests,
  - Vascular dementia or
  - Rarely normal pressure hydrocephalus(NPH)

Features suggesting DLB :

- Early appearance of parkinsonism
- Fluctuating alertness
- Visual hallucinations or
- Delusional misidentification

- Features of typical of FTD :
  - Prominent behavioural abnormalities and impairment of language
  - Memory loss is not a presenting feature
  - Focal anterior-predominant atrophy

Investigations

Should be aimed at finding reversible etiologies :

- Blood tests:
  - Full blood count, Urea and electrolytes, glucose
  - Calcium, liver function tests, Thyroid function tests, HIV, Syphilis serology
  - Vitamin B12, ANA, anti-dsDNA

Investigations

- Chest X-ray
- Electroencephalography
- Imaging of head

Investigations

Main purpose of imaging is to exclude :

- Primary and secondary neoplasms
- Vascular dementia
- Diffuse white matter disease, and
- Normal-pressure hydrocephalus (NPH)

Investigations

Neuroimaging studies in AD :

- May be normal in early stage
- As AD progresses :
  - Usually posterior-predominant cortical atrophy
  - Atrophy of the medial temporal memory structures

Investigations

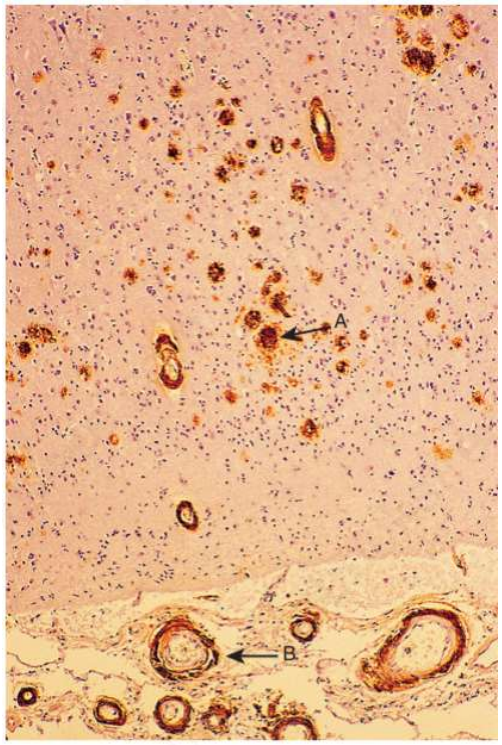
Functional imaging studies, PET shows :

- *Hypometabolism* in the posterior temporal-parietal cortex in AD
- Presence of *fibrillar amyloid* in the brain

PATHOLOGY

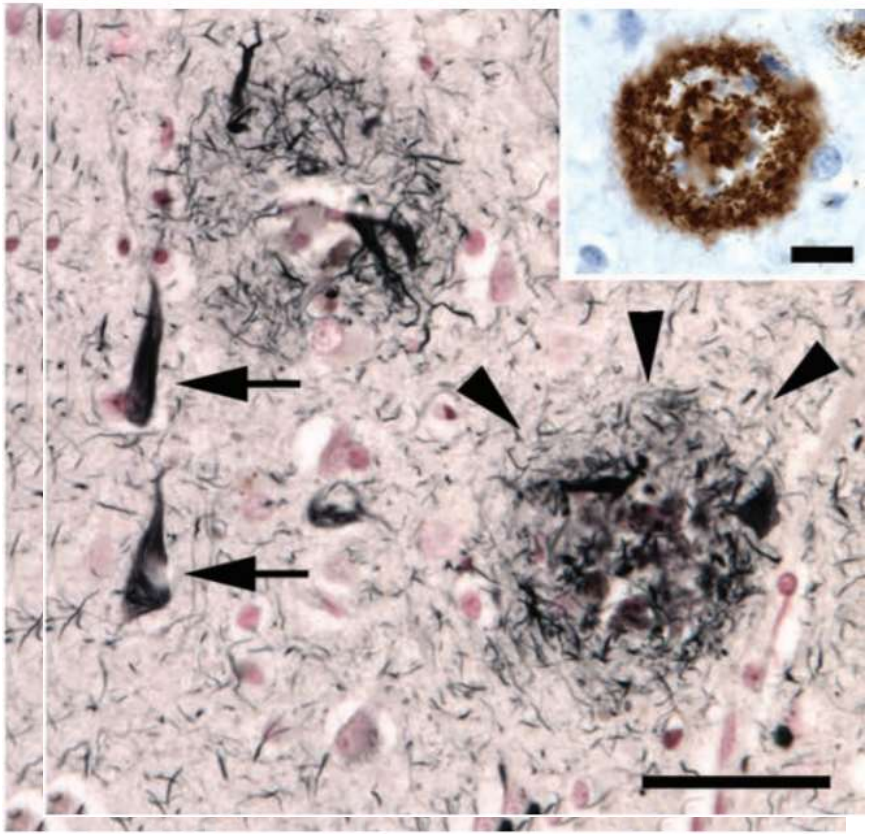
- In AD, microscopically :
  - Widespread *neuritic plaques* which contains amyloid beta (Aβ)
  - *Neurofibrillary tangles (NFTs)* composed of hyperphosphorylated tau filaments
  - *Amyloid angiopathy,* accumulation of Aβ in cerebral arterioles

