NHS
Health Education England

MRCPsych Old Age Module

Alzheimer's Disease

Developing people
for health and
healthcare

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OA Module: Alzheimer's disease

Aims and Objectives

The overall aim is for the trainee to gain an overview of Alzheimer's disease

- **By the end of the session trainees should:**
- Understand the epidemiology of Alzheimer's disease.
- Understand the risk factors, genetics, neuropathology, neurotransmitters and neuroimaging associated with Alzheimer's disease.
- Understand the clinical features of Alzheimer's disease, the assessment process and the principles of management.
- Understand the carer burden related to Alzheimer's disease.

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OA Module: Alzheimer's disease

To achieve this

- Case Presentation
- Journal Club
- 555 Presentation
- Expert-Led Session
- MCQs

- Please sign the register and complete the feedback

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OA Module: Alzheimer's disease

Expert Led Session

Alzheimer's disease

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Lancashire Care NHS Foundation Trust
University of Manchester

Peer reviewed Dr Richard Atkinson and Dr Anthony Peter, 2020

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Epidemiology

- 850,000 people in the UK with dementia
- Projected rise of 40% over next decade

- 1 in 3 people born in the UK this year will develop dementia in their lifetime
- 50 million people have dementia worldwide
- 10 million new cases each year
- 63% of these live in low and middle- income countries, this is projected to increase to 71% by 2050
- Alzheimer's accounts for 62% of all cases

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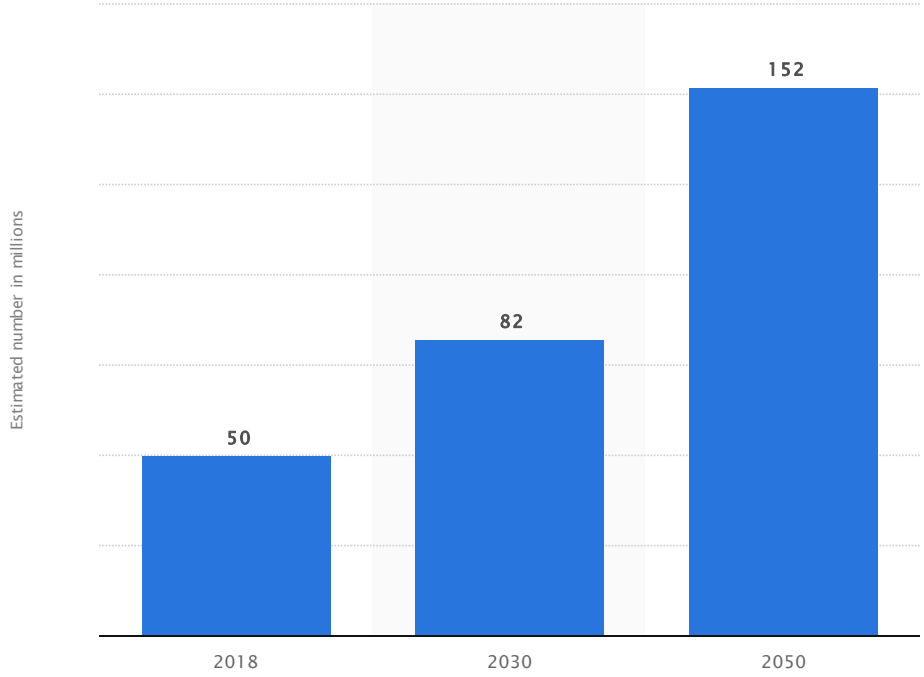
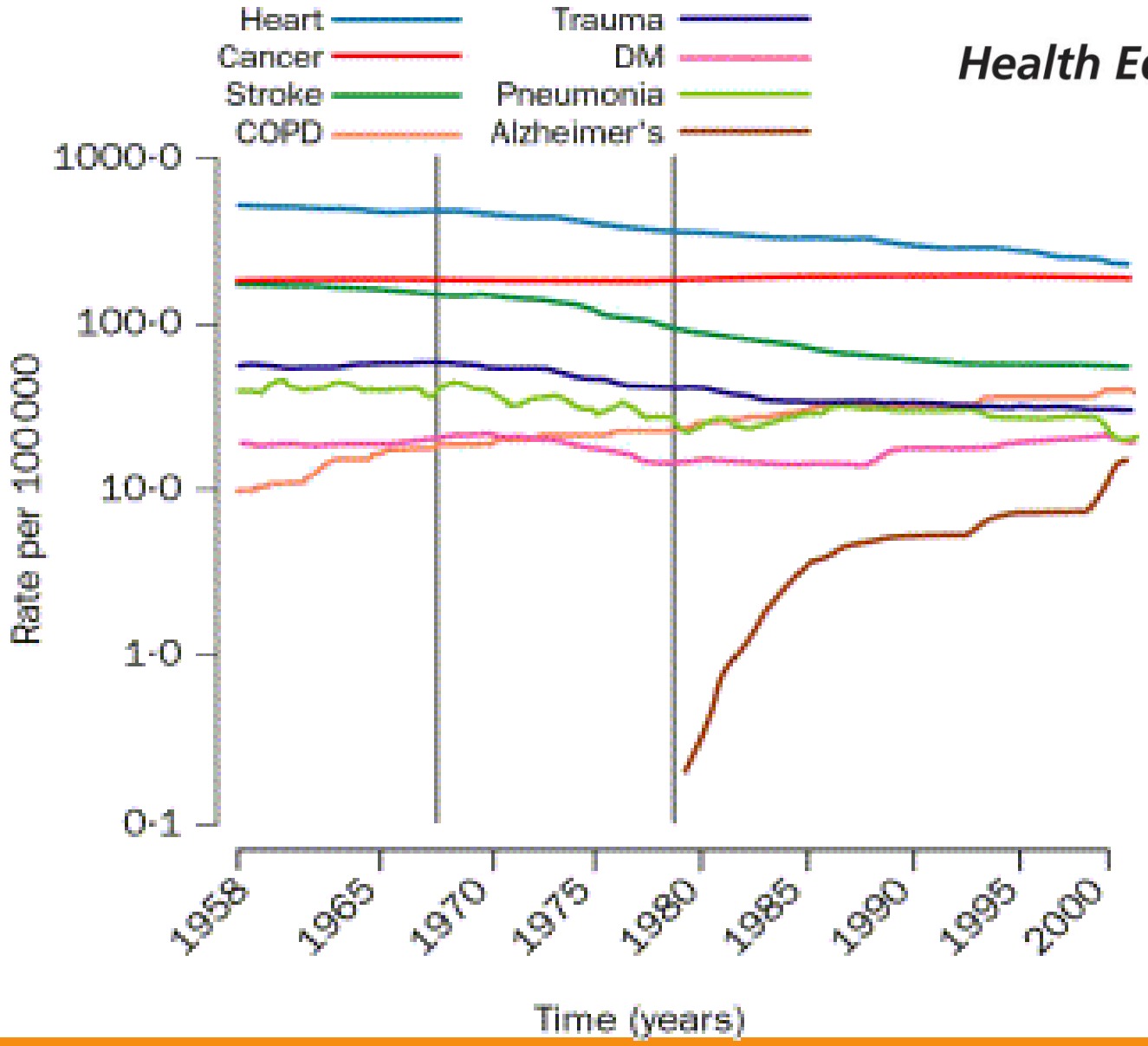
Estimated number of people with dementia worldwide in 2018, 2030 and 2050




Heart
Cancer
Stroke
COPD
Trauma
DM
Pneumonia
Alzheimer's
1000·0
100·0
10·0
1·0
0·1
Rate per 100 000
1958
1965
1970
1975
1980
1985
1990
1995
2000
Time (years)

