Case 01

A 64 years old physician is brought to OPD by his wife who expresses concern regarding 3 years of progressive memory impairment. He frequently forget the details of conversations, misplaces objects at home specially keys, making mistakes in the steps of prayer (Namaz) and repeat question, seeming not to realize they had been answered one minute before but he felt nothing is wrong. In the past years he had developed difficulty in finding words and became disoriented in familiar places including his chamber building where he practiced for last 35 years.

He retried from his practice 2 years ago, owing to difficulty in recalling the medicine to be prescribed and also difficulty in communicating with the patients. He became quitter in social situations, more reluctant to go out and no longer interested in going to mosque.

Recently his wife noticed him to have difficulty in wearing cloths properly and became agitated with simple words and occasionally wonders room to room at night.

He is hypertensive & non-diabetic, his order sister age 73 years living in UK having a diagnosis of Alzheimer disease.

Key problems of case 01

1. Memory Loss-Progressive
2. Apraxia- dressing difficulty
3. Decline executive functions- writing prescriptions
4. Behavioral problem- aggressive, wondering and depressive
5. Feeling nothing wrong- Anosognosia
6. Family History-Elder sister AD

Question

A. What medical problem the physician has?
B. What are possible causes of his presentation?
C. How to reach a diagnosis to help that physician?
D. How to manage him to maintain a sound healthy life?

DEMENTIA IN ELDERLY APPROACH TO DIAGNOSIS & MANAGEMENT

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FCPS, MD

Professor of Neurology,
Anwer Khan Modern Medical College & Hospital, Dhanmondi, Dhaka

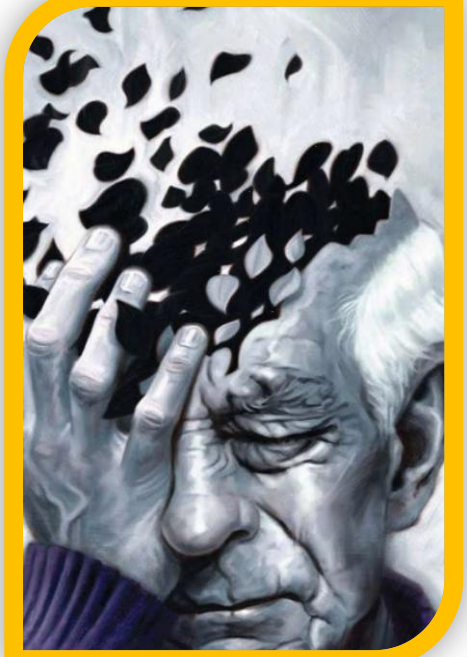
Dementia

Impairment of multiple domains of cognitive functions:

Memory impairment a. New material learning,
b. Forget previous learning

With at least one of the following cognitive disturbance:

- **Aphasia-language disturbance**
- **Apraxia- impaired ability to carry out motor activities despite intact motor function**
- **Agnosia- failure to recognize/ identify familiar object despite intact sensory function**
- **Disturbance in executive functions**



Dementia

Faces of Dementia

Cognitive

Learning and memory
Language
Executive function
Complex attention
Perceptual-motor
Social cognition

Behavioral

Depression
Anxiety
Psychosis
Agitation

Significant impairment of social & occupational functioning- decline from previous level

Gradual onset, continuing cognitive decline with alert & normal arousal.

DSM (V)

3 cognitive syndromes

No cognitive impairment

MCI

50%, 4 Years

Dementia

Dementia: acquired cognitive impairments.

MCI: single cognitive deficit or multiple mild deficits.
No significant limitations of daily function

No cognitive impairment

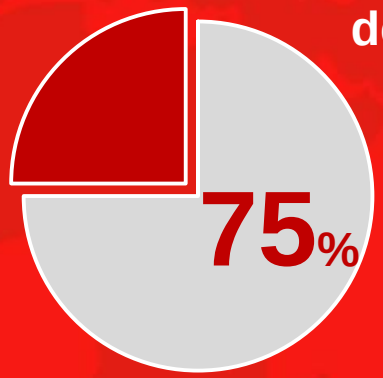
DEMENTIA EPIDEMIOLOGY

1 in **3** seconds

46.8 million people worldwide living with dementia in 2015

It is now close to **50 million** people in **2017**

9.9 million new cases of dementia each year worldwide



of people with dementia have not received a diagnosis

DEMENTIA EPIDEMIOLOGY PRESENT

ECONOMIC BURDEN

DEMENTIA EPIDEMIOLOGY FUTURE

Much of the increase will take place in low and middle income countries (LMICs): 58% of all people with dementia live in LMICs, rising to 63% in 2030 and 68% in 2050.

DEMENTIA EPIDEMIOLOGY BANGLADESH

No exact epidemiological data

Peak age – 54 yrs.

Hasan M, Khan B

Classification of Dementia

What type of memory impairment of the CASE 01 has?

Primary degenerative dementia

Cognitive impairment is the major presenting features

Dementia plus Syndrome (Secondary)

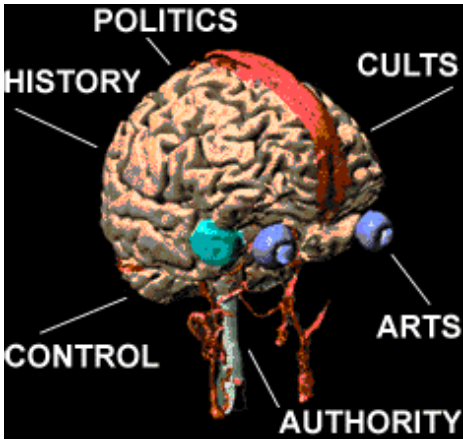
Cognitive impairment just one face of more wide spread disorder

Primary degenerative dementias

Alzheimer's disease: 50-75%

Dementia with Lewy bodies: 15-35%

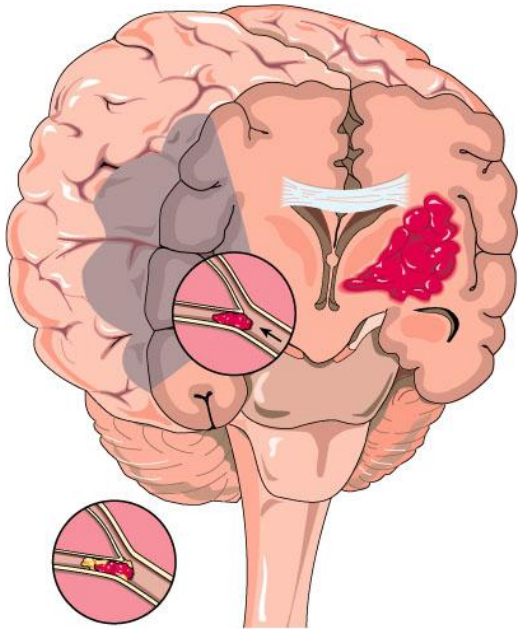
Frontotemporal Dementia & Pick's disease



Dementia plus Syndrome (Secondary) VITAMINS D4

V: Vascular

- Multi infarct dementia
- Lacunar state
- Binswargner disease
- CADASIL
- Amyloid angiopathy



I : Infections/Inflammations-

Viral

AIDS dementia complex

Encephalitis – HSV

SSPE

PMLE

Classification (Secondary)

Bacterial

- Tuberculosis (CNS)
- Syphilis
- Whipple's, Lyme

Prion: CZD

Fungal: Crytococcus, deep fungal infectors

T: Traumatic

- Subdural hematoma
- Dementia pugilistica
- Chronic post traumatic encephalopathy

Classification (Secondary)

- **A: Autoimmune**
  - CNS Vasculitis
  - SLE, PAN
  - Sarcoidosis
- **Autoimmune Encephalopathy**

  Limbic encephalitis, NMDA receptor antibody, AMPA receptor antibody, GABA A& B receptor antibody, VGKC complex antibody

- **I: Iatrogenic/toxin**
  - Substance abuse (chronic)
  - **Alcohol (chronic)**
  - Arsenic
  - Lead
  - CO exposure
  - Organic solvents

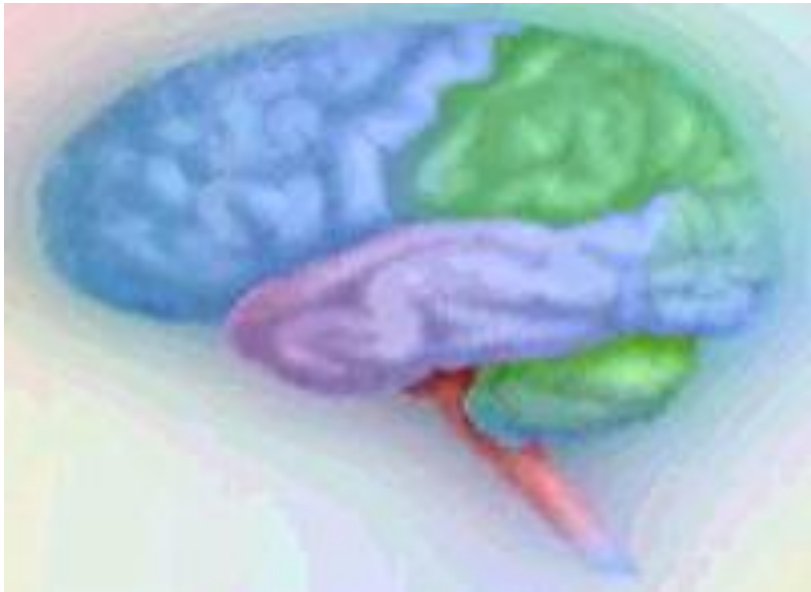
Classification (Secondary)

- **N: Neoplasm**
    - Primary
    - Secondary
    - Paraneoplastic
        - #Progressive limbic encephalitis
    - Treatment effect
        - #Post radiation effect

- **S: Structural**
    - Normal pressure hydrocephalus

- **D1: Demyelinating**
    - Multiple sclerosis

- **D2: Deficiency**
    - Niacin- Pellagra
    - Vitamin B1
    - Vitamin B12



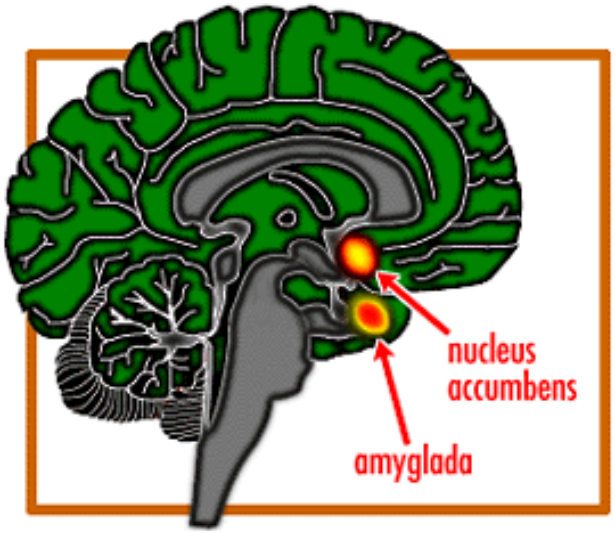
Classification (Secondary)

D3: Degenerative

- Parkinson's disease
- PSP
- Huntington's disease
- ALS dementia complex
- Cortico-basal degeneration

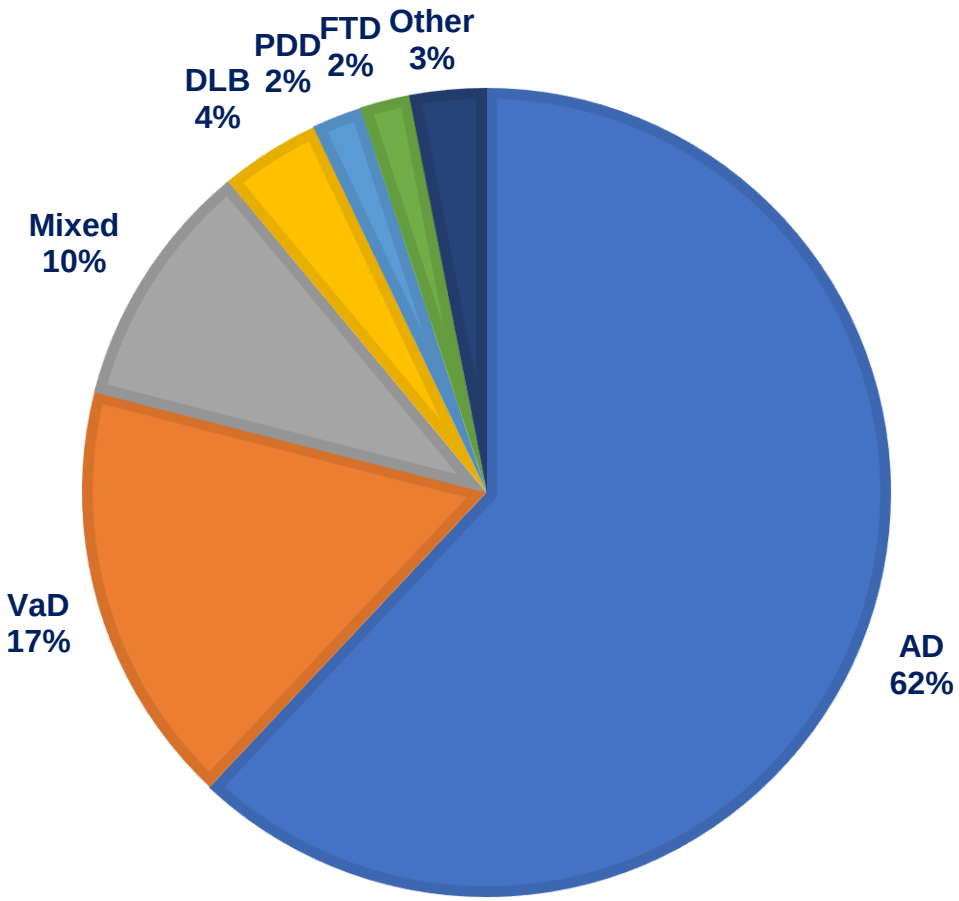
D4: Developmental

- Dawn syndrome
- Wilson disease
- Porphyria
- Homocysteinuria
- Mitocondrial cytopathies