Alzheimer's Disease



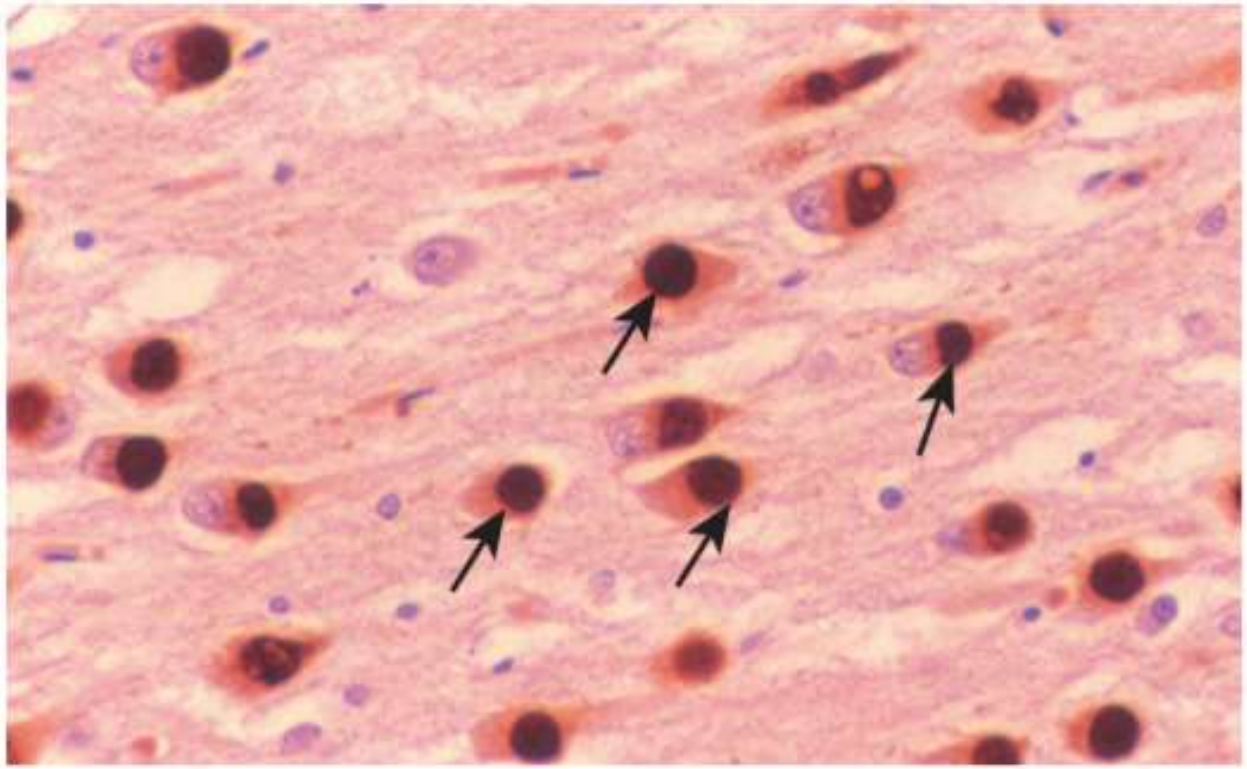
Section of neocortex showing amyloid deposits in plaques and in blood-vessel walls