Epidemiology

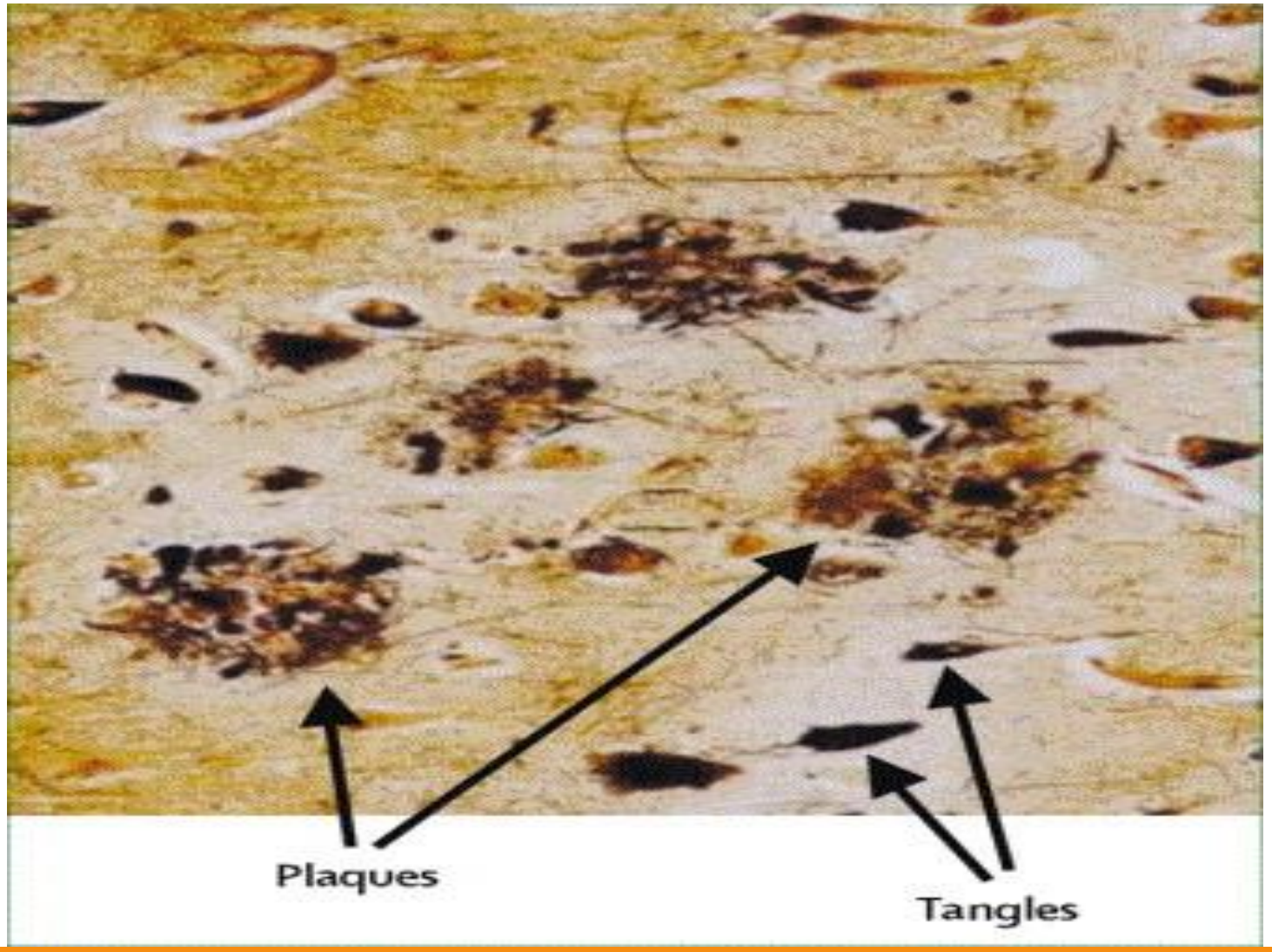
- Total cost of care in the UK is £26.3 billion
- The NHS picks up £4.3 billion of the costs and social care £10.3
- This is set to rise sharply in next two decades to £94.1 billion in 2040
- Costs include healthcare, social care and unpaid care (that provided by family members)
- This does not include carer burden

NEUROPATHOLOGY

- Senile Plaques :

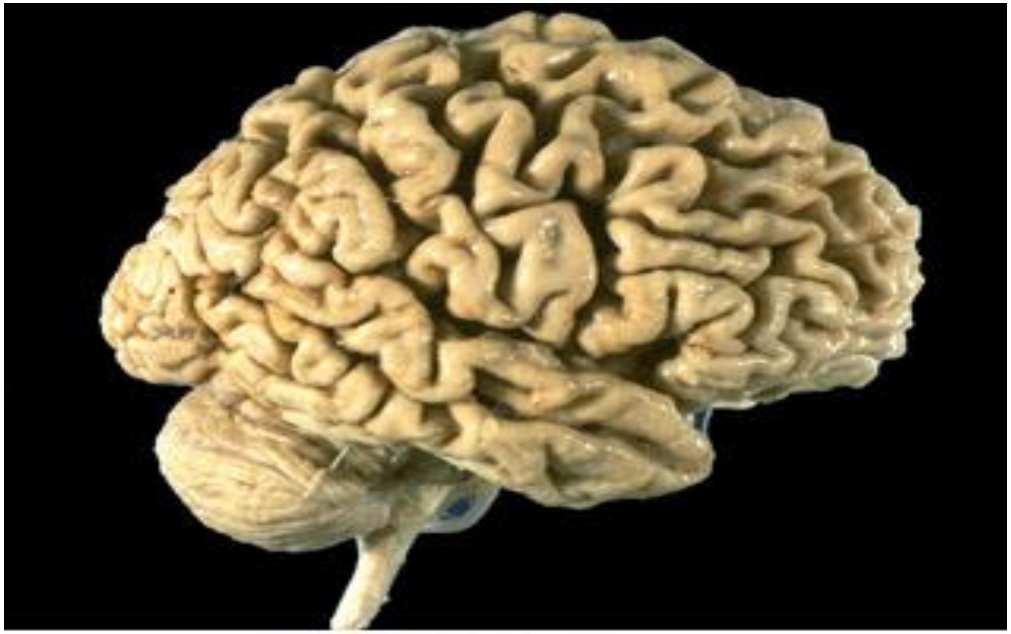
  Extra-cellular amyloid beta-peptide
- Neurofibrillary Tangles :

  Intra-cellular fibrillary proteins
- Tau deposits
- Reduction of neurons and synapses
- Reduction in cellular energy metabolism
- Neuronal dysfunction/ death


Plaques
Tangles

Neurotoxic action of Beta amyloid

- Oxidative stress
- Impaired cellular metabolism
- Mitrochondial dysfunction
- Impaired calcium metabolism
- Impairment of long term potentiation
- Increased neuro-fibrillary tangle formation



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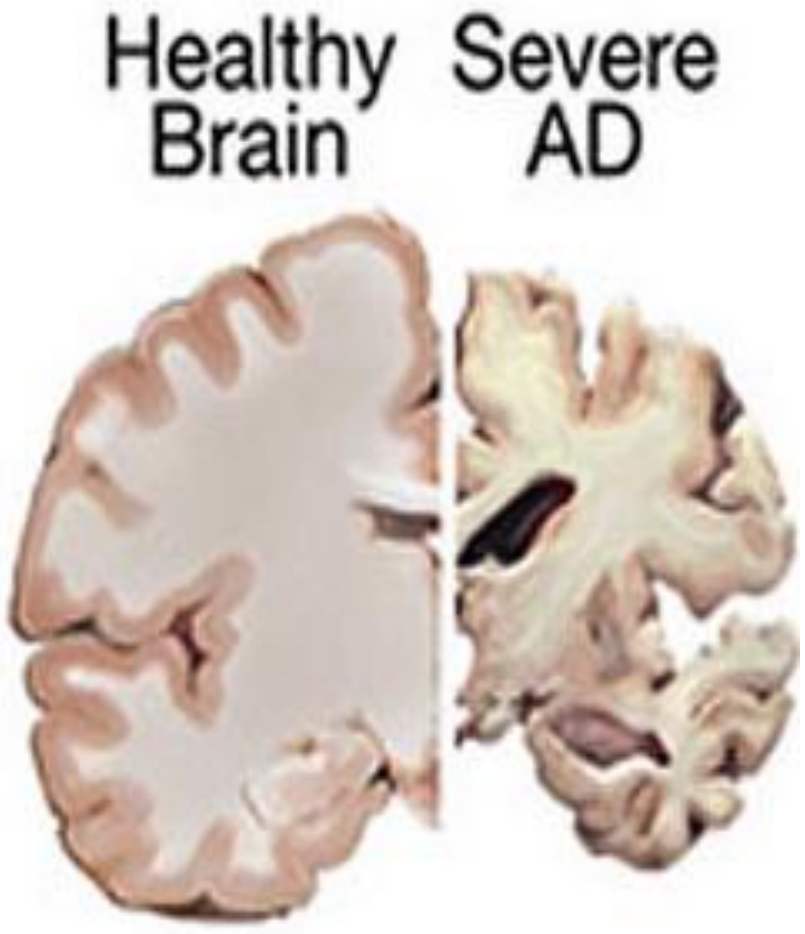
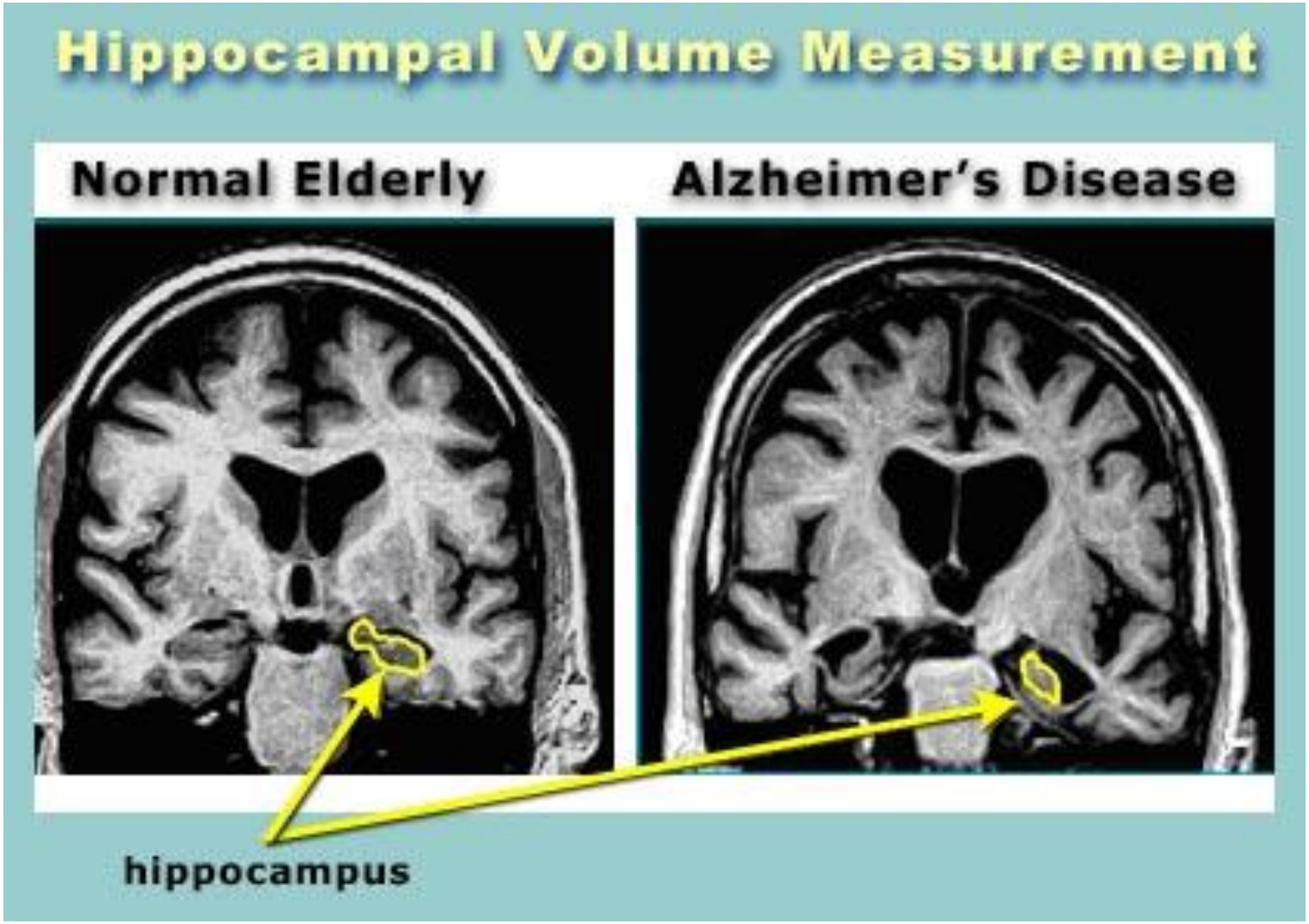