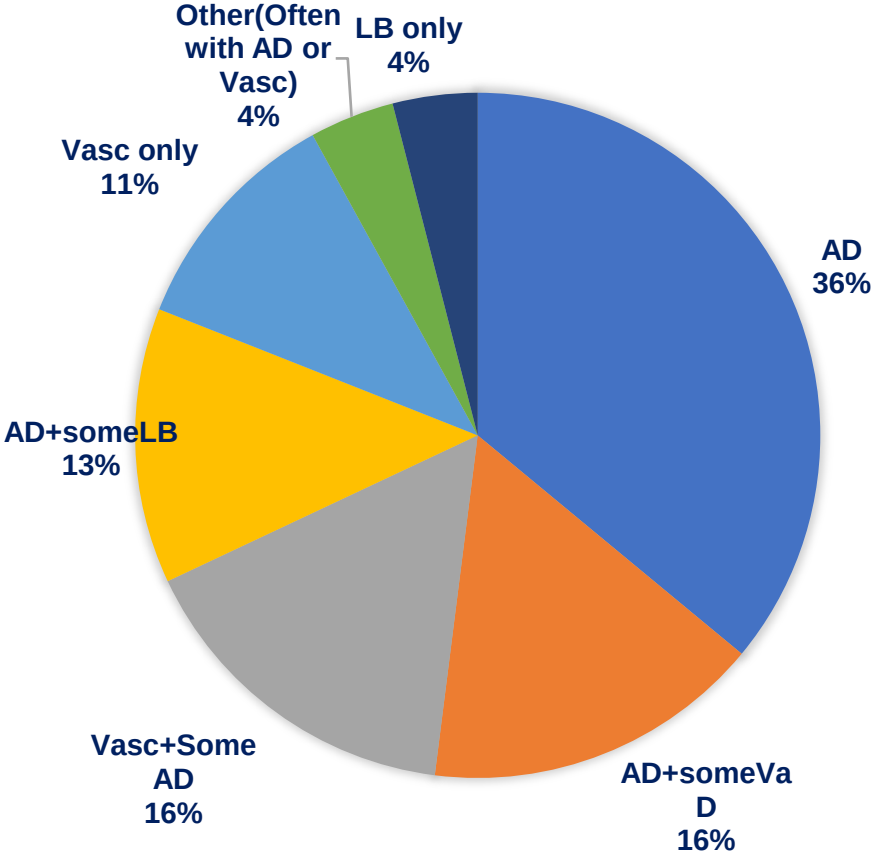


DISTRIBUTION OF DEMENTIA DIAGNOSES

Textbook

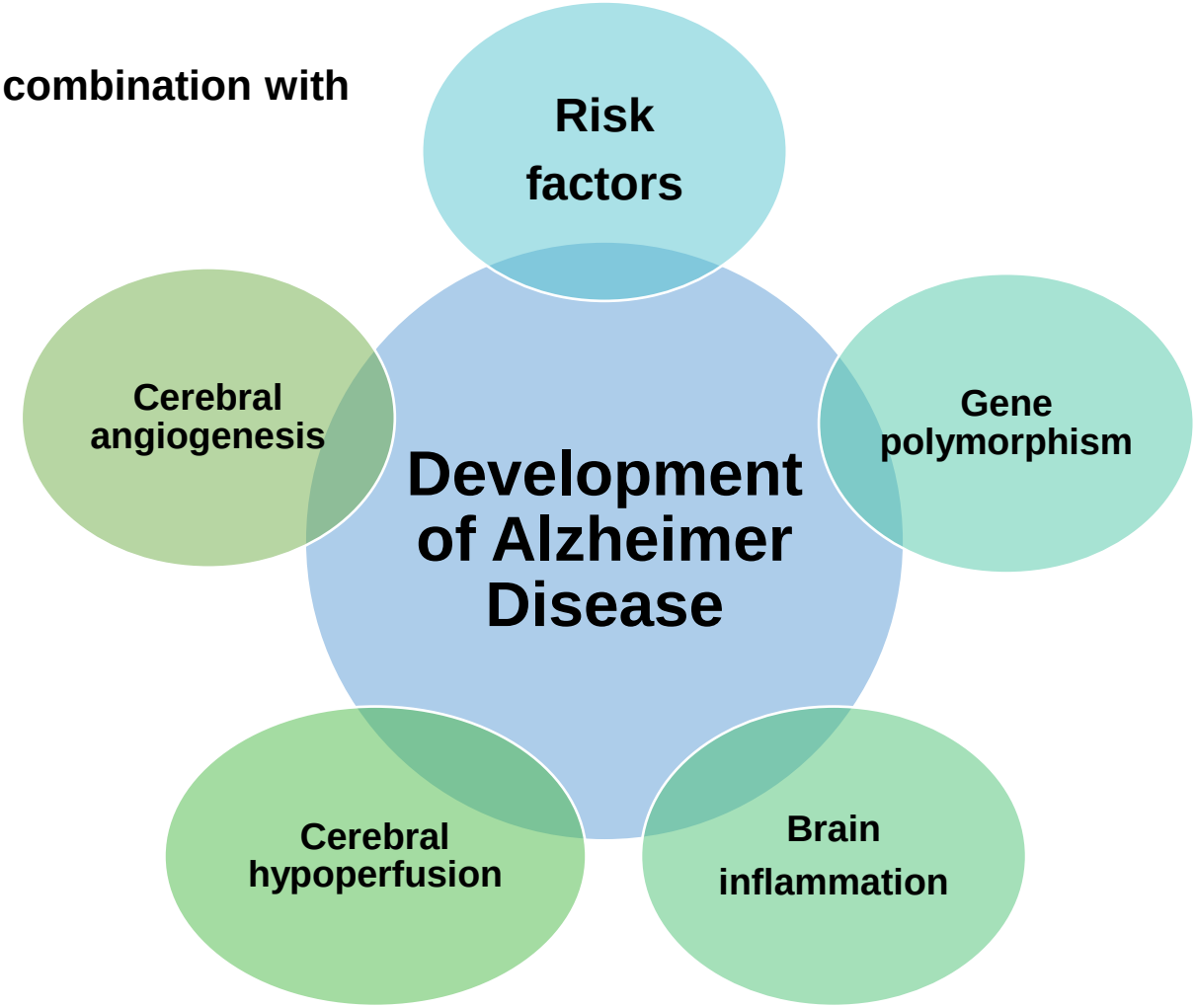


PATHOLOGICAL SERIES



Pathophysiology of Dementia

Multifactorial in combination with



Pathophysiology of Dementia

What are the RISK FACTORS?

AGE

5-8% at age 65-70
15-20% at age 75-80
40-50% over age 85

Genetic

5% AD
Autosomal dominant
Chromosome
(1,14,21,)
(PS-1,PS-2)

APO E Gene

APO E protein involved in cholesterol transport
Three alleles-E2 (rare), E3(most frequent), E4

Pathophysiology of Dementia

What are the RISK FACTORS?

Female gender: 2/3 of population over 75 yrs.

Lack of education

Under & over 75 yrs. age in twice the risk

than education to standard VIII

Head trauma
Cerebral atherosclerosis
Dyslipidemia
Alcohol use
Tobacco use
Iodine deficiency
Chronic use of PPI

ALZHEIMER'S DISEASE (AD)

CASE 02

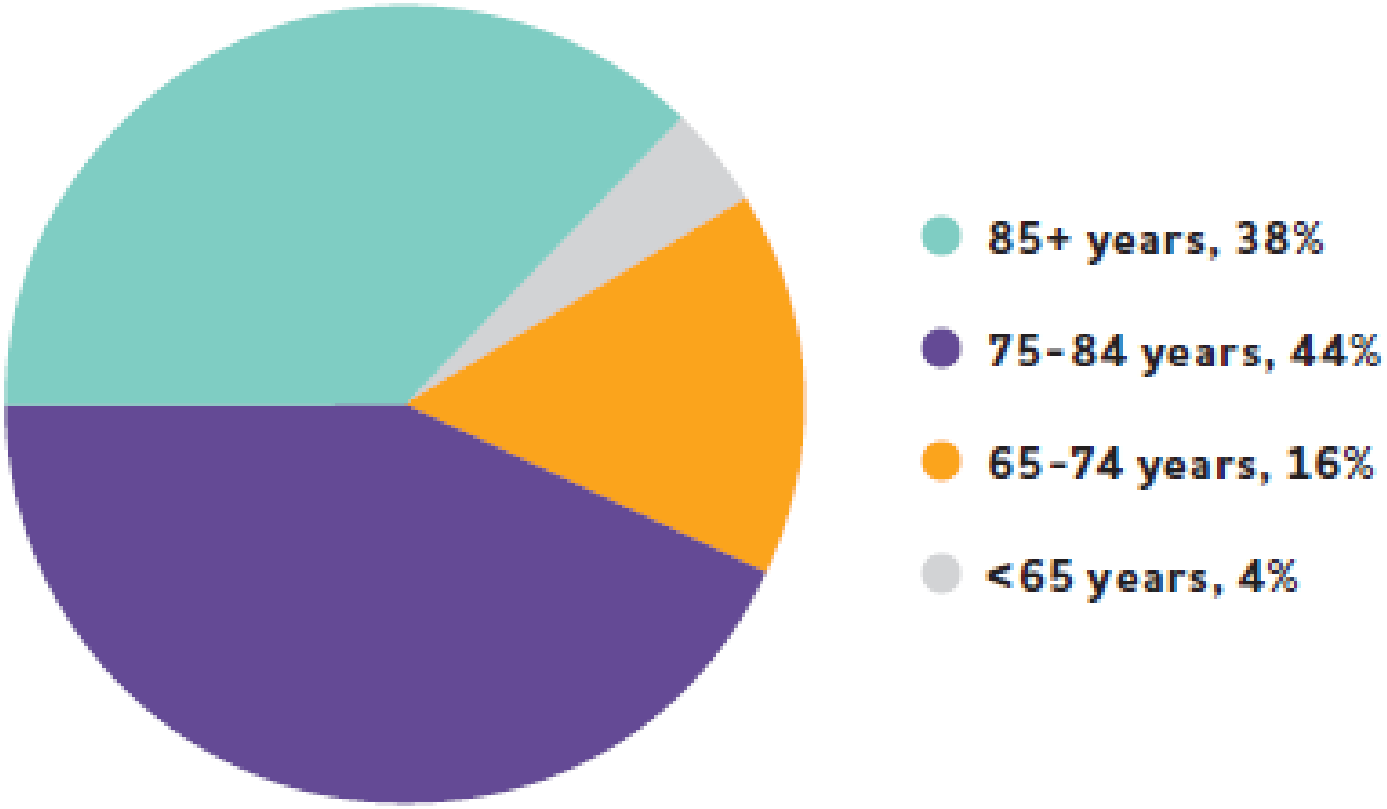
65 yr old male present with progressive memory loss for past 2 yr.
He also complaints of difficulty in naming objects and lost 4 times from coming from market to house in last 2 month.
He has difficulty in dressing ,eating and gets agitated easily and wanders around at night at others room.

MMSE – 15/30
Neurological exam- normal
Vision & hearing- normal

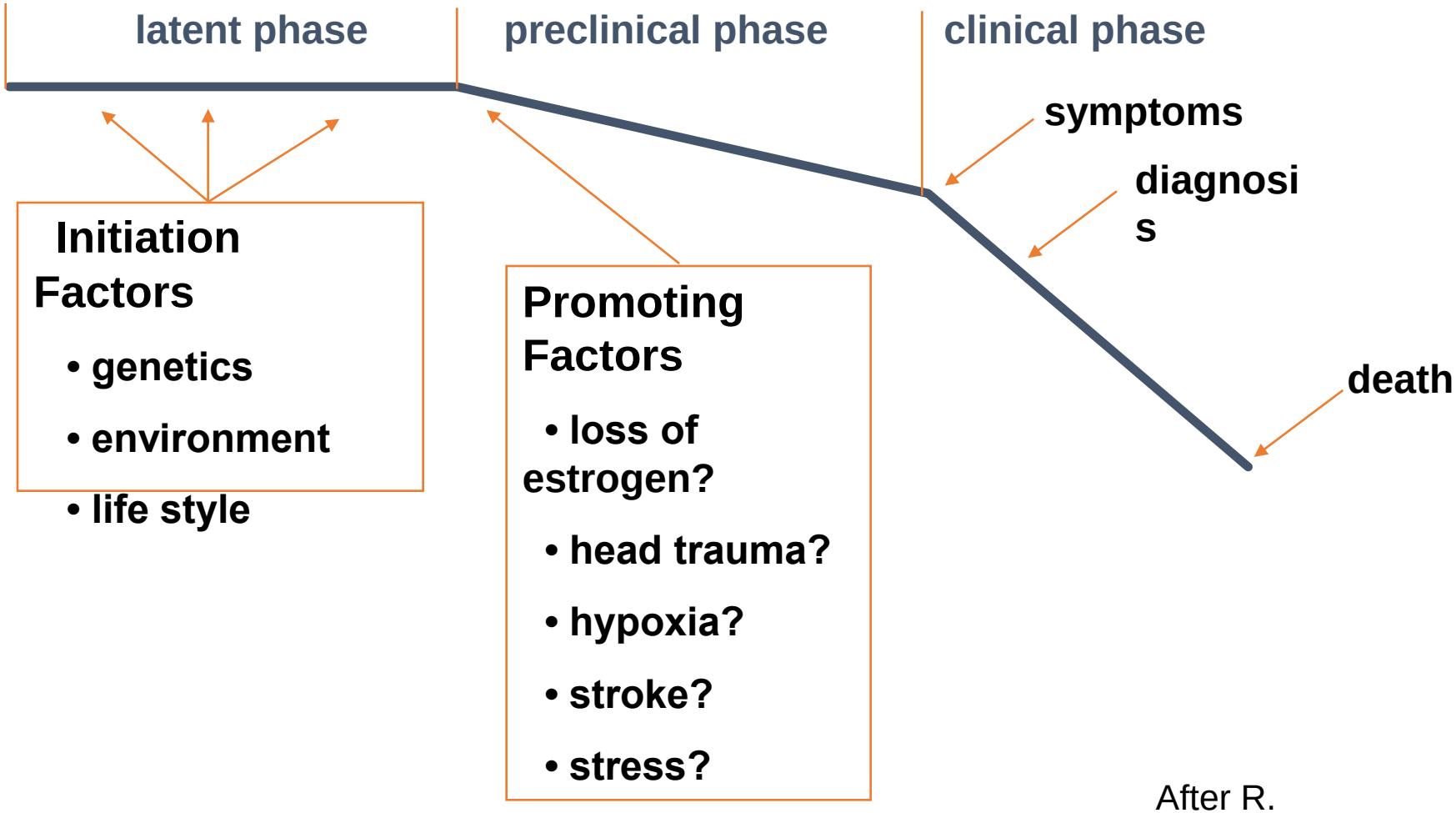
- Memory impairment- 1st
- Language problem- Naming, word finding
- Visuospatial defect- Dressing
- Navigational difficulty- Lost
- Progressive
- Behavioral problem- Agitation, wondering