Alzheimer's Disease



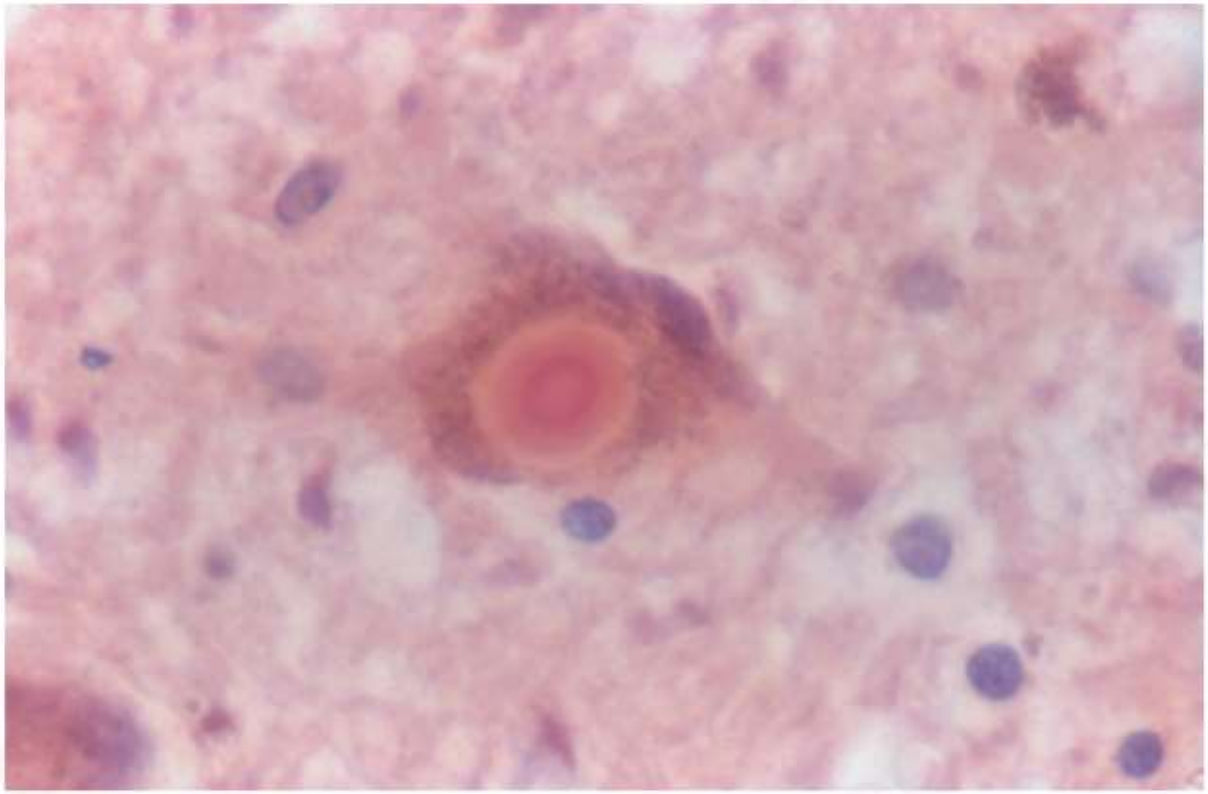
Fibrillar tangles and **the neuritic plaques,**
whose major component is Aβ

Fronto-temporal dementia



Section of hippocampus, prepared with monoclonal anti-tau antibody, **spherical cytoplasmic inclusion bodies (Pick bodies)**

Dementia with Lewy bodies (DLB)