Healthy Brain
Severe AD


Hippocampal Volume Measurement
Normal Elderly
Alzheimer's Disease
hippocampus

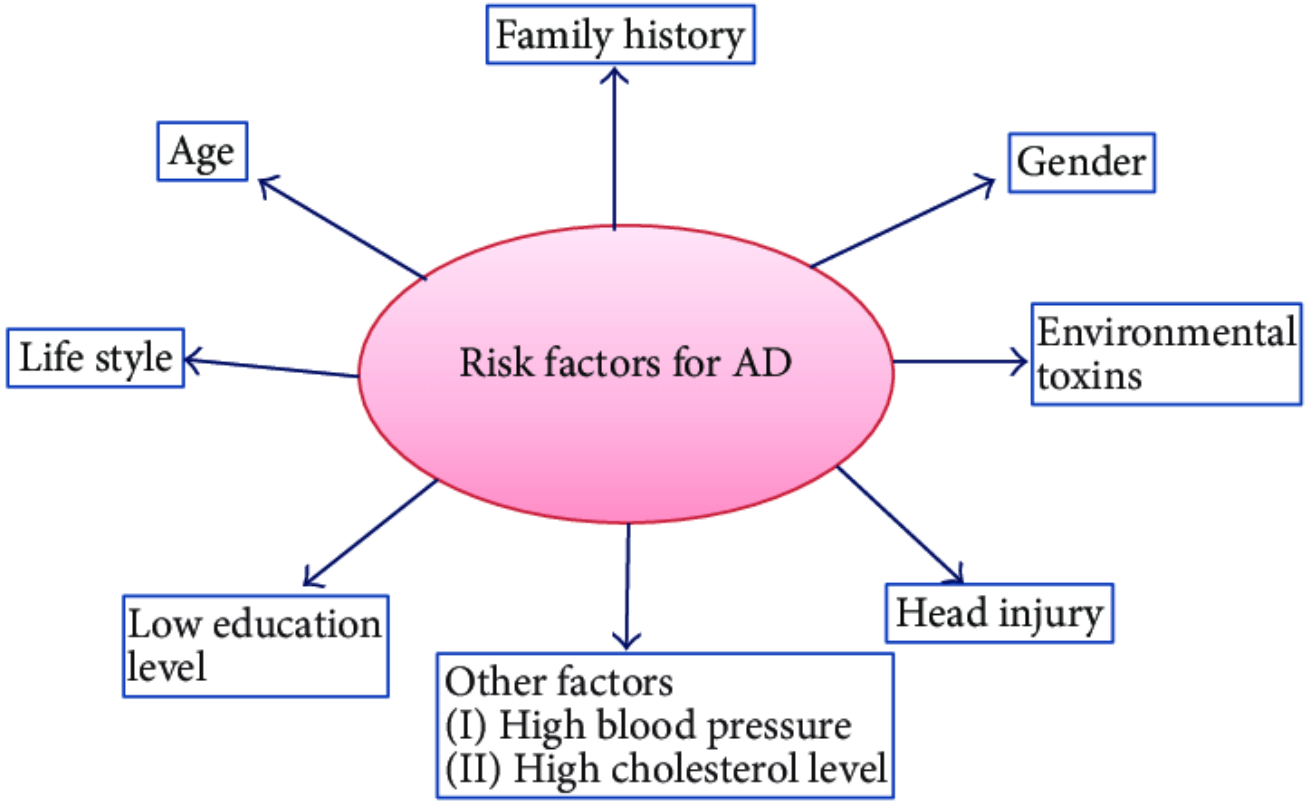
Aetiology

- **Late-Onset AD (LOAD)**
  - Not directly caused by gene
  - APOE variant on chromosome 19 increases risk
  - APOE = gene involved in making protein which carries cholesterol
  - Different forms of APOE (E2,3,4)
  - APOE4 allele – 3x increased risk of disease
  - 1 in 4 inherit APOE4

Aetiology

- **Early-Onset AD (EOAD)**
- 1 in 20 AD patients have EOAD
  - 50% risk if have gene mutation below
  - 3 faulty genes linked to EOAD
  - Mutation causes build up of amyloid
    - Amyloid precursor protein on chromosome 21
    - Presenilin 1 on chromosome 14
    - Presenilin 2 on chromosome 1

Risk Factors



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Genetic Testing

- Offered by NHS if risk of FTD or EOAD
- Genetic counselling before and after
- Test for which APOE allele you have
- Poor predictive value for disease but shows increased risk