ALZHEIMER'S DISEASE (AD)

Ages of People with Alzheimer's Dementia in the United States, 2017

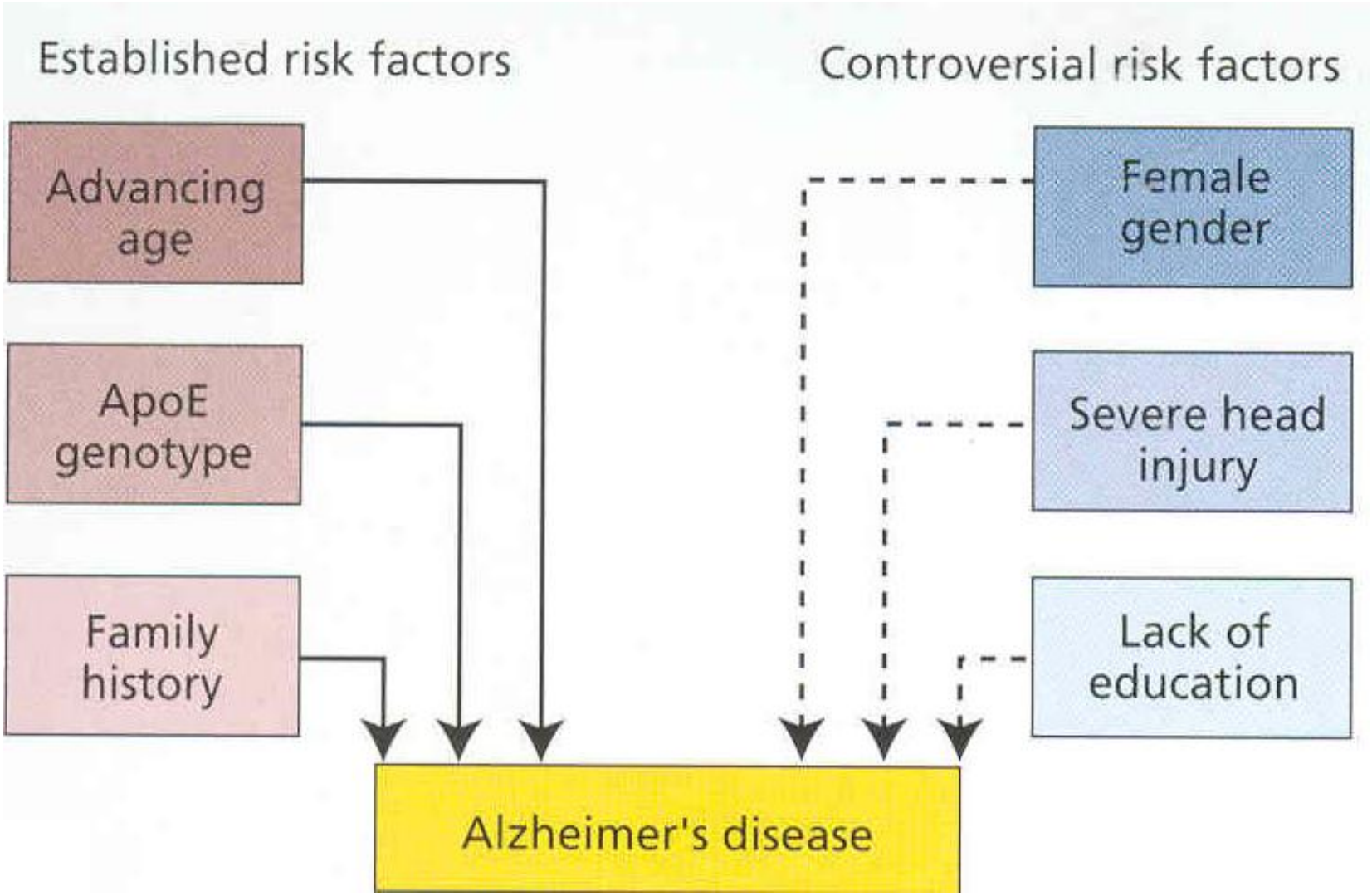


Alzheimer's disease as a chronic disease



After R. Katzman, 1993

Pathophysiology of AD



BIRDS EYE VIEW

Pathophysiology of AD

Pivotal role

- Production and accumulation of beta amyloid peptide
- All currently known Gene mutations associated with AD increases production of beta amyloid
- Accelerated deposition of beta amyloid occurs in apolipoprotien E4 genotype
- Beta amyloid is neurotoxic & leads to cell death
- Cell death and cell dysfunction leads to defect of specific neurotransmitter system i.e. Acetylcholine, Norepinephrine, Serotonin

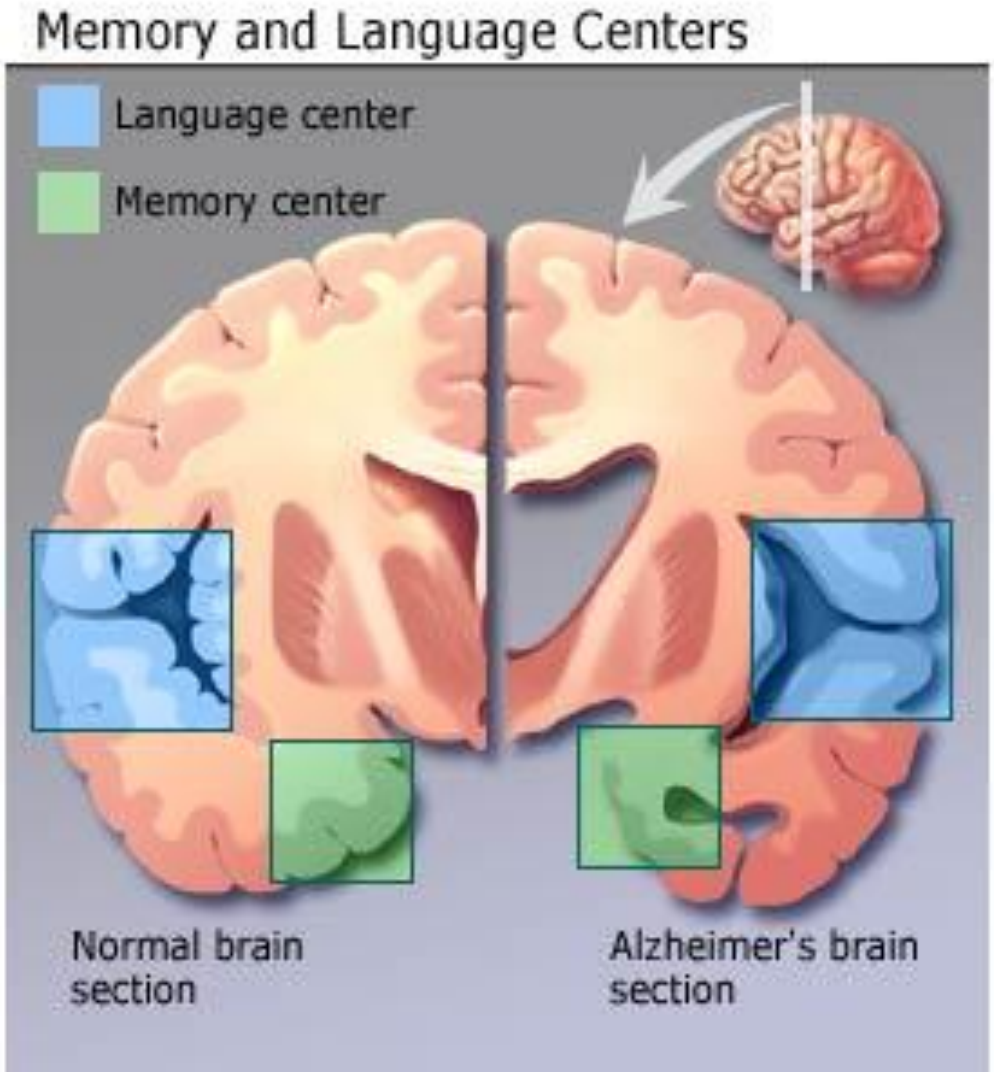
NEJM 351: 2004

Dementia (Alzheimer's disease)

Pathology (Gross)

- Every part of cerebral cortex is involved with relative sparing of occipital pole
- Marked atrophy, widened sulci
- Shrinkage of gyri
- Thinning of cortical ribbon
- Ventricular dilatation especially temporal horn, atrophy of amygdala & hippocampus

Pathology of AD



- Progressive loss of cortical neurons
- Widening of the sulci
- Temporal atrophy

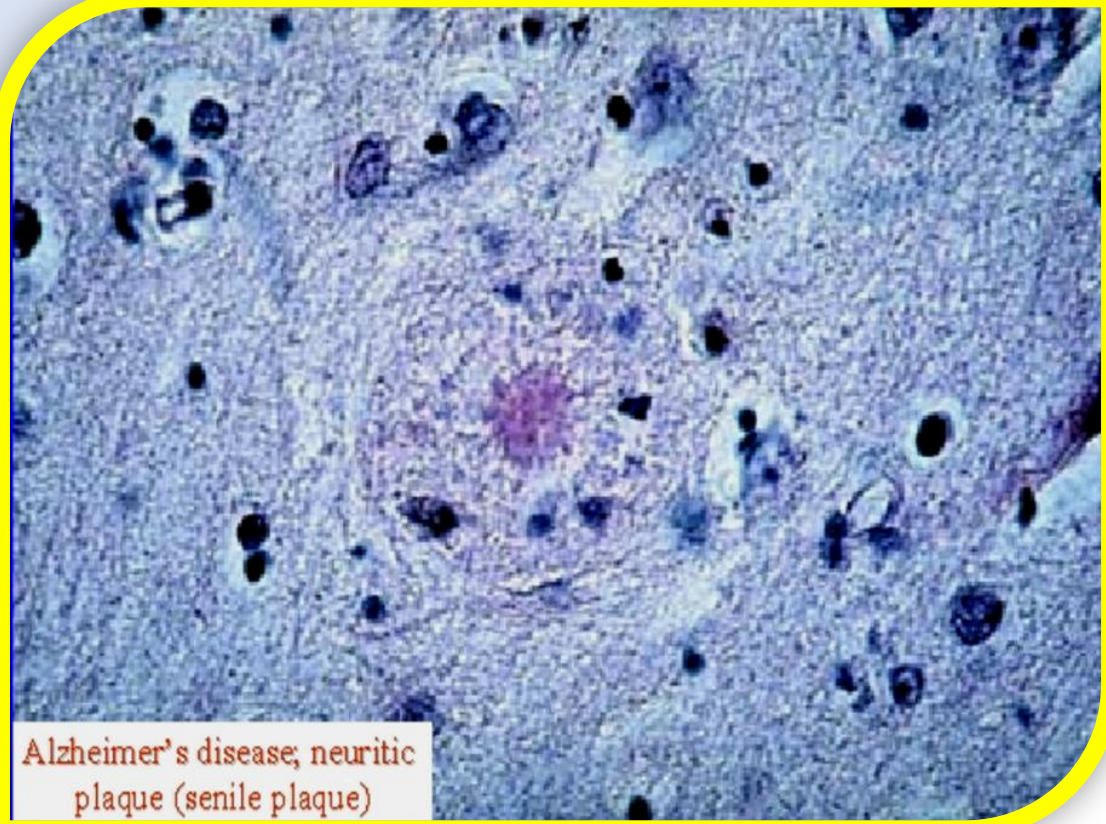
Pathology of AD (Microscopic)

Neuritic plaques (NP):

Extracellular, Spherical structures

Central core of fibrous protein known as amyloid

Surrounded by degenerating or dystrophic nerve endings (neuritis)

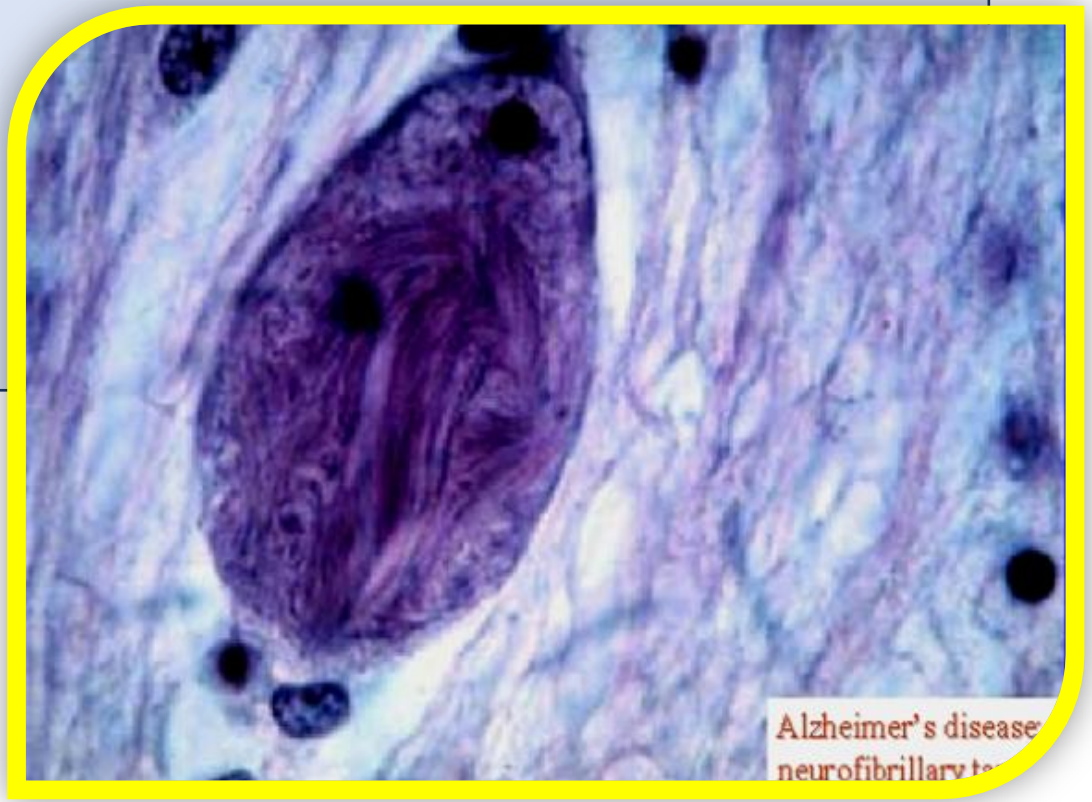


Pathology of AD (Microscopic)