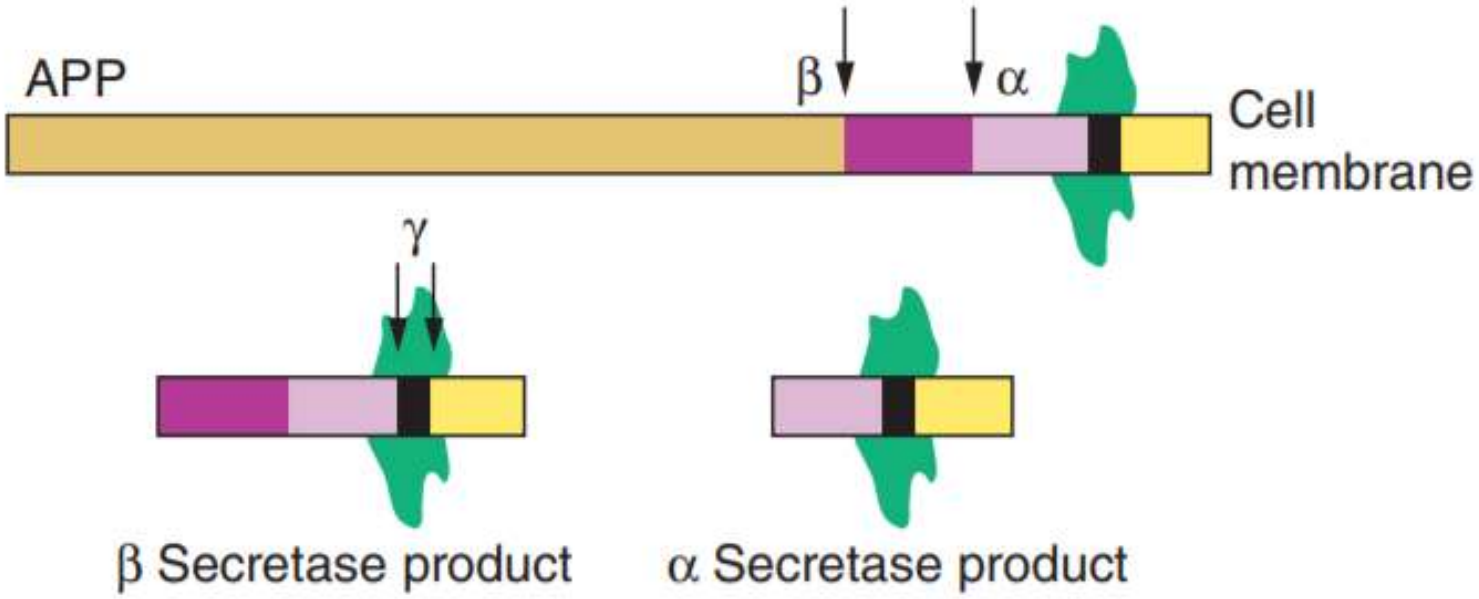


Section of substantia nigra showing classical **Lewy body** (haematoxylin and eosin)

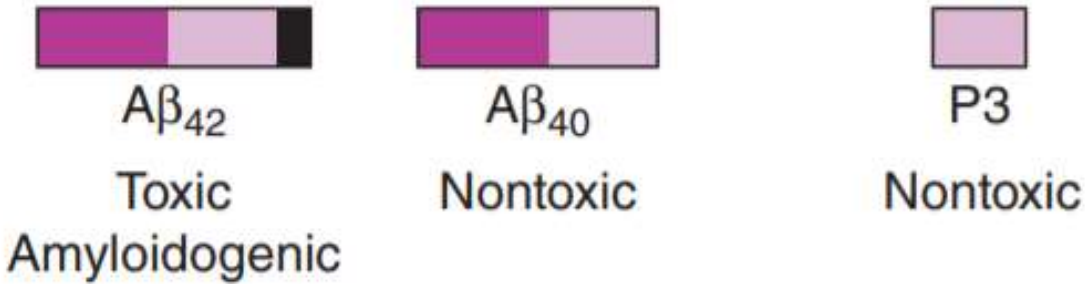
PATHOLOGY

- Aβ is derived from a transmembrane protein, amyloid precursor protein (APP)
- APP is catabolized by β, α, and γ secretases
- Initial step of it's digestion occurs either by β secretase or by α secretase
- Cleavage of the β secretase product by γ secretase (Step 2) results in either the toxic $A\beta_{42}$ or the nontoxic $A\beta_{40}$ peptide

Step 1: Cleavage by either α or β secretase



Step 2: Cleavage by γ secretase



PATHOLOGY

- Tau filaments binds to and stabilizes microtubules, supports axonal transport of important cargoes
  - Once hyperphosphorylated, loses it's function

PATHOLOGY

Biochemically, AD is associated with :

- A decrease in the cortical levels of several proteins and neurotransmitters, especially *acetylcholine*

Management of dementia

Major goals of management :

- To treat reversible causes and
- To provide comfort and support to the patient and caregivers

Management of dementia

Treatment of reversible causes as for example:

- Thyroxin replacement in hypothyroidism
- Thiamine or B12 for deficiency
- Ventricular shunting for NPH
- Removal of cognition-impairing drugs or medications

Treatment of vascular dementia

- Control of *modifiable risk factors* are key to prevent and slowing deterioration of this condition :
  - Hypertension, diabetes mellitus
  - Smoking, alcohol intake
  - Sodium consumption
  - Obesity, and the metabolic syndrome

Management of Alzheimer's Disease

- Management of AD is challenging as there is no cure
- Primary focus is on :
  - Long-term amelioration of associated behavioral and neurologic problems
  - Providing caregiver support

Drugs approved by FDA for AD

- Inhibitor of acetylcholinesterase :
  - Donepezil
  - Rivastigmine, and
  - Galantamine
- NMDA (N-methyl-d-aspartate glutamate) receptors blocker :
  - Memantine