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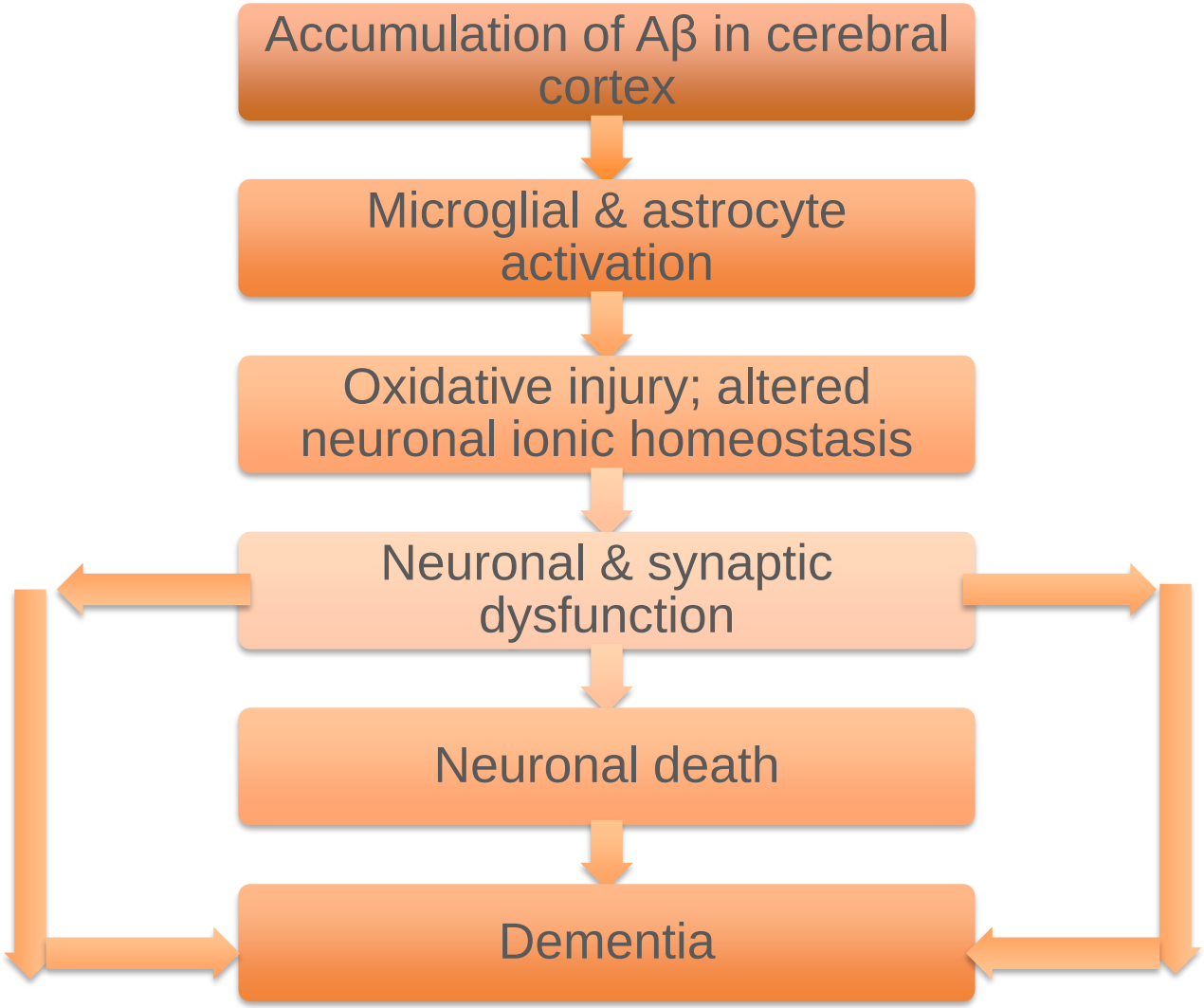
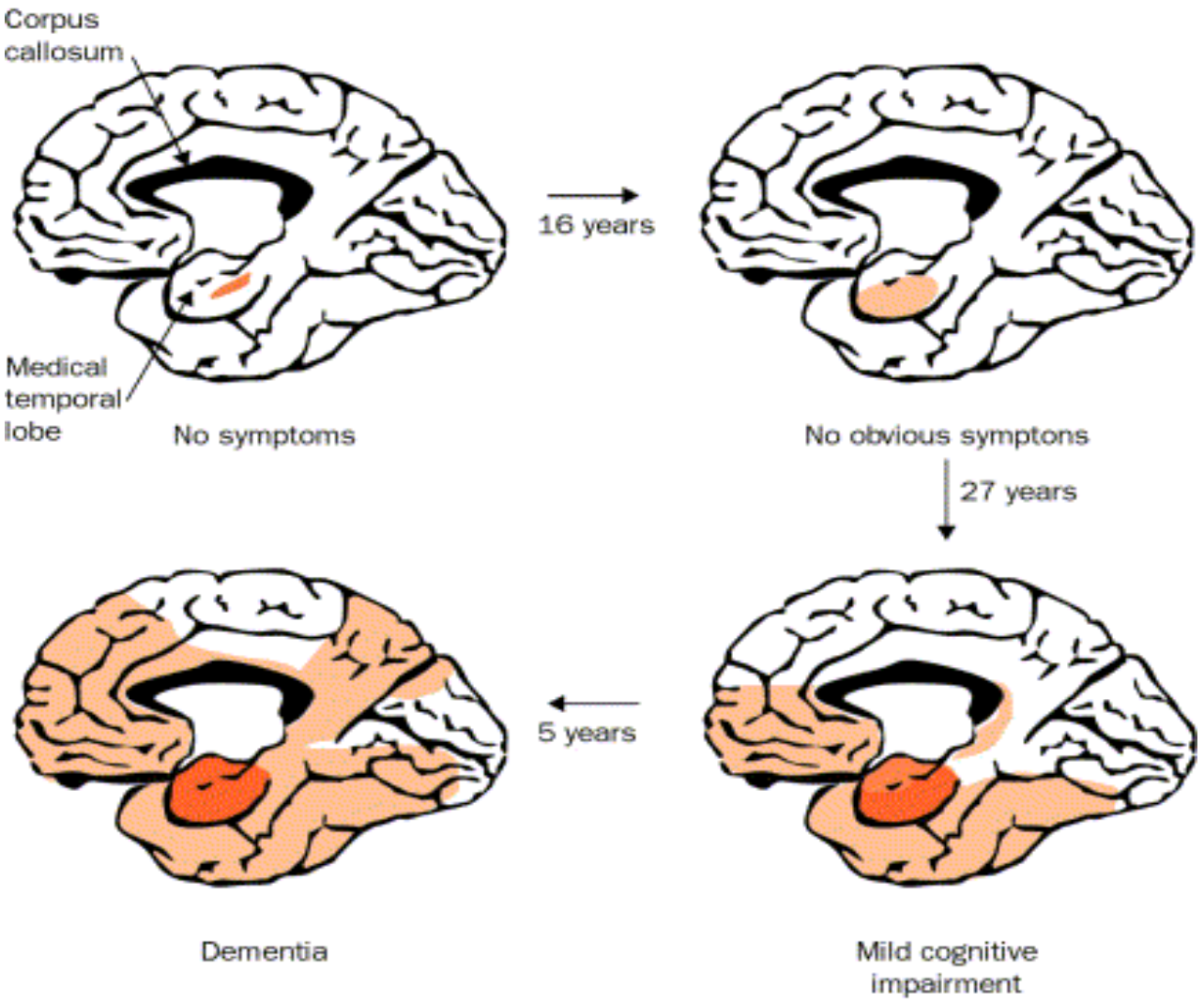
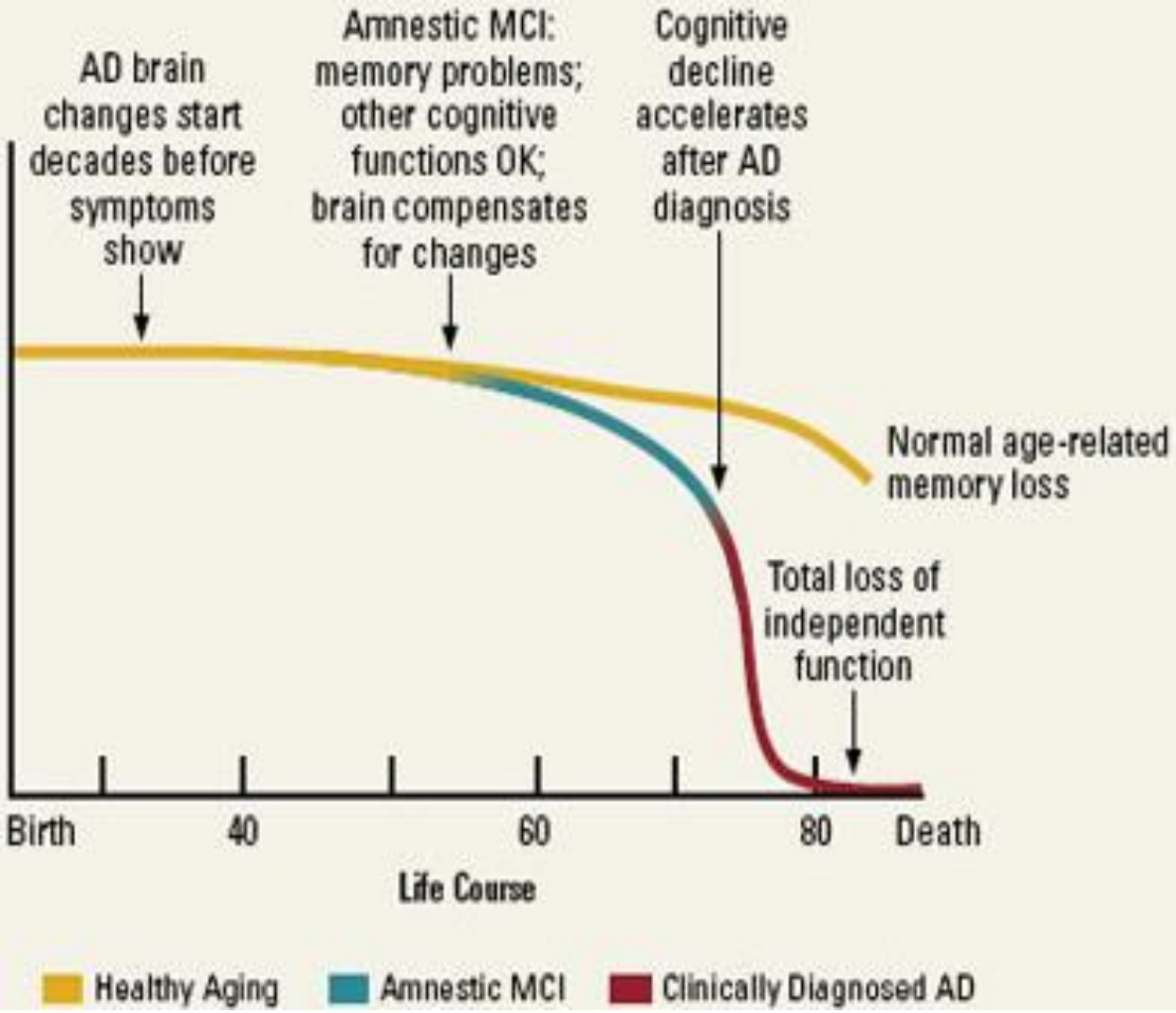
MECHANISM OF BETA AMYLOID DEPOSITION

- Faulty processing of amyloid precursor protein (APP)
- Increased accumulation of Beta-amyloid :
    - Toxic effect
    - Vulnerability to oxidative stress
    - Metabolic stress
    - Excitotoxicity
    - Disruption of calcium homeostasis


Accumulation of Aβ in cerebral cortex
Microglial & astrocyte activation
Oxidative injury; altered neuronal ionic homeostasis
Neuronal & synaptic dysfunction
Neuronal death
Dementia


Corpus callosum
Medical temporal lobe
No symptoms
16 years
No obvious symptons
27 years
Mild cognitive impairment
5 years
Dementia


AD brain changes start decades before symptoms show
Amnestic MCI: memory problems; other cognitive functions OK; brain compensates for changes
Cognitive decline accelerates after AD diagnosis
Normal age-related memory loss
Total loss of independent function
Birth
40
60
80
Death
Life Course
Healthy Aging
Amnestic MCI
Clinically Diagnosed AD

Neurochemistry of Alzheimer's disease

Acetylcholine:

- Perception, Attention, Learning, attention, Cognition and judgement

Noradrenaline:

- Alertness, Memory and Attention

Serotonin:

- Regulation of appetite and emotions

Glutamate (excitatory neurotransmitter):

- Neuronal cell death in many conditions is mediated by the effects of glutamate

CLINICAL FEATURES

Cognitive Symptoms :

- Amnesia
- Aphasia
- Apraxia
- Agnosia
- Frontal executive dysfunction

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CLINICAL FEATURES

Psychotic symptoms:

- Delusions
- Hallucinations
- Misidentifications

Affective Symptoms:

- Depression
- Anxiety
- Euphoria

CLINICAL FEATURES

Behavioural symptoms :

- Apathy
- Agitation
- Wandering
- Physical aggression
- Verbal aggression

CLINICAL FEATURES

Neuro-vegetative symptoms :

- Sleep disturbance
- Eating difficulty
- Sexual disinhibition
- Incontinence

- Personality changes – apathy, loss of inhibition

- LPPA – an atypical form of Alzheimer's

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Atypical Alzheimer's

- **Logopenic primary progressive aphasia (lvPPA):** word-finding pauses; impaired repetition of phrases, spared object and word comprehension