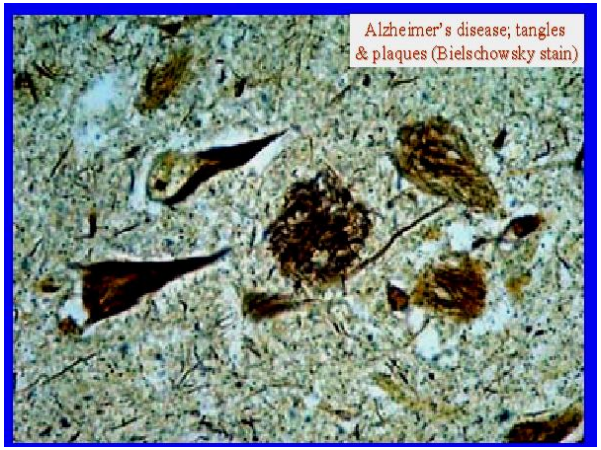
Neurofibirillary tangle (NFT) :

Intracellular
Paired helical strands of hyperphospharylated tau proteins

Microtubules associated tau Protein lie close to nuclei

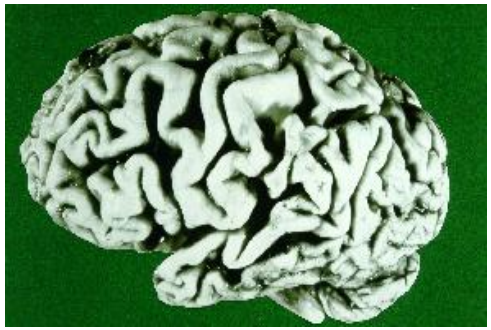


Pathology of AD (Microscopic)

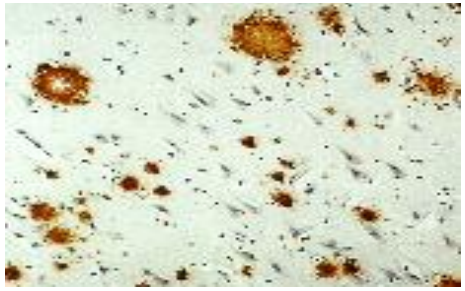


Neuritic Plaque &
Neurofibrillary Tangle

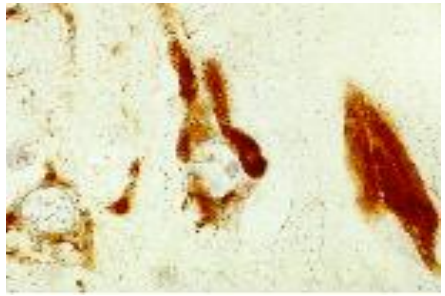
AD: a progressive CNS disorder with a characteristic pathology



Brain atrophy



Senile plaques



Neurofibrillary tangles

Biomarkers predicting
the risk of conversion Of MCI to dementia

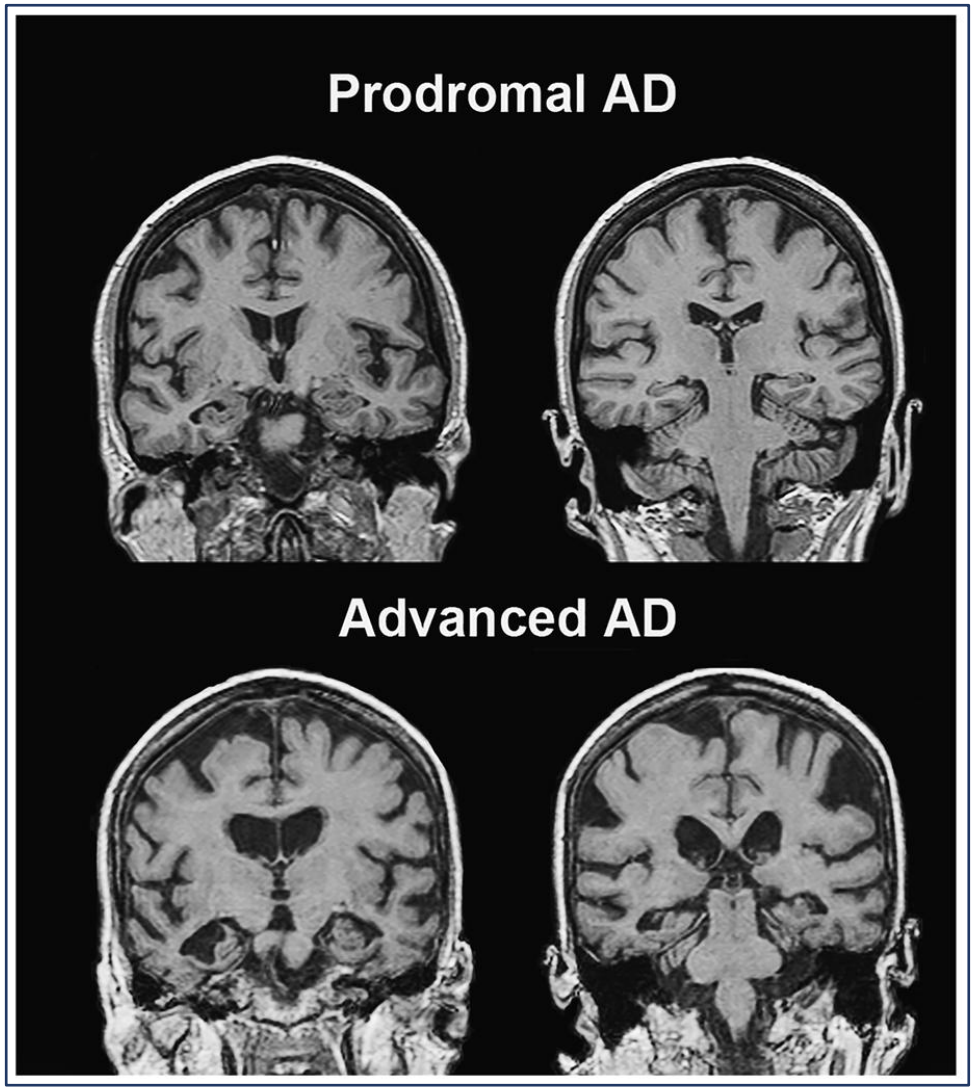
- MRI-MCI with hippocampal volumes -25th percentile – 2 to 3 times risk compared 75th percentile
- CSF-↓ Aβ 42 and ↑ t-tau and p-tau
- APOE4 allele
- Temporal-parietal hypometabolism on FDG-PET
- Amyloid deposition on Aβ PET imaging

(Jack et al., 2010, Mattsson et al.2009, Petersen et al., 1995, 2005, Chetelat et al., 2003,Wolk et al., 2009).

Staging of AD

Stage 1	No impairment (normal function)
Stage 2	Very mild cognitive decline
Stage 3	Mild cognitive decline (early-stage Alzheimer's can be diagnosed in some, but not all, individuals with these symptoms)
Stage 4	Moderate cognitive decline (Mild or early-stage Alzheimer's disease)
Stage 5	Moderately severe cognitive decline (Moderate or mid-stage Alzheimer's disease)
Stage 6	Severe cognitive decline (Moderately severe or mid-stage Alzheimer’s disease)
Stage 7	Very severe cognitive decline (Severe or late-stage Alzheimer's disease)

ALZHEIMER'S DISEASE (AD)
MRI FINDINGS



1. Mesial temporal atrophy/ Hippocampal atrophy (A, B, arrows)
2. Global brain atrophy
3. Pronounced ventricular enlargement.

VASCULAR DEMENTIA

CASE 03
76 yr old male presented in neuro opd with c/o progressive memory loss, emotional lability, gait disturbance for past 5 months

h/o of 3 episodes of stroke + recent attack 7 months back h/o HTN,DM,CAD+ with CABG 4 yrs back

O/E- increased tone in all limbs, power 3+ in RT.UL & LL. 4+ in LT side, B/L extensor plantar

- Multiple Vascular Risk Factor
- pyramidal signs/cerebellar signs
- gait disorder, urinary incontinence, dysarthria
- confusion, personality changes, psychosis
- emotional lability
- MRI- multiple areas of infarction

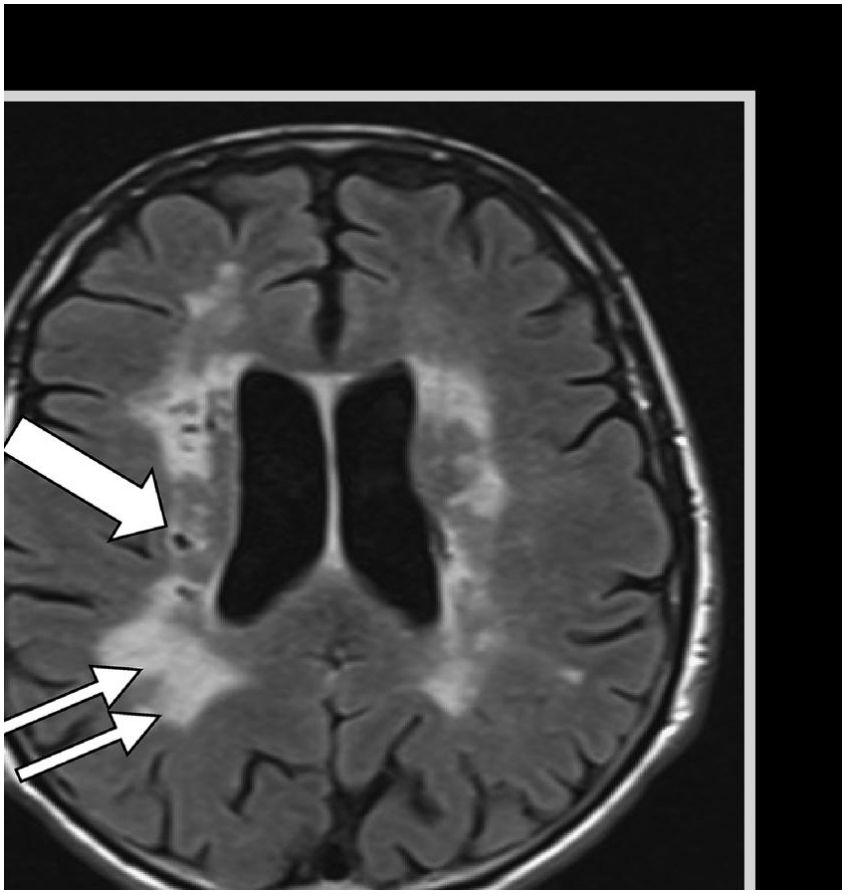
VASCULAR DEMENTIA

- **Cerebrovascular disease can cause**
  - **Large vessel infarcts (classic stroke)**
  - **Small vessel infarcts (may be silent)**
  - **Micro and incomplete infarcts**

Classification

- **Multi-infarct dementia-** recurrent strokes: step wise progression, HTN,DM,CAD
- **Binswanger's d/s:** Diffuse white matter disease
- **Lacunar Infraction**
- **Cerebral amyloid angiopathy**
- **CADASIL**

VASCULAR DEMENTIA



1. Severe white matter hyperintensities (double arrow)
2. Multiple lacunae of presumed vascular origin (single arrow).

PATHOLOGY OF VASCULAR DEMENTIA

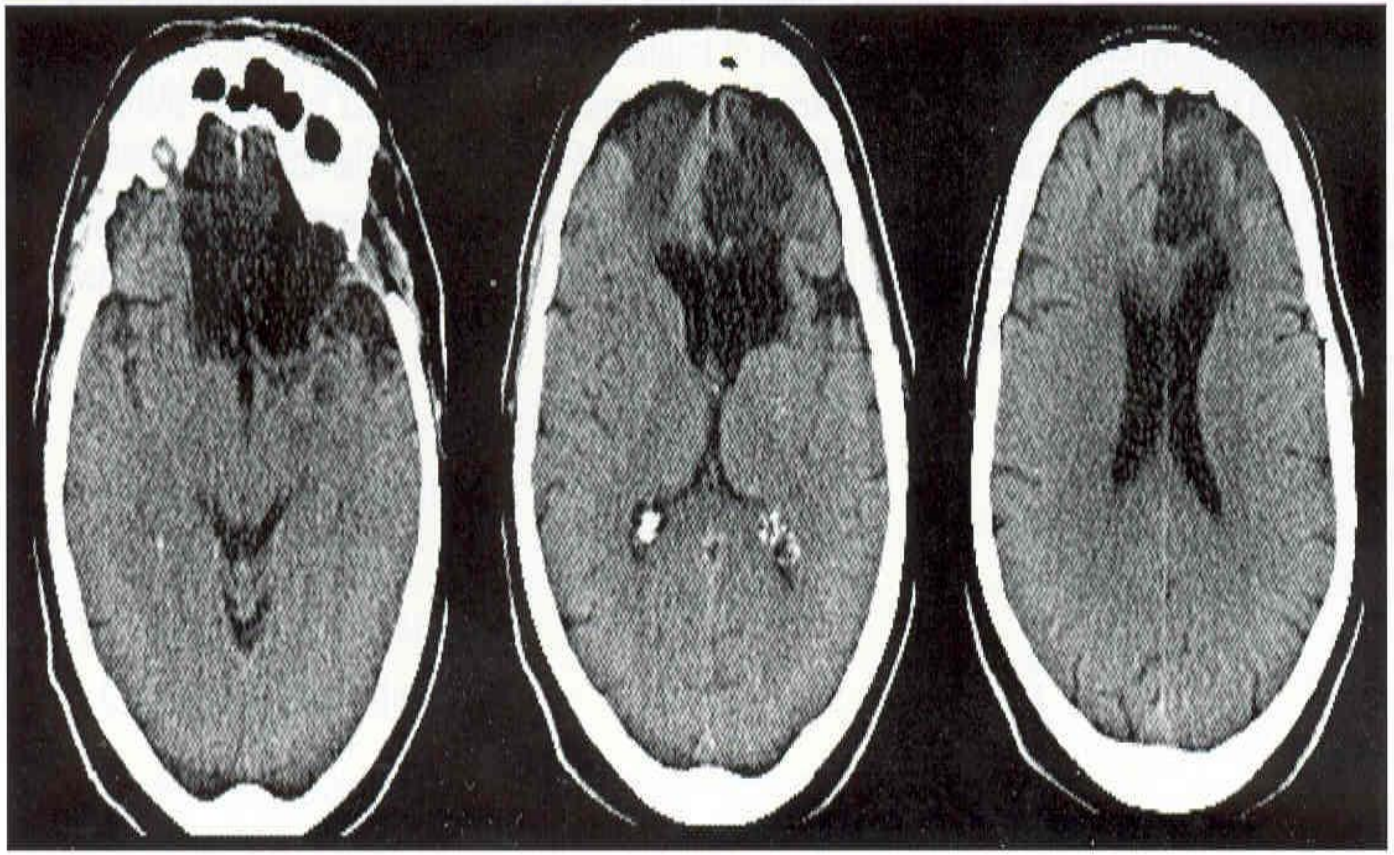


Figure 6-28. Computed tomography (CT) scans of a 47-year-old man with a history of "strategic infarct" dementia. Single-stroke vascular dementia may result from strategically placed infarcts in