Cholinesterase inhibitors

- Used to treat :
  - Alzheimer's Disease (AD)
  - PD-related dementia (PDD)
  - Dementia with Lewy bodies (DLB)

Cholinesterase inhibitors

- Major side effects :
  - G.I. symptoms (nausea, diarrhea, cramps)
  - Altered sleep with vivid dreams
  - Bradycardia and Muscle cramps
- Dose escalations :
  - Must be carried out over 4-6 weeks to minimize side effects

Dosage:

- Donepezil (target dose, 10 mg daily)
- Rivastigmine (target dose, 6 mg twice daily or 9.5-mg patch daily)
- Galantamine (target dose 24 mg daily, extended-release), and
- Memantine (target dose, 10 mg twice daily)

Cholinesterase inhibitors in moderate to severe AD

Double-blind, placebo-controlled, crossover studies over periods of up to 3 years showed :

- Improved patients' functioning and
- Decreased rate of decline in cognitive test scores

Memantine in moderate to severe AD

- In conjunction with cholinesterase inhibitors or by itself :
  - Slows cognitive deterioration
  - Decreases caregiver burden
  - Delayed nursing home placement

- Not approved for mild AD

Estrogen

- In a prospective observational study-
  - Estrogen replacement appeared to protect against development of AD

- But a prospective placebo controlled study of a combined estrogen-progesterone for asymptomatic postmenopausal women-
  - Increased the prevalence of dementia

Ginkgo biloba

- A controlled trial found-
  - Modest improvement in cognitive function in AD and vascular dementia
- But, a comprehensive 6-year multicenter prevention study found-
  - No slowing of progression to dementia

NSAIDS & STATINS

- Several retrospective studies suggest-
  - They might have a protective effect on dementia if used prior to the onset of disease

- Therapeutics for AD have focused on attempts to reduce $A\beta_{42}$ by :
  - Antagonizing β or γ secretases
  - Promoting α secretase, or
  - Clearing $A\beta_{42}$ that has already formed

Vaccination against $A\beta_{42}$

- Proved highly efficacious in mouse models of AD, clear brain amyloid

- In human trials in a minority of cases-
  - Led to life-threatening complications, including meningoencephalitis

β and γ secretase inhibitors

- β and γ secretase inhibitors diminish the production of $A\beta_{42}$
  - First two placebo-controlled trials of tarenflurbil and semagacestat, were negative, and
  - Semagacestat may have accelerated cognitive decline compared to placebo

Monoclonal antibodies against $A\beta_{42}$

- Tried in mild to moderate AD-
  - Some evidence for efficacy in the mildest groups
  - New trials have started in asymptomatic individuals with mild AD

Tau phosphorylation modifier

- Includes tau antibodies
- They are beginning to be studied as possible treatments for both AD and non-AD tau-related disorders

Antidepressants

- Mild to moderate depression is common in the early stages of AD

- Selective serotonin reuptake inhibitors (SSRIs)
  - Are used for their low anticholinergic and cognitive side effects
  - low dose is to be started to avoid toxicity

Treatment of psychiatric symptoms

- Agitation, hallucinations, delusions, and confusion are difficult to treat
- Represent major causes for nursing home placement and institutionalization

Treatment of psychiatric symptoms

Modifiable factors that precipitate psychiatric symptoms be aggressively sought out and treated :

- Toothache, constipation
- Urinary tract or respiratory infection
- Electrolyte imbalance, and
- Drug toxicity

Treatment of psychiatric symptoms

- Atypical antipsychotics such as quetiapine can be used in low doses
- A mistake is to advance to higher doses or to use anticholinergic drugs or sedatives

- Sometimes respond to the cholinesterase inhibitors, especially in DLB

Treatment of seizures

- Levetiracetam is useful for AD-associated seizures

Nondrug behavior therapy

- Important in dementia management
- Preparing lists, schedules, calendars, and labels is helpful
- Familiar routines, walks, and simple physical exercises are useful
- Safety measures be taken in the kitchen, bathroom, stairways

Nondrug behavior therapy

- Patients often object to losing control over familiar tasks e.g. driving, handling finances

- Hostile responses on the part of the caregiver are counterproductive
- Reassurance, distraction, and calm positive statements are more productive

Nondrug behavior therapy

- Frustration and depression among family members and caregivers are common

- Taking advantage of day-care facilities and respite break services be encouraged
- Education and counseling about dementia are important

Nondrug behavior therapy

- Local and national support groups are valuable resources :
  - The alzheimer's association and
  - The family caregiver alliance
  - Internet access to these resources has become available to clinicians and families

Thank You