- **Posterior cortical atrophy (PCA)**

- **Frontal variant (fv-Alz)**

- **Down's syndrome variant**

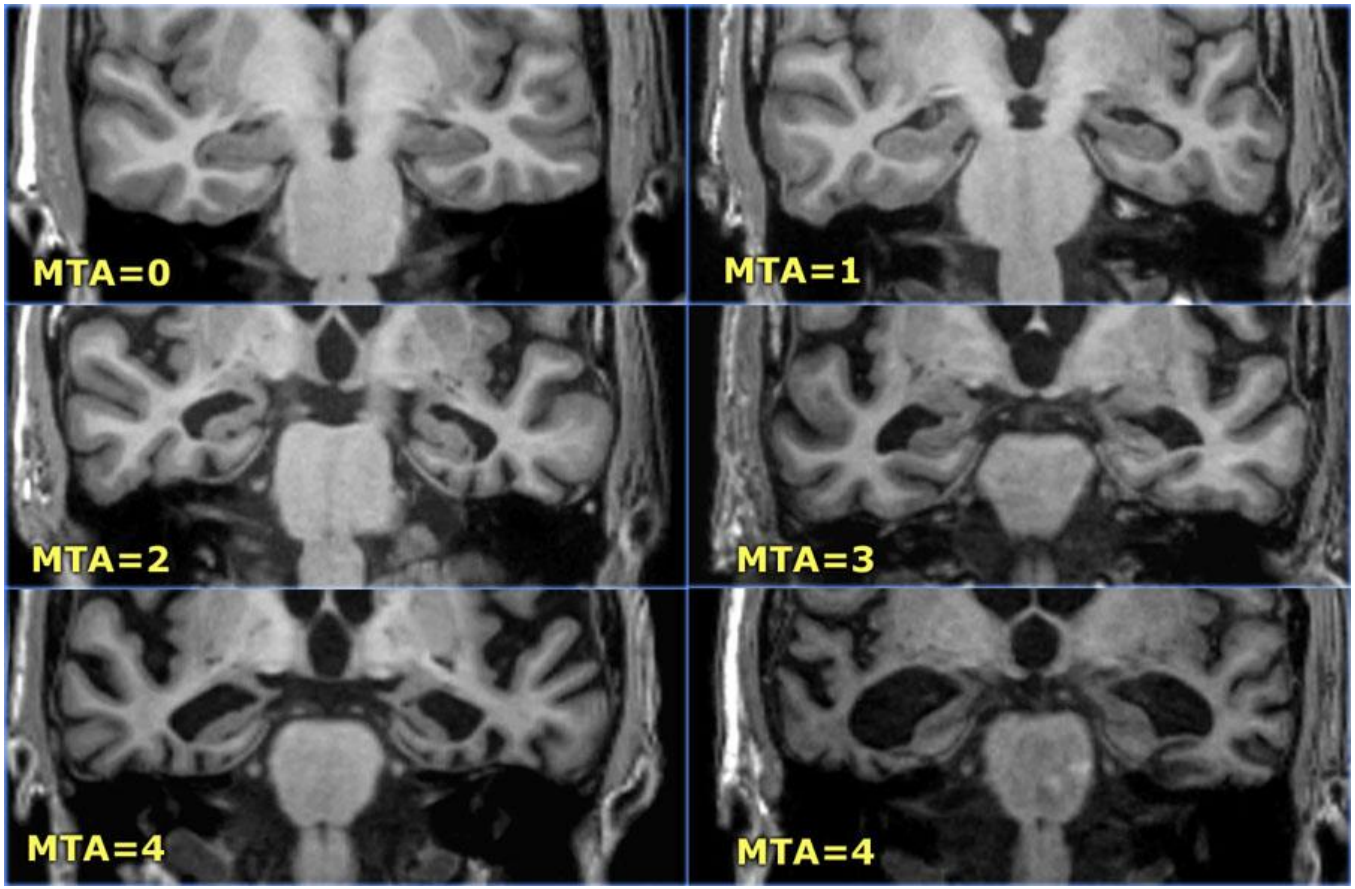
DIAGNOSIS

- Clinical diagnosis: **90% accuracy**
- History : insidious, gradual progression
- Physical examination : no focal neurological signs / no evidence of systemic disease
- CT scan : ventricular dilatation, cortical/temporal lobe atrophy
- EEG : Diffuse slow wave activity

Neuroimaging in AD

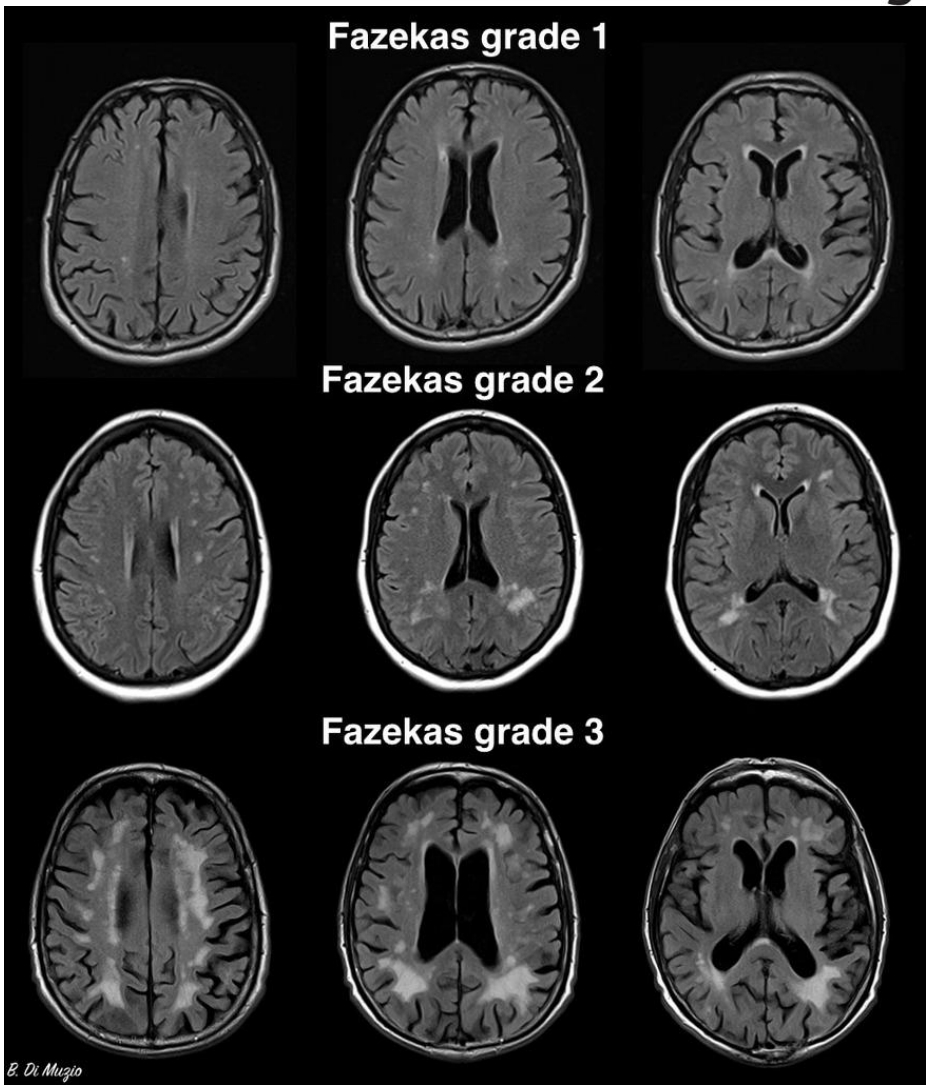
- Global Cortical Atrophy scale (0-3, 3 is severe)
- **Medial Temporal Lobe Atrophy (MTA)** (0-4)
  - < 75 years: score 2 or more is abnormal.
    > 75 years: score 3 or more is abnormal
- **Fazekas Scale** for white matter hyperintensities
  - Score 0-3, 3 is large confluent lesions
  - 2/3 are pathologic
- **Koedam Score** for Parietal Atrophy (0-3)

MTA Score



https://radiologyassistant.nl/neuroradiology/brain-dementia-role-of-mri

Fazekas Score



- https://radiopaedia.org/cases/fazekas-scale-for-white-matter-lesions

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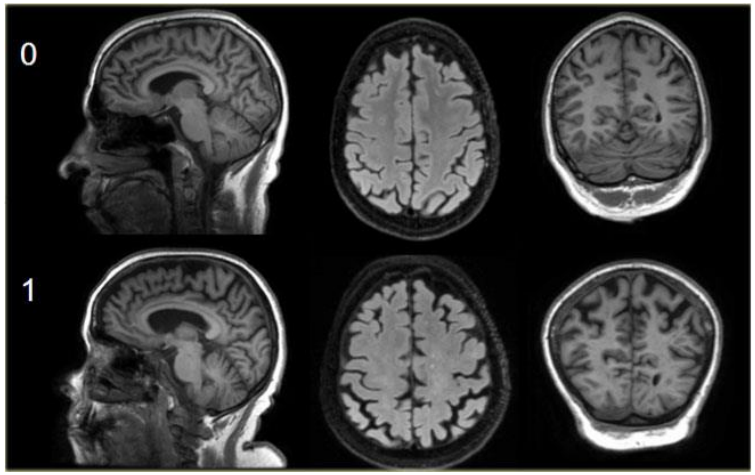
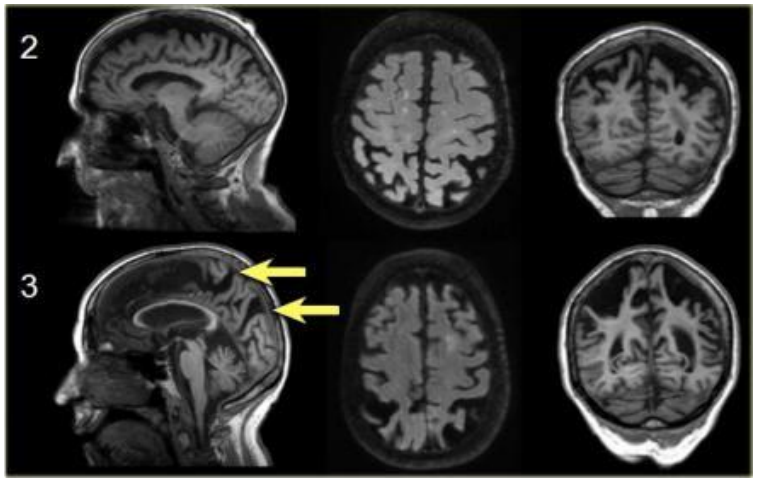
Koedam Score