FRONTOTEMPORAL DEMENTIAS

CASE 04

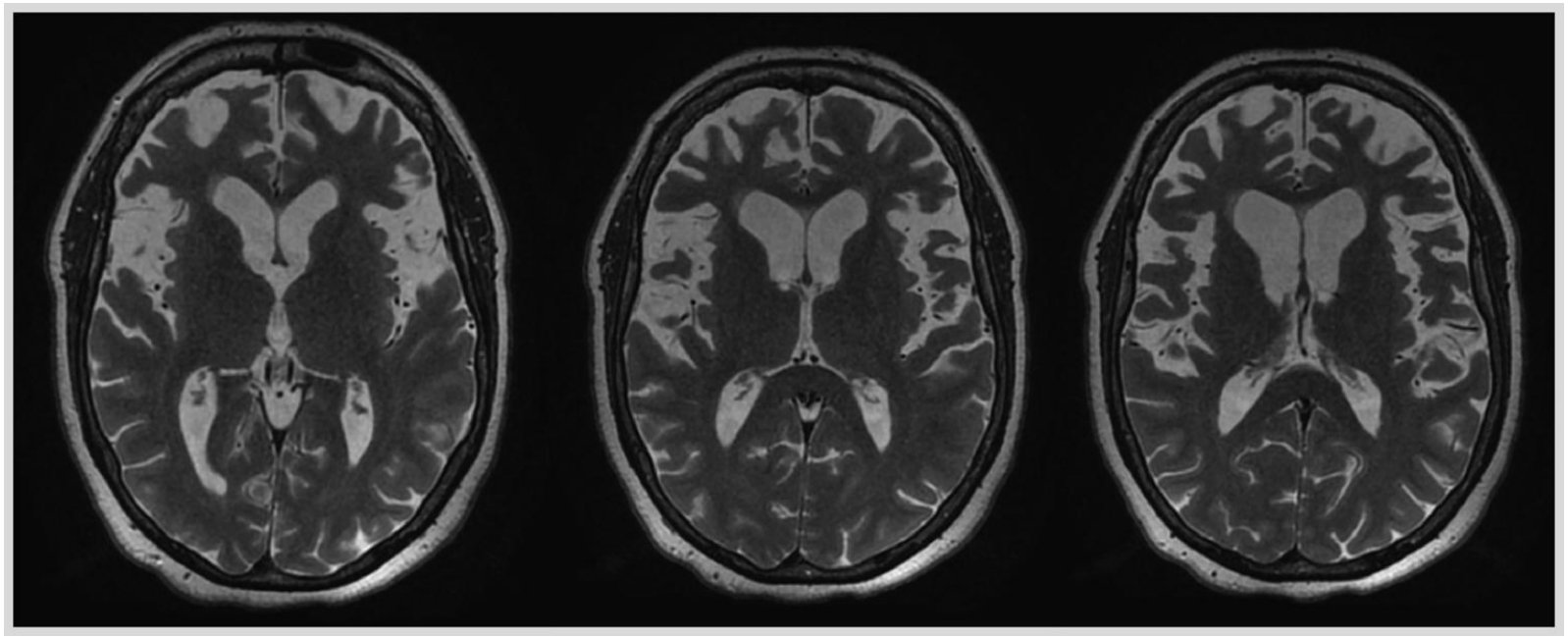
55 YR old woman presented with 2yr history of progressive alteration in social behavior. Her husband complaint of increased disclosure of personal information to others, loss of manner and using racist language in public and inappropriate spending of money in shopping despite of financial difficulties. She spend more time at staring at TV. There is complaints of excessive food intake and weight gain for past 1 yr and pt was taken to psychiatrist once.

O/E- vitals stable..neurological exam –WNL

MMSE-18/30

1. Often begins with marked behavioral Disturbances- Personal information discloser
2. Impulsive behavior: Spending money
3. Language problem
4. Impairment of planning, judgement
5. Hot-tempered and socially disinhibited
6. Memory & visuospatial skills spared
7. Echolalia +
8. Illness progresses for years, like AD
9. Inevitable decline

FRONTOTEMPORAL DEMENTIAS



T2-weighted axial MRI shows bifrontal and temporal atrophy

DIFFUSE LEWY BODY DISEASE

CASE 05

62 yr old male came to opd with c/o progressive decline in memory for the past 6-8 months. He also complaints of having decreased sleep and occasional nightmares. He occasional sees his deceased wife at times. He then developed shuffling gait, postural tremor special on fastening buttons.

O/E- vitals stable ,rigidity of limbs+

- gait- slow stepping gait, bradykinesia+ MMSE-

1. Patients have clinical parkinsonism with early and prominent dementia
2. Visual hallucinations: Sees deceased wife
3. Cognitive fluctuations common, 4.Capgras syndrome
5. REM sleep disorder
6. Better memory but severe visuospatial deficit
7. Patients sensitive to adverse effects of neuroleptics
8. May be second most common cause of dementia after AD
9. Lewy bodies found in brain stem, limbic system, and cortex
10. Deposition of protein alpha synuclein and ubiquition

Major Dementia's: Key of Differences

Parameter	AD	VaD	LBD	FTD
History	Gradual onset and progression	Abrupt/gradual onset, Stepwise / gradual progression	Insidious onset Progression with fluctuations	Early onset, insidious onset Rapid progression
Physical Signs and Symptoms	Normal gait & neurological exam in the early-mid stages	Gait abnormalities, sign of vascular disease and focal neurological signs	Shuffled slow gait, increased tone, tremors	Gait abnormities along with primitive reflexes
Other signs and symptoms	Memory loss, language deficits, mood swings and personality changes	Memory loss, language deficits, dysarthria, emotional lability	Hallucination, Depression, variable in day to day symptoms	Language Problem, Poor judgement, social withdrawal and socially inappropriate behavior
Imaging	Generalized atrophy, medial temporal lobe atrophy	Strokes, lacunar infarcts, white matter lesion are noted	Generalized atrophy throughout	Frontal and temporal lobes are atrophied
Pathology	Beta amyloid plaques and neurofibrillary tangles	Vascular risk factor	Lewy Bodies in both the cortex and the midbrain areas	Absence of plaques and tangles, Pick cells and bodies are present in the cortex

PARKINSON'S DISEASE

CASE 06

82 yr old male came to opd with unilateral resting tremor of right upper limb followed by right lower one from last 4 years which gradually increases and affects all 4 limbs. He has also difficulty in initiating movement which gradually increase to difficulty in rolling over the bed at night, he also compliance of occasional fall and imbalance with progressive declining of his hand writing. Recently there is gradual loss of memory and forgetfulness complaint by his family.

O/E expression less face infrequent blinking, cogwheel rigidity, resting tremor, slow stepping gait, vitals stable, bradykinesia+
MMSE- 22/30

About 50% of patients have dementia by 85 years old

- Classic Presentation of PD, Tremor, Rigidity, Bradykinesia
- Affects executive function disproportionately
- Dementia occur in later stage
- Depression & anxiety
- Frontal lobe dysfunction- complex tasks, planning, - memorizing
- Language & mathematical skills spared

NORMAL PRESSURE HYDROCEPHALUS

CASE 07

65 YR old male presented to neuro opd with c/o gait disturbance for past 1 yr, his son complained his father is having memory loss for past 6 months and it is progressing. The pt also c/o of urinary incontinence+ Neurolog exam- no focal deficits, difficulty tandam walking

MMSE- 23/30

Triad

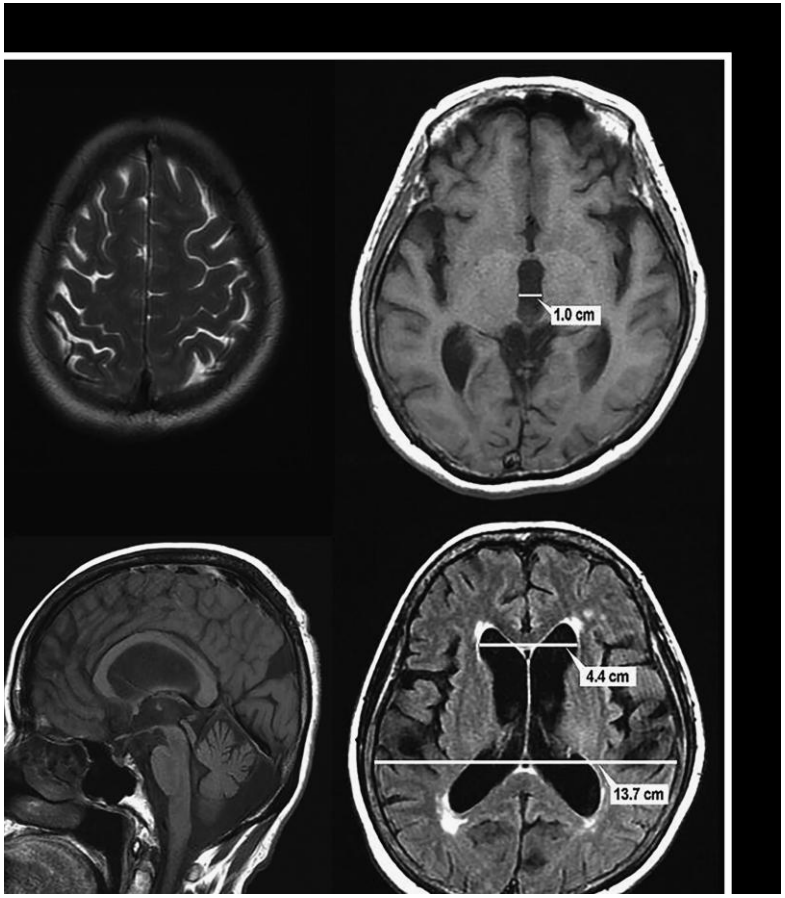
1. Dementia: typically subcortical
2. Gait instability
3. Urinary incontinence

Walk with “feet stuck to floor”- difficulty tandam walking
Symptoms progress over weeks to months

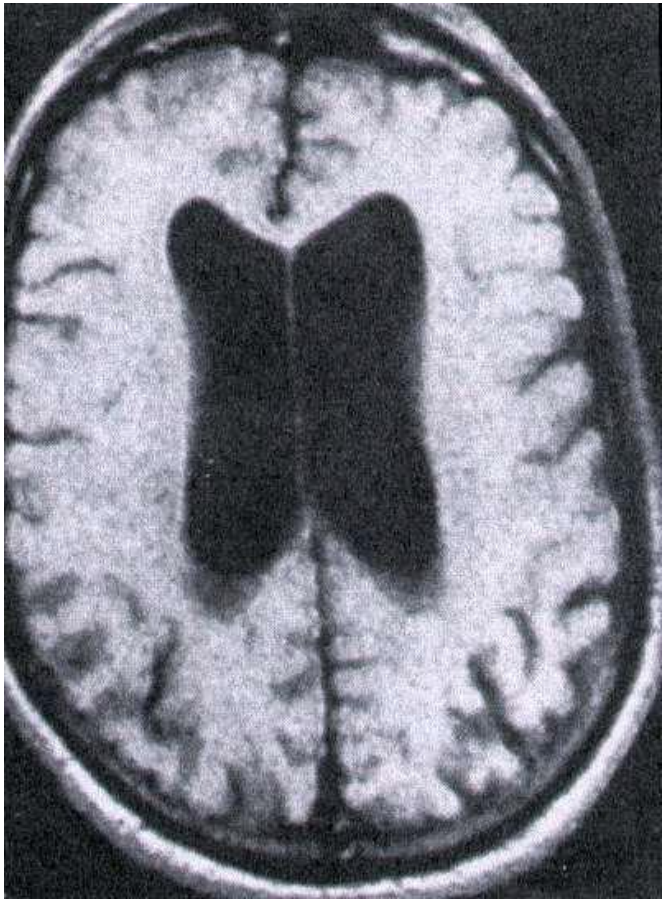
Most important test – therapeutic LP
1. Remove large amount of CSF
2. Examine gait and cognitive function

NORMAL PRESSURE HYDROCEPHALUS

MRI



CT



CRUETZFELDT-JAKOB SYNDROME(CJD)