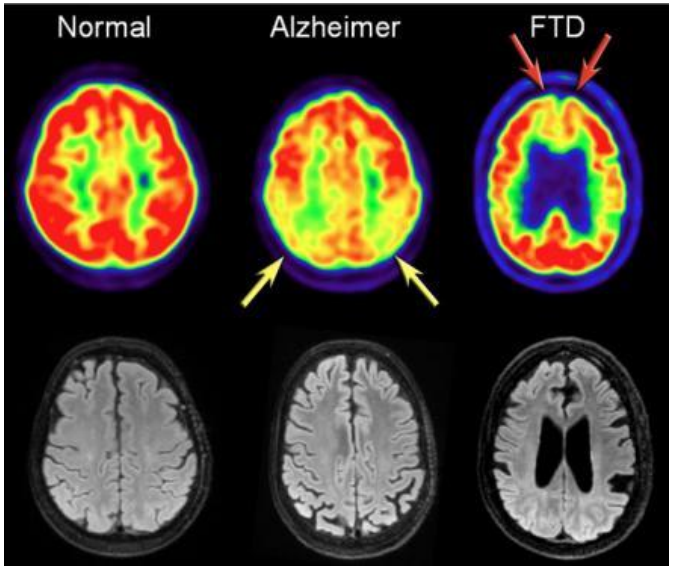


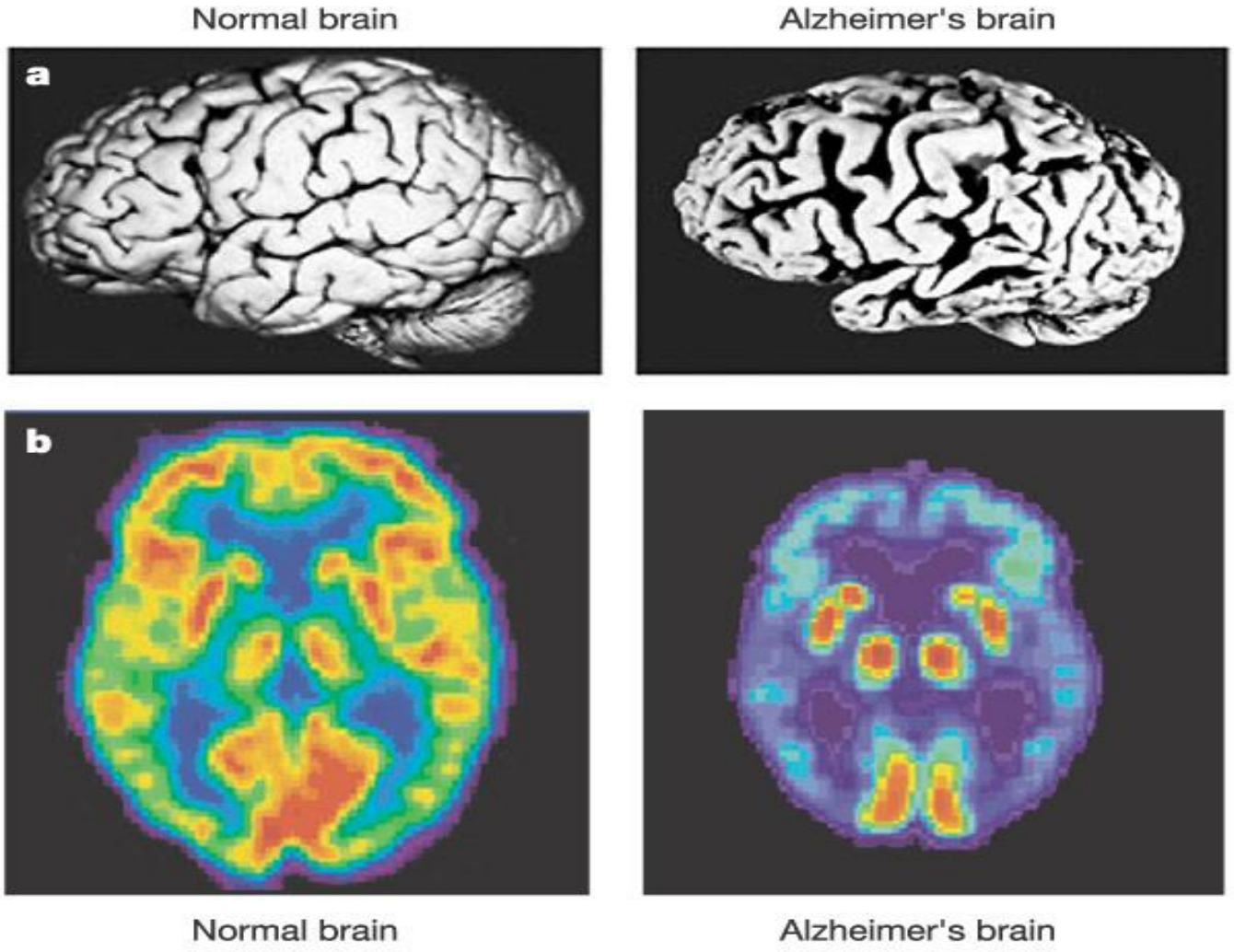


https://radiologyassistant.nl/neuroradiology/brain-dementia-role-of-mri

PET Imaging

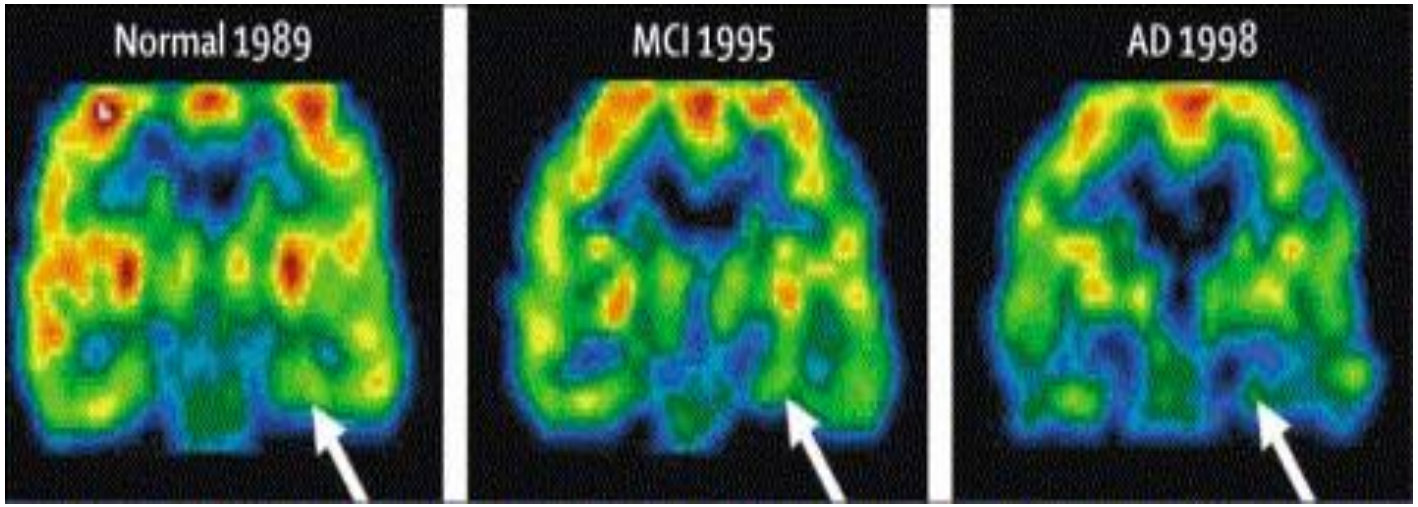
- Hypometabolism in temporoparietal regions
- Helps differentiate AD from FTD which shows frontal hypometabolism

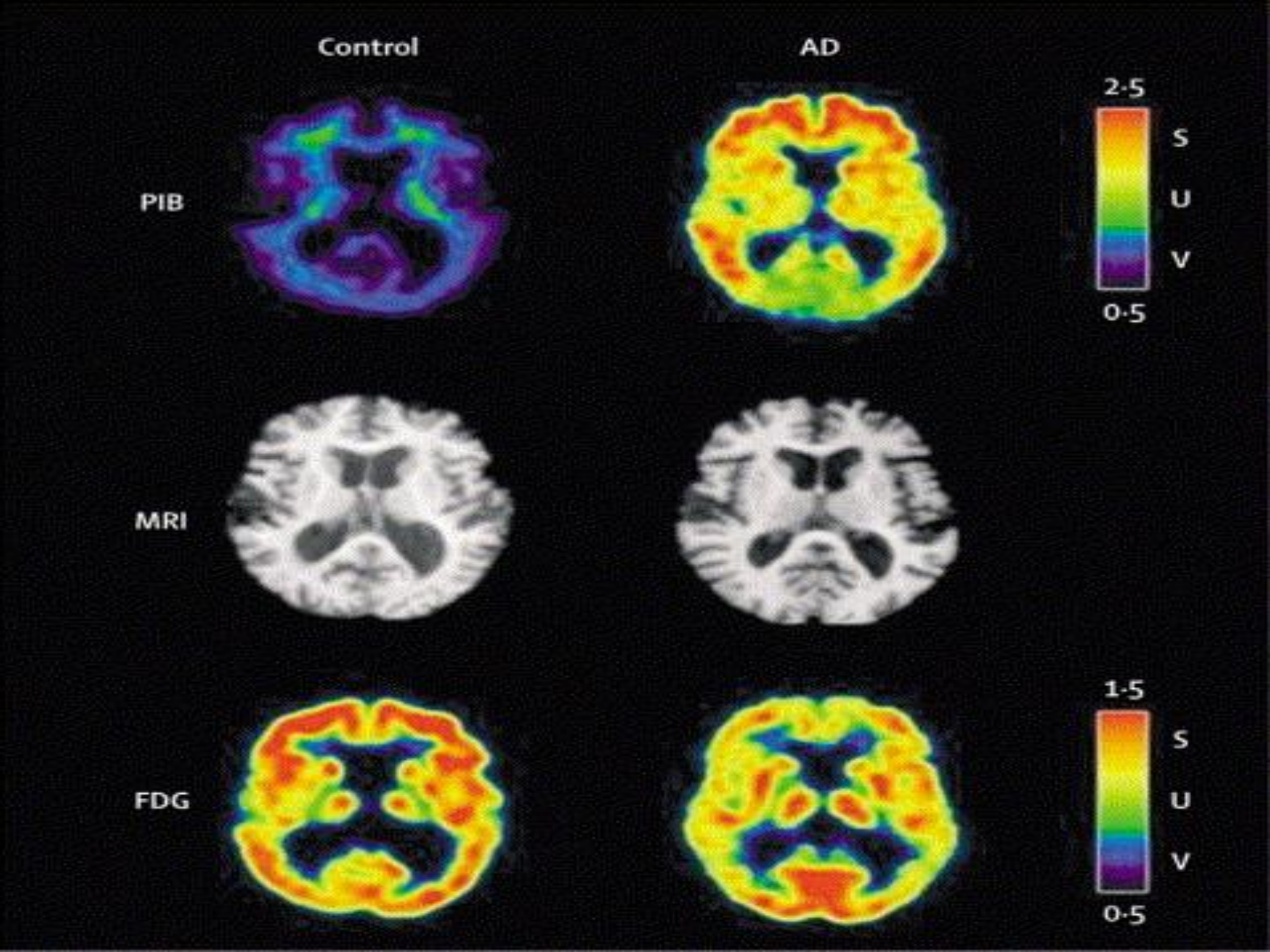




Pet scans (glucose utilization)

PET FDG in AD




Control
AD
PIB
MRI
FDG
2·5
S
U
V
0·5
1·5
S
U
V
0·5

National Institute on Ageing-Alzheimer's Association Research Framework 2018 update: Biomarker grouping

Table 1
AT(N) biomarker grouping

A: Aggregated Aβ or associated pathologic state
CSF $A\beta_{42}$, or $A\beta_{42}/A\beta_{40}$ ratio
Amyloid PET
T: Aggregated tau (neurofibrillary tangles) or associated pathologic state
CSF phosphorylated tau
Tau PET
(N): Neurodegeneration or neuronal injury
Anatomic MRI
FDG PET
CSF total tau

Abbreviations: Aβ, β amyloid; CSF, cerebrospinal fluid.
NOTE. See section 9.4 for explanation of (N) notation.

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National Institute on Ageing-Alzheimer's Association Research Framework 2018 update: biomarker profiles and categories

AT(N) profiles	Biomarker category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N)-	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	

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National Institute on Ageing-Alzheimer's Association Research Framework 2018 update: cognitive staging combined with biomarkers

Biomarker Profile	Cognitive stage: Cognitively Unimpaired	Mild Cognitive Impairment	Dementia
$A^- T^-(N)^-$	normal AD biomarkers, cognitively unimpaired	normal AD biomarkers with MCI	normal AD biomarkers with dementia
$A^+ T^-(N)^-$	Preclinical Alzheimer's pathologic change	Alzheimer's pathologic change with MCI	Alzheimer's pathologic change with dementia
$A^+ T^+ (N)^-$	Preclinical Alzheimer's disease	Alzheimer's disease with MCI(Prodromal AD)	Alzheimer's disease with dementia
$A^+ T^+(N)^+$			
$A^+ T^- (N)^+$	Alzheimer's and concomitant suspected non Alzheimer's pathologic change, cognitively unimpaired	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with MCI	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with dementia
$A^- T^+(N)^-$	non-Alzheimer's pathologic change, cognitively unimpaired	non-Alzheimer's pathologic change with MCI	non-Alzheimer's pathologic change with dementia
$A^- T^-(N)^+$			
$A^-T^+(N)^+$			

MANAGEMENT

Medications:

- Cholinestrase inhibitors
- Memantine
- Ginkobiloba?
- Vitamin E?

Non pharmacological interventions

Cholinesterase Inhibitors

- Statistically superior to placebo in improving cognition
- Corner stone of AD treatment
- Higher doses more effective than lower doses
- Treatment efficacy is similar for the three drugs available
- GI side effects: nausea, vomiting, diarrhoea
- Cardiac side effects: bradyarrythmia and syncope

Donepezil (Aricept)

- Introduced in UK in 1997
- 5–10mg daily dose
- Long plasma half life of 70 hours
- Oral bioavailability unaffected by food
- 10mg dose more effective
- Specific side effects: headache, anaemia, thrombocytopenia, insomnia, agitation

Rivastigmine (Exelon)

- 6–12mg daily dose
- Effect on aceytlcholinesterase and butyrylcholinesterase
- Short half life, transdermal patch available
- Patch reduces GI side effects
- Requires slower titration
- Also licensed for Parkinson disease dementia

Galantamine (Reminyl)

- 8–24mg daily dose (optimal dose 16-24mg/day)
- Dual action: CHEI and modulating effect on nicotinic receptors
- Can be given once or twice daily
- Bioavailability not affected by food
- Similar side effect profile to other CHEIs

Memantine (Ebixa)

- 10–20mg daily dose
- Partial glutamate receptor antagonist
- Can be titrated quickly
- Better tolerated than CHEIs
- Problematic side effects: dizziness, fatigue,restlessness and hyper-excitation
- Alternative to CHEIs: cardiac conduction problems, severe asthma, GI ulcers

Management Strategies

Early diagnosis

Family education

Early treatment intervention

Effective management of concurrent conditions

Ongoing caregiver support

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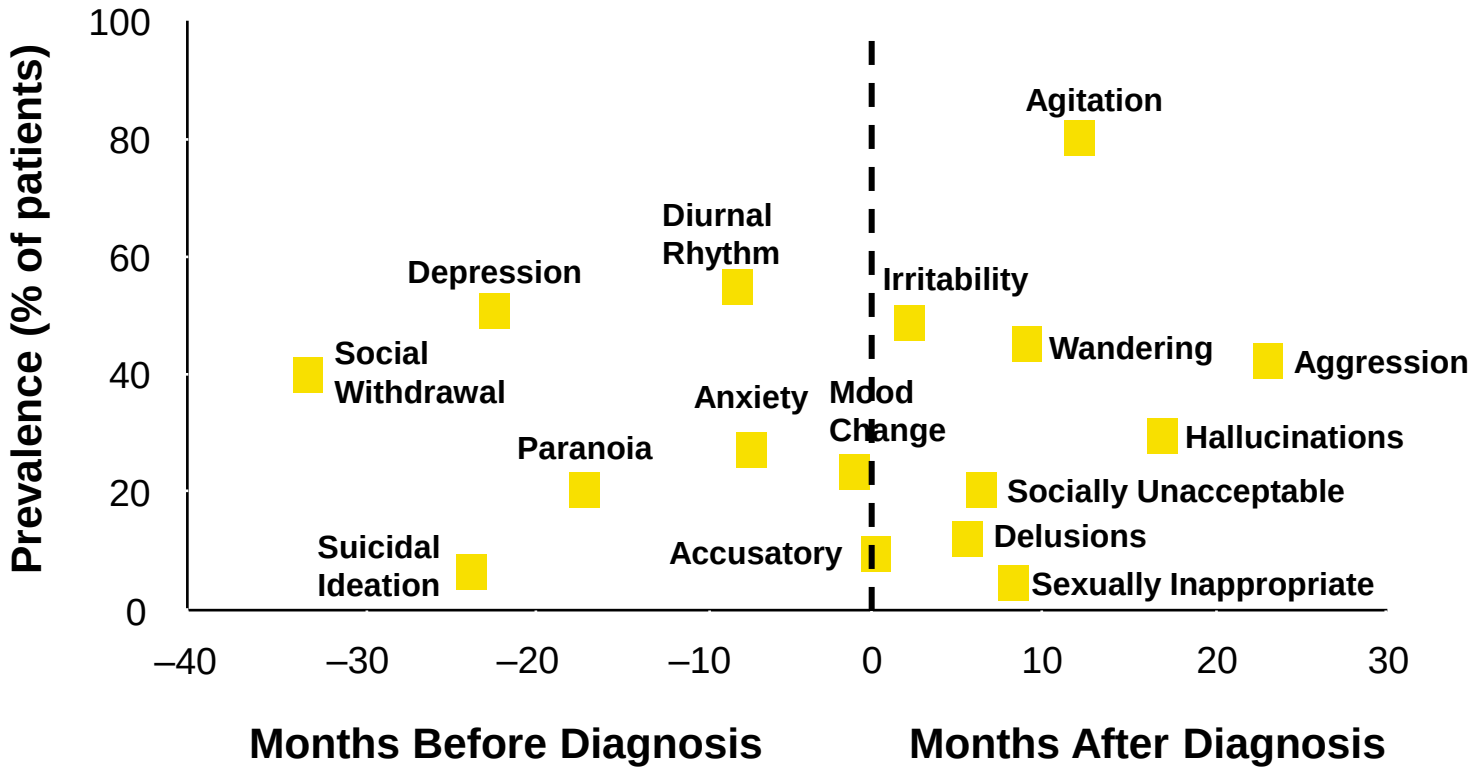
Behavioral symptoms as progresses



Jost BC, Grossberg GT. *J Am Geriatr Soc.* 1996;44:1078-1081.