CASE 08

50 yr old woman was admitted with c/o progressive memory loss and gait problem ,slurred speech within one month; The pt also had behavioral problem -
insomnia, agitation, aggression duration of 3 weeks.
the pt also has abnormal jerky hand movements for past 1 month

O/E- limb & gait ataxia +, reflexes- exagg. - tone increased all limbs, plantar b/l extensor, no focal weakness

MMSE- 16/30

Rapid progressive dementia, prion disorder

1. Focal cortical signs, rigidity
   Onset between 40- 75 years
2. MYOCLONUS: 90% vs 10% in AD
3. Progressive dementia
4. personality changes over weeks to months
5. Death <1 year from first symptom
6. EEG- diffuse slowing and periodic sharp waves or spikes
7. MRI- basal ganglia abnormalities
8. CSF- detect specific aminoacid sequence (PrPSc)

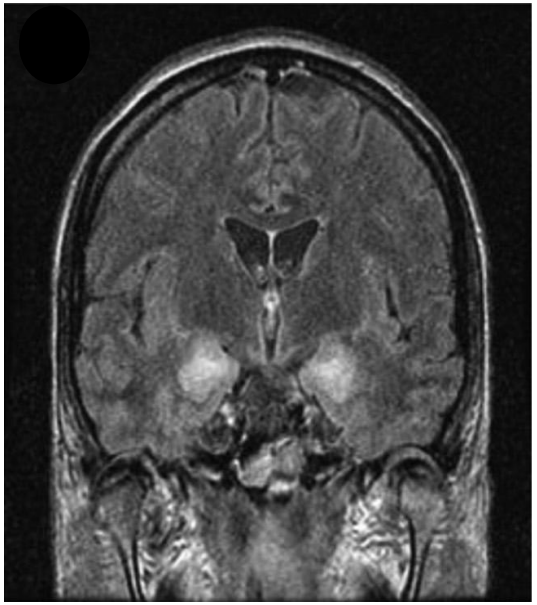
Autoimmune Encephalopathy

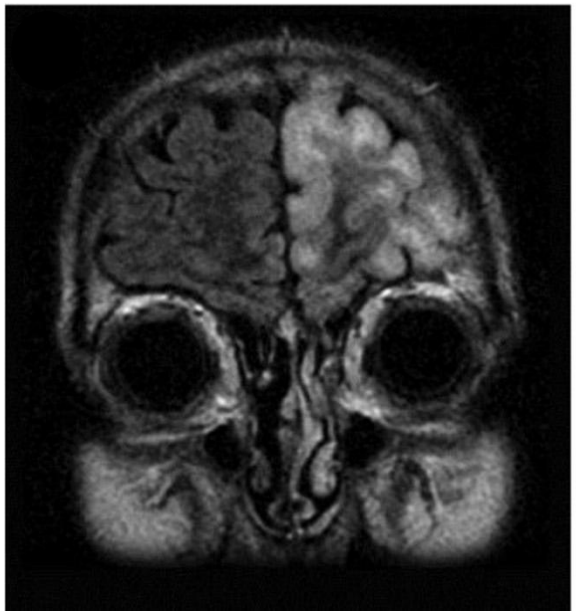
CASE 09

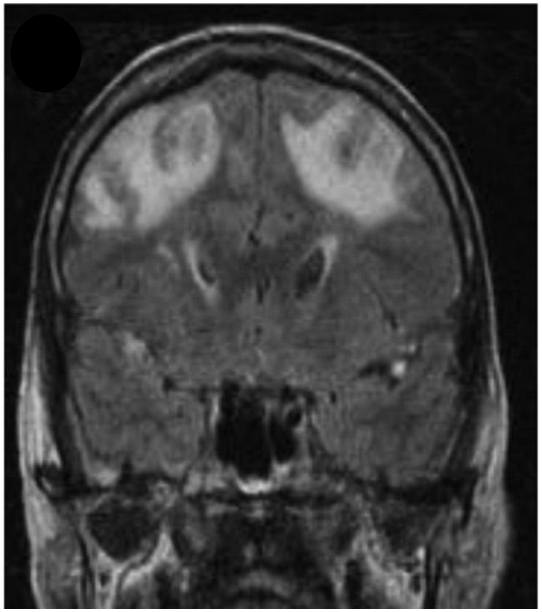
35 yr old female was admitted in hospital for headache, irrelevant behavior for last 4 months together with low grade fever. For last 3 months she develop difficulty in walking with problem in performing daily activities and also slurring of speech & tremor, one month before she had 3 episodes of generalized tonic clonic seizures. After admission into the hospital she was evaluated for infectious disease of CNS and revealed negative. She had a past history of Hasimoto thyroiditis 01 Year back and her elder sister is on treatment of Graves disease.
On 4th day of admission she went to COMA.

- Sub-acute onset
- Fluctuating course
- Tremor, Headache
- Personal or family history (first-degree relative) of autoimmunity
- History of recent or past neoplasia
- Evidence of CNS inflammation on CSF (elevated protein, pleocytosis, oligoclonal bands, elevated CSF index)
- Detection of neural autoantibody - NMDA receptor antibody, AMPA receptor antibody, GABA A& B receptor antibody, VGKC complex antibody

Autoimmune Encephalopathy : MRI Features

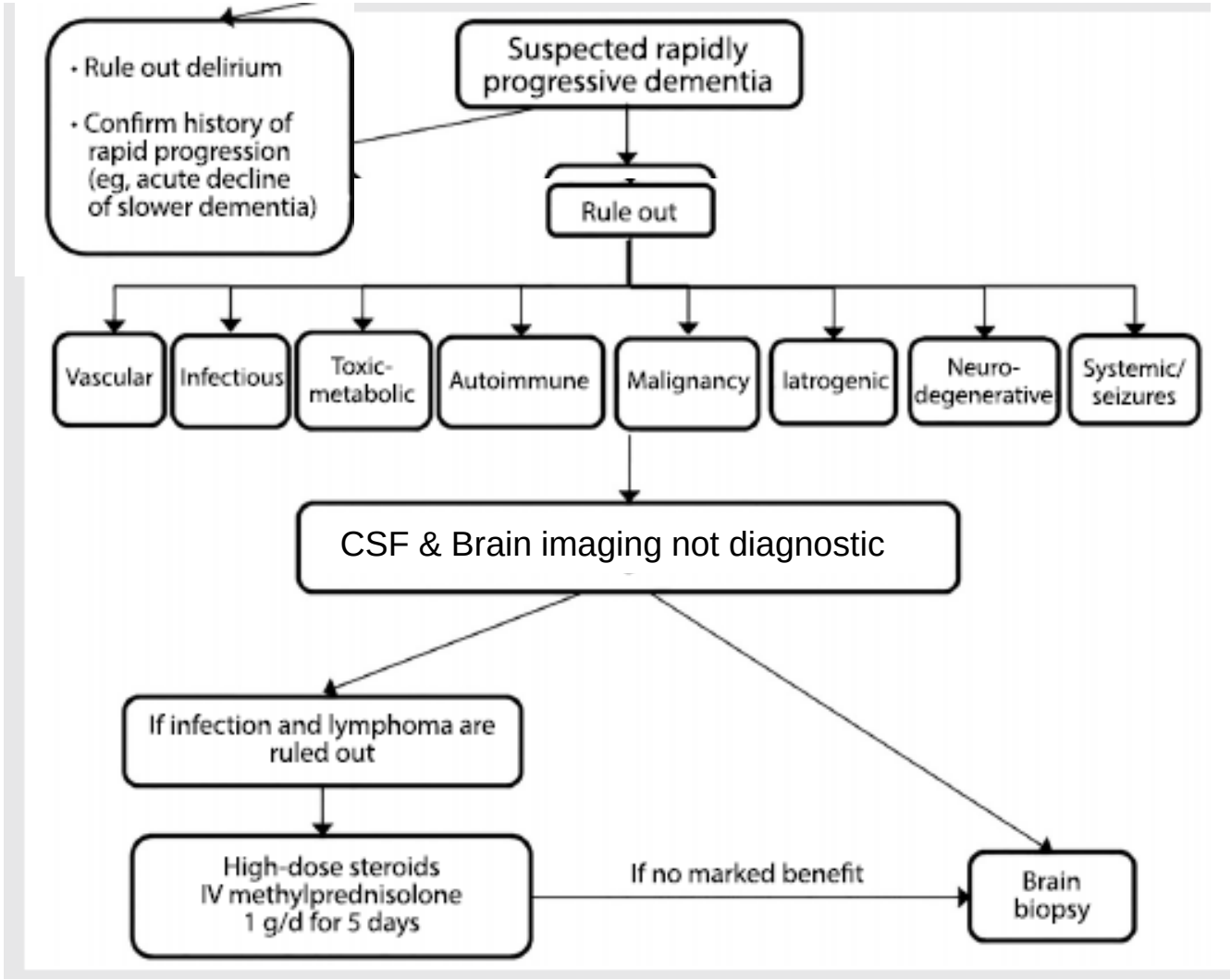






- **Evidence of central nervous system inflammation on MRI (mesial temporal or other regional T2 hyperintensity)**
- **Hypometabolism on functional imaging**

Rapidly Progressive Dementia



APPROACH ;
Questions to solve

1. What is the best fit clinical diagnosis ?

2. Treatable or reversible ?

HOW TO DIAGNOSE A CASE OF DEMENTIA?

- Clinical history
- Symptoms analysis
- Focused physical examination
- Cognitive and neuro behavioral examination
- Laboratory evaluation

History : onset; duration; temporal profile

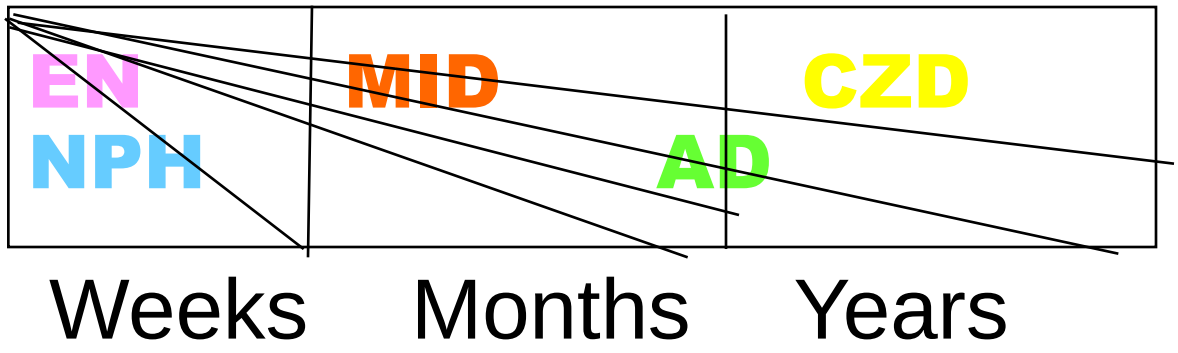
1. Acute/ sub-acute confusion; Delirium– infection, metabolic, intoxication.
2. Slowly progressive Memory loss ; AD
3. Personality change, compulsive eating, loss of empathy :FTD
4. Visual hallucinations + PD like features, RBD sleep disorder - Capgras syndrome ; DBL
5. Stroke history, HTN, DM, AF, PVD - MID
6. Gait disorder: NPH, PD, PD Plus, DBL, VD, PSP
7. Motor rigidity, myoclionus :CJD.
8. Seizures ; Neoplasm, stroke. AD.

History : onset ; duration ; temporal profile

9. I.V. drug use/ sexual polygamy ; CNS infections
10. Recurrent head trauma ;SDH, Chronic traumatic encephalopathy- Boxers , NPH.
11. Facio-brachial dystonic seizures ; Anti -NMDA
12. Myokymia ; Anti-VGKC.
13. Alcohol use ; B1 deficiency,
14. Gastric surgery; B12 deficiency.
15. Battery/ chemical factory worker; metal intoxication.
16. Family history; HD,AD, FTD, DBL.
17. Mood disorder, Depressive symptoms, insomnia ; Depressive related cognitive deficit.

Approach to Dementia - History

Time course & progression



- ✓ Encephalitis
- ✓ MID-Stroke for stroke
- ✓ CZD
- ✓ NPH
- ✓ AD

FOCUSED HISTORY

Chronology of the problem- from loved ones

- Medical history- Comorbid condition, HTN, DM, IHD
- Family history-AD, HD
- Socio-economic history
- Evaluation for toxic agent/drug exposure- Substance abuse
- Occupational- Boxer

Physical Examination General & Systematic

1. Document Dementia- from history/exam
2. Nervous system involvement
3. Clues searching systemic disease

- **Clues searching systemic disease**

I. Anaemia -B12 Deficiency
II. Hair loss ,Voice alteration- Hypothyroidism
III. Skin rash /skin change - SLE ,HIV, Malignancy
IV. Lymph node- malignancy

Physical Examination General & Systematic

Document Dementia

CLINICAL SYMPTOMS

A. COGNITIVE IMPAIRMENT- Memory, Apraxia, Agnosia, executive function

B. BEHAVIORAL IMPAIRMENT

- AGITATION, HALLUCINATIONS, DELUSIONS
- MOOD CHANGES
- ANXIETY
- PERSONALITY CHANGES
- PSYCHOSIS
- SLEEP DISTURBANCES
- DEPRESSION

Approach to Dementia – Examination

Nervous system involvement

Physical examination: Neurological

1. Higher psychic function and mental state:

Difficulties in assessing in

- Lethargic
- Inattentive
- Aphasic
- Agitation: Evening disorientation- Sun downing

1(a). Alertness/ attentiveness:

- ❑ Depends on education level
- ❑ Serial 7s
- ❑ Count back words

Nervous system involvement

1 (b). Memory:

- ❑Immediate recall
- ❑Short term/long term memory

1(c). Language - Aphasia:

- ❑Fluency
  - -Non fluent speech
  - -Loss of grammar/syntax
  - -Word finding difficulties
- ❑Naming
  - -Anomia- Non specific
- ❑Auditory comprehension of single & multi step commends
  - -Single step: Show two fingers
  - -Multi step: With your eyes closed tap your right knee with two fingers of your left hand

Nervous system involvement

1(c). Language - Aphasia:

Repetition of unfamiliar phrases

- ❑ Reading aloud
- ❑ Writing
  - -Name
  - -Directed sentences
  - -Spontaneous sentences

- ❑ Listen for paraphasic error
  - -Phonemic: tadle for table
  - -Semantic: door for window

1 (d). Calculations:

- ❑ Educational level
  - -Two digit addition/multiplication

Nervous system involvement

e. Hemineglect:

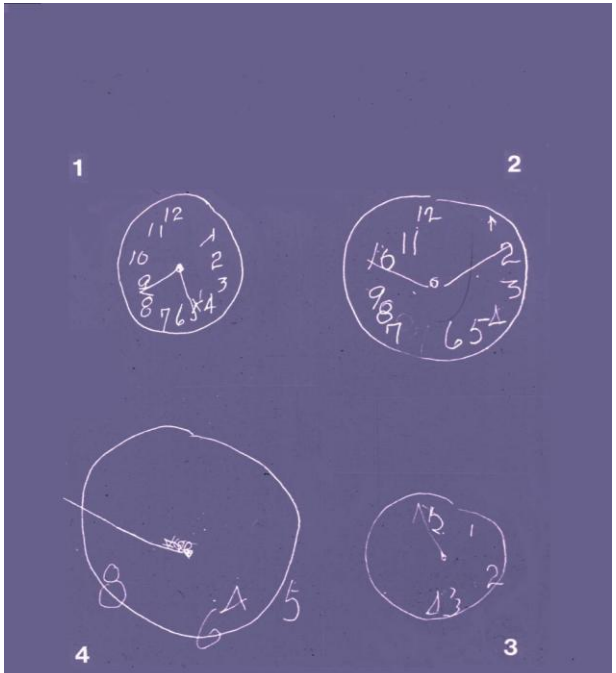
- ❑ Target cancellation
  - Circle all letters
  - Look for left right asymmetry
  - Bisect horizontal line

f. Apraxia:

- ❑ Impairment of the execution of a learned/ imitated movement in absence of weakness/sensory loss/ incordination
- ❑ Opening a look with key
- ❑ Ideometer
- ❑ ideational

g. Drawing

- ❑ Copy a complex figures



Impairment of drawing over 4 years

Nervous system involvement

1. **Motor system:**

a. Focal weakness/neurological sign:

- ❑ Structure brain disease
  - MID, SDH, ICSOL

b. Adventitial movements :

- ❑ Tremor, chorea, myoclonus
  - degenerative dementia, sub cortical

c. Co-ordination & gait:

- ❑ Slow settling- PD/PD plus
- ❑ Ataxia- Wernick-korsakoff
  NPH

Nervous system involvement

d. Frontal release signs:

- ❑ Snout reflux
- ❑ Palmo-mental reflux
- ❑ Grasp reflux
- ❑ Myerson's sign

❖ **Selected physical examination**

- Secondary reversible causes;

Infection, Metabolic, Toxic, Drug, Medical illness

Nervous system involvement

Neurological Examinations- for exclusion of secondary dementia

1. Gaze disorders - FTD, B1 DLB ,PSP
2. Tremor, rigidity bradykinesia-PD
3. Hemiparesis & Focal signs- MID, Neoplasm
4. Myelopathy - B12, Paraneoplastic
5. Peripheral neuropathy-B12, Toxic, Thyroid Vasculitis, Lyme
6. Myopathy - Malignancy, channelopathy, mitochondrial

Nervous system involvement

Determine cortical/sub-cortical or mixed dementia

Parameter	Cortical	Sub-Cortical	Mixed
Affected brain regions	Medial temporal, parietal and frontal cortex	Thalamus, striatum, midbrain, striatofrontal projections	Both cortical and sub-cortical area involved.
Examples	AD, DLB, VD, FTD	PD, PSP, NPH, HD, CJD, Chronic meningitis	VD, DLB, CBD, Neurosyphilis

Nervous system involvement

Features differentiating cortical/sub-cortical dementia

Function Affected	Subcortical Dementia	Cortical Dementia
Cognition		
Attention	Impaired	Intact
Mental processing	Slow	Normal
Language	Relatively intact	Impaired
Orientation to time and place	Often preserved	Often impaired
Memory (short-term recall)	Impaired retrieval	Impaired storage
Movement		
Speed of movement	Slow	Normal
Gait	Slow	Normal
Sense of equilibrium	Imbalanced	Normal
Posture	Stooped	Normal

Determine REVERSIBLE or IRREVERSIBLE DEMENTIA?

REVERSIBLE

D = Delirium

E = Emotions (depression)& Endocrine Disease

M= Metabolic Disturbances

E = Eye & Ear Impairments

N = Nutritional Disorders

T = Tumors, Toxicity, Trauma to Head

I = Infectious Disorders

A= Alcohol, Arteriosclerosis

IRREVERSIBLE

Alzheimer's

Lewy Body Dementia

Pick's Disease (Frontotemperal Dementia)

Parkinson's

Vascular

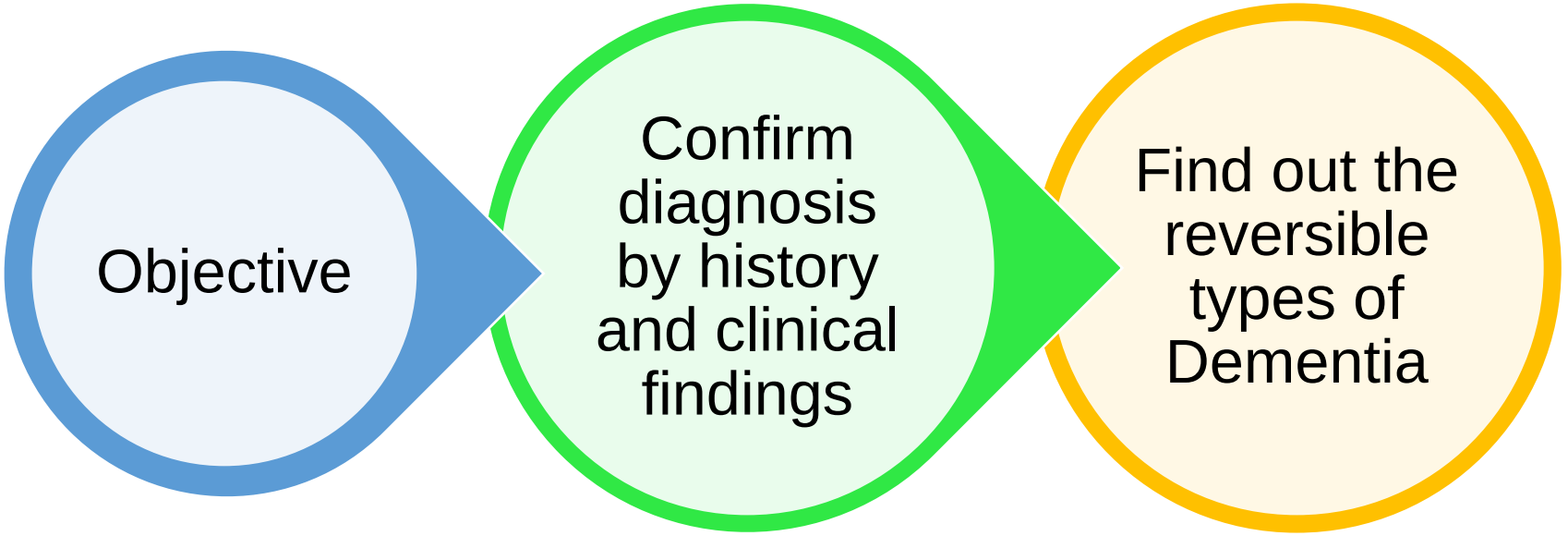
Huntington's Disease

Jacob-Cruzefeldt Disease

Assessment Scales of Dementia

- Mini mental scale (MMS)
- Clinical dementia rating (CDR)
- Geriatric mental state (GMS)
- Cambridge evaluation for mental disorders (CAMDEX)
- Community screening instrument for dementia (CISD)

Investigations in Dementia



Investigations in Dementia (contd.)

A. Routine:

1. CBC, PBF Blood sugar, RFT, LFT
2. Thyroid function test: eg. Hypothyroidism
3. Serum Vit. B_{12} Assay- Pernicious Anaemia
4. Complete blood count (may give a clue):
   - Vitamin deficiency states
   - Organ failure
   - Neoplastic conditions
   - Basophilic Stippling of RBC in lead poisoning
   - Vacuolated lymphocytes in Niemann-Pick disease
5. Electrolytes: CRF, Addison's Disease

Investigations in Dementia (contd.)

A. Routine (contd.):

6. VDRL: Neurosyphilis, False positive in SLE

7. CT/MRI of brain (MRI preferable in most cases)
   - Brain atrophy
   - Stroke, Binswanger's disease
   - CNS infections/ Viral / tubercular/ Leutic
   - ICSOL
   - Hydrocephalus
   - Leukodystrophies
   - Wilson's Disease
   - Hallervorden-Spatz Disease

Investigations in Dementia (contd.)

B. Other Focused Tests:

1. Chest Skiagram:-
   - ❖ Cardiomegaly- Stroke, Hypothyroidism, Anaemia, Alcoholism, Etc.
   - ❖ Ca- Bronchus
   - ❖ Pulmonary Tuberculosis
   - ❖ Vasculitis- SLE, Wegener's Granulomatosis
   - ❖ Sarcoidosis

2. CSF Study:
   - ❖ CNS INFECTIONS. Eg. HIV, Tuberculosis, Neurosyphilis
   - ❖ Decreased $A\beta_{42}$- Amyloid & increased tau protein in AD

Investigations in Dementia (contd.)

B. Other Focused Tests:

3. EEG:-
   - ❖ Repetitive bursts of diffuse high voltage sharp waves in CJD
   - ❖ Non-convulsive seizure
   - ❖ Encephalopathies

4.Parathyroid function

5. Adrenocortical function

Investigations in Dementia (contd.)

Occasionally helpful: Specific

1. Angiogram: Specially isolated CNS vasculitis

2. Brain & Meningeal biopsy:
   - ❖Isolated CNS vasculitis
   - ❖Potentially treatable neoplasm
   - ❖Uncertain diagnosis in young

3.SPECT:
   - ❖In atypical “AD”- Hypometabolism & hypoperfusion in posterior temporo-parietal cortex

4.PET:

   FDG PET

   Amyloid PET

Biomarkers predicting
the risk of conversion Of MCI to dementia

- MRI-MCI with hippocampal volumes -25th percentile – 2 to 3 times risk compared 75th percentile
- CSF-↓ Aβ 42 and ↑ t-tau and p-tau
- APOE4 allele
- Temporal-parietal hypometabolism on FDG-PET
- Amyloid deposition on Aβ PET imaging

(Jack et al., 2010, Mattsson et al.2009, Petersen et al., 1995, 2005, Chetelat et al., 2003,Wolk et al., 2009).

Investigations in Dementia (contd.)

Role of Biomarkers: Evidence

- Large body of evidence supports use of biomarkers (Noel-Storr et al., 2013)

- Current biomarkers for AD - CSF and brain amyloid-beta protein depositions through CSF or positron emission tomography (PET) amyloid imaging (Ferreira et al., 2014; Jack et al., 2008).

    - currently 3 tracers with FDA approval for brain amyloid PET imaging: florbetapir, flutemetamol, and florbetaben.

- Combining the 2 biomarkers provides greatest sensitivity and specificity (Ferreira et al., 2014).

- **No CSF biomarkers can consistently distinguish between the different dementias (Ewers et al., 2015; Ferreira et al., 2014).**

How to manage dementia?

Dualistic Approach

- **AIM ; TREAT TWO INDIVIDUALS**

1. **Person with the disease- DEMENTIA**

2. **Person / Persons serve as primary caregiver**

General principles of management:

Person with the disease- DEMENTIA

Aim of management :

- Achieve optimal daily function
- relieve distress

Attention must be paid to the :

- maintain personal hygiene
- safety
- nutrition
- care of incontinence of bowel & bladder
- avoid dehydration / infection

Management of Dementia

A. Supportive treatment

- Non-pharmacological
- Pharmacological

B. Symptomatic treatment

C. Treatment of other medical problems & Co-morbidities

Supportive treatment: Non-pharmacological

- Use a gentle, calm approach
- Use nonverbal communication
- Keep it simple
- Give re-assurance
- Don't boss
- Maintain routines
- Increase daytime activities
- Provide an open, safe, Non-overstimul-ating environment
- Reduce evening and nocturnal confusion
- Increase calming sensory stimulation: Music

Supportive treatment: Pharmacological

Manage behavioral symptoms of Dementia

- Apathy 72%
- Delusions 70%
- Aggression/agitation 60%
- Anxiety 48%
- Psychomotor disturbance 46%
- Irritability/lability 42%
- Sleep/wake disturbance 42%
- Depression/dysphoria 38%
- Disinhibition 36%
- Sundowning 18%
- Hallucinations 15%
- Hypersexuality 3%
- Euphoria 2%
- Obsessive–compulsive 2%

Behavioral symptoms Management (agitation, hallucinations, delusions)

Look for modifiable environmental, metabolic factors ;

- Constipation
- Hunger
- Lack of exercise
- Tooth ache
- UTI
- RTI
- Electrolyte imbalance
- Drug toxicity

Behavioral pharmacotherapy in Dementia

Commonly used drugs are-

ANTIDEPRESSANTS

Avoid tricyclics, anticholinergic.