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Behavior Management Principles

Non-drug management generally provides better results

How pharmacotherapy can be beneficial

- Target medication to specific behavior
- Avoid caregiver interpretation of PRN orders
- Consider the patient's physical health status
- Consider drug pharmacokinetic and pharmacodynamic properties

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Managing Aggression

- Identify the cause (noise, fear, etc.)
- Simplify the environment to limit distractions
- Music, exercise, etc. as a soothing activity
- Shifting the focus to another activity

OUTCOME

Depends on the severity

Rate of institutionalization :

- mild cases 12% after 1 year
- severe cases 40% after 1 year

Median survival : 5-6 years

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PREVENTION

Protective factors:

- Anti-inflammatory drugs
- Statins
- Oestrogen
- Alcohol

Life style:

- Physical activity
- Mental activity
- Social Integration

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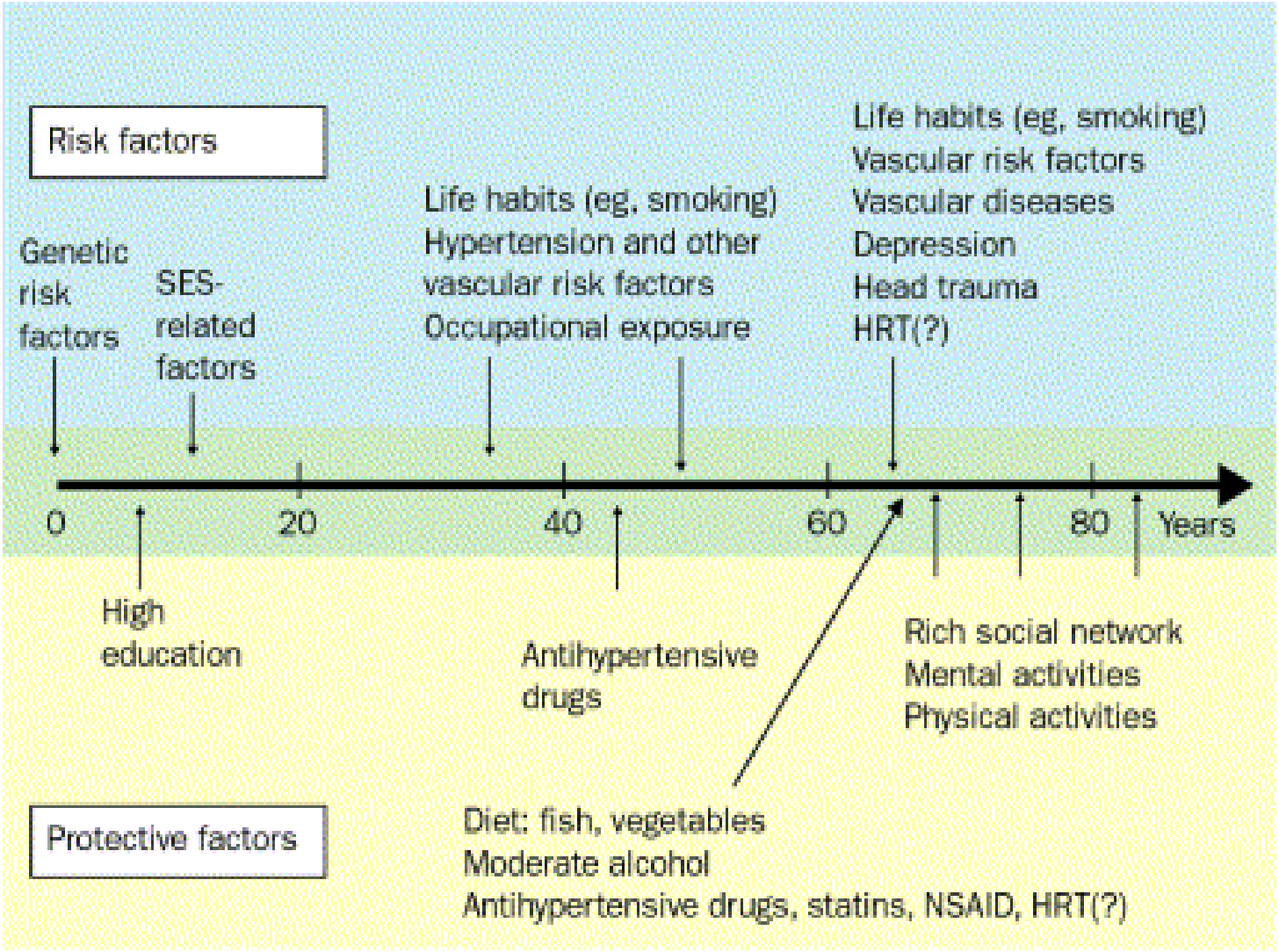
RISK FACTORS

- Age: Risk doubles every 5 years after 60
- Diabetes
- IHD
- Hypertension
- Low intelligence/ education
- Smoking
- Head injury


Risk factors
Genetic risk factors
SES-related factors
Life habits (eg, smoking)
Hypertension and other vascular risk factors
Occupational exposure
Life habits (eg, smoking)
Vascular risk factors
Vascular diseases
Depression
Head trauma
HRT(?)
0
20
40
60
80
Years
High education
Antihypertensive drugs
Rich social network
Mental activities
Physical activities
Protective factors
Diet: fish, vegetables
Moderate alcohol
Antihypertensive drugs, statins, NSAID, HRT(?)

Please provide feedback/suggestions on this presentation to the module lead mark.worthington@lancashirecare.nhs.uk

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OA Module: Alzheimer's

Any Questions?

Thank you…. MCQs are next...

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OA Module: Alzheimer's

MCQs

1. The prevalence of dementia in the general UK population older than 65 is approximately:

A. 0.5-1%

B. 2-4%

C. 7%

D. 15%

E. 20%

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OA Module: Alzheimer's

MCQs

1. The prevalence of dementia in the general UK population older than 65 is approximately:

A. 0.5-1%

B. 2-4%

C. 7%

D. 15%

E. 20%

OA Module: Alzheimer's

MCQs

2. In Alzheimer's Disease, the gene for Amyloid Precursor Protein (APP) is found on the long arm of chromosome:
   A. 1
   B. 14
   C. 21
   D. 19
   E. 27

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OA Module: Alzheimer's

MCQs

2. In Alzheimer's Disease, the gene for Amyloid Precursor Protein (APP) is found on the long arm of chromosome:
   A. 1
   B. 14
   C. 21
   D. 19
   E. 27

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OA Module: Alzheimer's

MCQs

3. As regards biomarkers in Alzheimer's disease:

   A. The first biomarker change in Alzheimer's disease is reflected by a decrease in CSF tau levels
   B. β amyloidosis can only be detected in venous plasma samples
   C. Amyloid-β accumulation is not sufficient to cause disease progression
   D. PET imaging is estimated to be able to predict changes 25 years prior to symptoms
   E. All individuals that have positive biomarker results progress at the same rate

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OA Module: Alzheimer's

MCQs

3. As regards biomarkers in Alzheimer's disease:

A. The first biomarker change in Alzheimer's disease is reflected by a decrease in CSF tau levels
B. β amyloidosis can only be detected in venous plasma samples
C. Amyloid-β accumulation is not sufficient to cause disease progression
D. PET imaging is estimated to be able to predict changes 25 years prior to symptoms
E. All individuals that have positive biomarker results progress at the same rate

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OA Module: Alzheimer's

MCQs

4. A frail elderly gentleman is diagnosed with Alzheimer's dementia in the clinic. He has a history of moderate COPD and 1st degree heart block. He also has a history of peptic ulcers.

Which would be the most appropriate first line drug to prescribe to slow cognitive decline and alleviate the behavioural and psychological symptoms of the dementia?

A. Rivastigmine patch.

B. Galantamine

C. Memantine

D. Donepezil

E. Risperidone

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OA Module: Alzheimer's

MCQs

4. A frail elderly gentleman is diagnosed with Alzheimer's dementia in the clinic. He has a history of moderate COPD and 1st degree heart block. He also has a history of peptic ulcers.

Which would be the most appropriate first line drug to prescribe to slow cognitive decline and alleviate the behavioural and psychological symptoms of the dementia?

A. Rivastigmine patch.

B. Galantamine

C. Memantine

D. Donepezil

E. Risperidone

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OA Module: Alzheimer's

MCQs

5. Which of the following combination of APOE alleles confers the highest risk of developing AD?

   A. 4:2
   B. 2:3
   C. 3:3
   D. 3:4
   E. 4:4

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MCQs

5. Which of the following combination of APOE alleles confers the highest risk of developing AD?

   A. 4:2
   B. 2:3
   C. 3:3
   D. 3:4
   E. 4:4

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Any Questions?

Thank you