SSRIs are better tolerated

NEUROLEPTICS

Improves behavior, suspicious, hallucination, sleeplessness , agitation

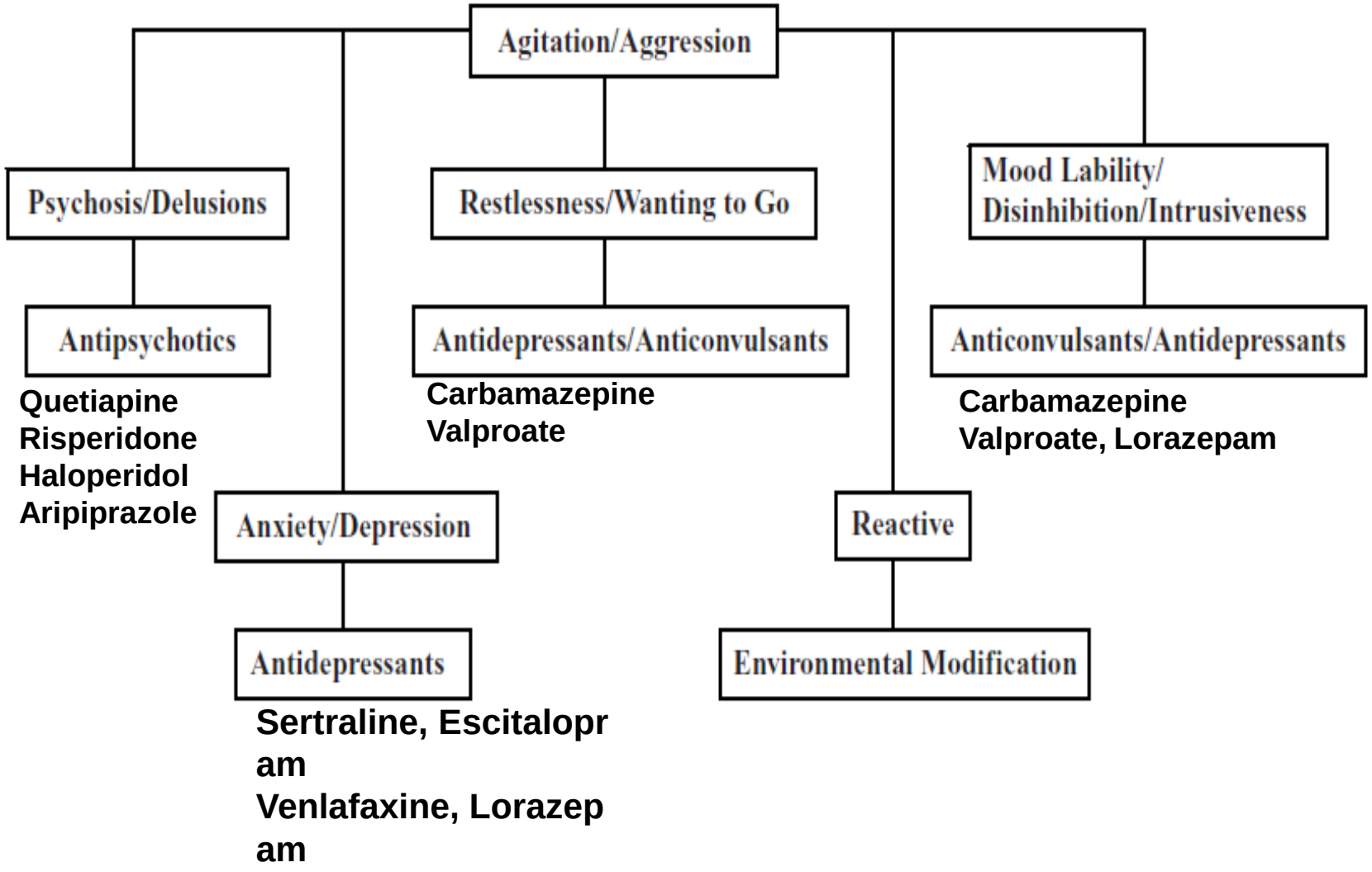
Quetiapine, Risperidone, Olanzapine, Haloperidol

ANXIOLYTICS

Non aggressive agitation and insomnia; benzodiazepines

Lorazepam, Midazolam preferably short acting.

Behavioral pharmacotherapy in Dementia



Drugs to avoid in Dementia

Antipsychotics :
- Chlorpromazine
- Clozapine
- Olanzapine
- Promazine
- Thioridazine

Antidepressant : - TCA, - MAOIs, - Paroxetine

Anticholinergics :
- Benzhexol
- Benztropine
- Hyoscine
- Orphenadrine
- Procyclidine

Note: Anticholinergic drugs may reduce the effects of anticholinesterase in all domains of efficacy: memory, activity, behaviour all may be worsened.

Supportive treatment: Pharmacological

Cognitive Symptoms Management

Common cognitive symptoms to be managed

- Memory, Amnesia and Forgetfulness
- Aphasia
- Agnosia
- Apraxia
- Visuospatial and visuoperceptual dysfunction
- Executive dysfunction

Supportive treatment Pharmacological

Cognitive Symptoms Management

- Lack of novel drug in spite of very active research & expenditure
- Rationalised all drugs
- Start low, Go Slow
- Look for adverse affects
- AD patients are very sensitive to the cognitive adverse effects of drugs

Symptomatic treatment of AD

CholinEsterase (ChE) inhibitors

- Oldest (and probably most extensively tested): physostigmine
  - Obsolete because- very short lasting (half life 30 mints) necessitating frequent oral administration
  - Potentially serious dose-limiting side effects

- In the past: Tacrine
  - 50% of the patients treated with Tacrine discontinued treatment because of adverse events esp. hepatotoxicity

Symptomatic treatment of AD

CholinEsterase (ChE) inhibitors

- Currently: CholinEsterase (ChE) inhibitors
  - ❖Donepezile-
    - Modest benefits in terms of cognition
    - S/E are cholinergic problems
  - ❖Galantamine-
    - Similar to tacrine; currently being used in UK, USA and other EU countries

Symptomatic treatment of AD

CholinEsterase (ChE) inhibitors

Recently: Rivastigmine

- Launched in April 2000; received approval for use in 60 countries including all member states of EU and USA

- Improvements were seen in cognition, ADL & severity of dementia

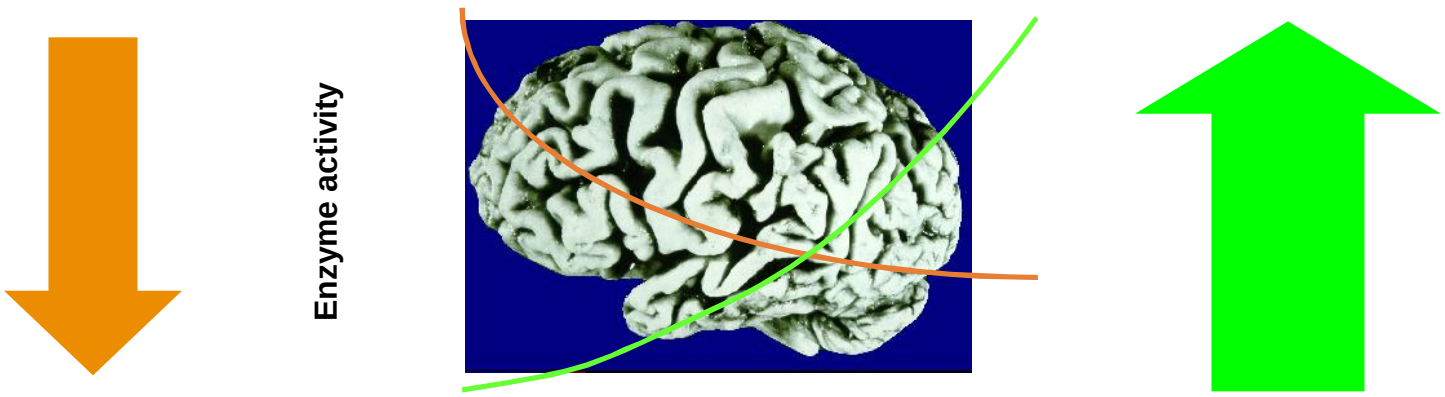
-Dose of 6-12 mg/day

- Lower risk of adverse effects

Cholinergic function in neuro-degenerative dementias: from pathology to therapy

AChE

BuChE



- Cortex (–30%)
- Hippocampus (–40%)

- Cortex (+40%)
- Hippocampus (+65%)

Cholinesterase inhibitors: two classes comparison

Class	Inhibit
Dual ChE inhibitors	
– Rivastigmine	Both AChE
– Tacrine	and BuChE
Single ChE inhibitors	
– Donepezil	AChE
– Galantamine	

Weinstock, 1999

Specific Treatment

Summary of ChE Inhibitors in Dementia

Drug	Mode of action	Efficiency in			
		Global	Cognitive	Functional	Tolerability
Rivastigmine	AChE inhibitor	+	+	+	++[1]
Donepezil		+	+	+	++[1]
Galantamine		+	+	+	++[1]
Tacrine		+	+	?	--

++	: Good	?	: Evidence absent/equivocal
+	: Moderate	1	: Tolerability depends on dose & Speed of titration
--	: Poor		

Symptomatic treatment of AD

NEW CLASS

NMDA Receptor Antagonist : MEMANTINE

- N-methyl-D-aspartate receptor antagonist
- Approved of moderate to severe AD.
- Benefit in cognitive and psychomotor functioning, ADL, reduce care dependence & excellent tolerability
- Helpful in mild to moderate vascular dementia.
- Devoid of concerning side effects at daily dose of 20mg

Symptomatic treatment of AD (Other Options)

Passive immunization

- **Bapineuzumab**

first humanized monoclonal antibody.
S/E: Vasogenic edema and intracerebral microhemorrhages

- **Solanezumab- specific to (Ab16–24**)

- mild to moderate AD revealed a reduction in cognitive decline by 34%; in mild form of the disease

Gantenerumab- specifically bind to aggregated Ab- phase II/III trials

Crenezumab - a novel human IgG4 monoclonal antibody- phase II trial

Symptomatic treatment of AD (Other Options)

Proposed or unregulated drugs require further studies

- Selegeline
- Vit-E- 1200mg
- Oestrogen
- Prednisolone
- NSAIDs
- Ginkgo biloba
- Statins
- IVIg
- Omega 3 Fatty Acid

Future possible therapies under study

- Glycogen syntehtase kinase 3 (GSK 3)
- β-secretase inhibitors
- γ-secretase inhibitors
- α-secretase enhancers
- Biomarkers
- Tau antibodies

The Future Treatment of Alzheimer Disease-Ongoing studies …

- The ApoE 4/4 study is investigating cognitively normal APOE 4 carriers, in a double-blind fashion, using an active amyloid vaccine and a β secretase inhibitor.

- The Columbian kindred study will study Crenezumab in asymptomatic carriers with PSEN1 mutation.

- “Tomorrow” trial of pioglitazone.

Treatment of AD (Preventive Factors)

AAIC 2017: Preventive factors— stress, diet, lifestyle

• Nine modifiable risk factors account for approximately 35% of all cases of dementia.

• (1) early education up to age 15 years,
• (2) hypertension,
• (3) obesity,
• (4) hearing loss in mid-life,
• (5) depression,
• (6) diabetes,
• (7) physical inactivity,
• (8) smoking, and
• (9) low social contact in later life.

Treatment of AD (Preventive Factors)

Diet- "**Mediterranean- DASH Intervention** for Neurodegenerative Delay" or MIND diet includes 10 "brain-healthy" food groups –

• Green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, fish, poultry, olive oil.

• Red meat, butter, margarine, cheese, pastries, sweets, and fried or fast food are avoided.

Management of Vascular Dementia

1. Treat risk factor: Primary & Secondary Prevention
- Hypertension
- Diabetes mellitus
- IHD/AF
- Heart failure

2. Aspirin

3. Perindopril (Progress Trial)

4. ChE Inhibitors (modest)

Management of other neurodegenerative dementias:

- No curative treatment is available till now

- Specific symptomatic treatment by ChE inhibitors remains the mainstay of treatment

- Amongst the ChE inhibitors, Rivastigmine is the most preferred one because of it's-
  - effectiveness in wide range of dementias
  - relatively less S/E profile
  - available in our country

*But it's use may be limited for it's relatively higher cost

Reversible causes require specific treatment accordingly

Autoimmune encephalopathy

Acute Treatment:
IV Methylpednisolone 3-5 days

Then weekly for 6-8 week
Or IV Ig (0.4g/3-5 days)

Then weekly for 6-8 weeks
Or Plasma Exchange

Chronic or Maintenance:
IV Methylpednisolone/IV Ig

Tapper over 4-6 months
Or Oral Steroid or Prednisolone
4-6 Months consider oral Azathioprine or mycophenolate mofetil or IV rituximab or Cyclophosphamide

Case 01: Recall

A 64 years old physician is brought to the neurology OPD by his wife who expresses concern regarding 3 years of progressive memory impairment, he frequently forget the details of conversations, misplaces objects at home specially keys, making mistakes in the steps of prayer (Namaz) and repeat question, seeming not to realize they had been answered one minute before but he felt nothing is wrong. Within the past year he had developed difficulty in finding wards and became disoriented in familiar places including his chamber building where he practices for last 35 years……..

Investigation: Normal biochemical investigations

MRI: BITEMPORAL ATROPHY

PET Scan: Positive for AD

Diagnosis: Alzheimer disease

Dementia in Oldest Old: Over 85 years

- **Fasted growing population**
- Sweden- over 17.9 %
- Norway- 16.3%
- USA- 2010 (0.5%)
  2020 (1%)
  2030 (1.1%)
  2040 (1.7 %)
  2050 (2.5%)

Problem in evaluation: 72% of Oldest Old have hearing loss, visual loss or both, lack of concentration and fatigue

CONCLUSION

- Accurate diagnosis, type and state of Dementia is mandatory
- Dementia Management should be multidirectional
- Supportive treatment of comorbidity is common for all types
- Sought treatable causes
- Neurodegenerative dementias need symptomatic treatment with ChE inhibitors as indicated
- Rivastigmine is possibly the best choice of ChE inhibitor so far and covers wider range for mild to moderate cases; Donepezil is a suitable and cheaper alternative
- Memantine is being tried for moderate to severe cases
- Behavioural disturbance are common, respond to supportive treatment

Take-Home Messages

- Dementia is a group of symptoms and not a part of normal aging
- There are several brief validated tests that can detect dementia.
- Dementia is caused by many diseases and conditions affecting the brain.
  - The most common type of dementia is Alzheimer's disease, followed by vascular dementia
  - Early diagnosis of dementia and its underlying causes allows appropriate medical management
- Use of biomarkers for Alzheimer's disease is an emerging field – brain amyloid PET scans are available with FDA-approved radioactive tracers.

WARNING for developing countries

By 2025- 75% of estimated 1200 million people aged 60 yrs & older will be in developing counties.

This graying of the developing world will pose a great medical, social & financial impact & will create a accelerated burden to infectious diseases & poverty.

We achieve this flag

Let us fight together to achieve this