What is dementia?

*De mens = without mind*

Dementia: “an acquired clinical syndrome characterized by the development of multiple cognitive deficits that are severe enough to interfere with daily life/functioning, including social and professional functioning”.

(DSM-III-R, APA 1987)
What is dementia?

- Cognitive impairment (memory, abstract thinking, judgement, language, executive function, visuospatial abilities)
- Behavioural problems (anxiety, depression, agitation, delusions, hallucinations, psychosis)
- Functional disability

Different combination of signs and symptoms
- Different progression
- Different prognosis

Brain disease(s)
Distribution of brain damage

Cognitive continuum

NORMAL  DEMENTIA
Cognitive continuum

Age Associated Memory Impairment (AAMI)
Age Related Memory Decline (ARMD)
Age Related Cognitive Decline (ARCD)
Benign Senescent Forgetfulness (BSF)
Cognitive Impairment No Dementia (CIND)
Memory Impairment
Mild Cognitive Disorder (MCD)
Mild Cognitive Impairment (MCI)
Mild Neurocognitive Disorder (MND)
Questionable dementia (QD)

What causes dementia?

Neurodegenerative diseases
• Alzheimer’s disease (AD)
• Lewy Body dementia (LDB)
• Frontotemporal dementia (FTD)

Vascular dementia

Dementia due to treatable illnesses
• Toxic disorders (alcohol, drugs)
• Nutritional deficits (B12, folate))
• Infections disorders (HIV, Lyme disease, Syphilis)
• Brain tumors
• Depression
• Hydrocephalus
Both vascular and degenerative diseases often contribute to the development of dementia among the elderly.

Viswanathan et al., Neurology 2009

In the general population, 70% of the patients with dementia are over 75 years old.
Clinical aspects of Vascular dementia and Alzheimer’s disease

Vascular dementia (VaD)
- Large vessel VaD
  - Multi-infarct VaD
  - Strategic-single infarct VaD
- Small vessel VaD (Subcortical VaD)
- Hemorrhagic VaD
- Hypoperfusion

Roman et al., Neurology 1993
Vascular dementia (Vad)

**Large vessel VaD**

- Multi-infarct VaD
- Strategic-single infarct VaD

Infarcts in the right dorsolateral frontal region and the bilateral posterior parietal regions (T1-weighted axial MRI).

Small infarcts involving the anterior dorsomedial nucleus of the thalamus bilaterally (T1-weighted axial MRI).

*Black., J R Coll Physicians, 2011*

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**Small vessel VaD (Subcortical VaD)**

Obliteration and occlusion, ↑ resistance, ↓ autoregulation, endothelial changes in small vessels

Sub-cortical brain changes: ischaemic white matter lesions (WMLs) and lacunar infarcts (T2-weighted MRI).

*Image from Westman E*
Vascular dementia

Clinical features:
• Abrupt onset
• Stepwise progression
• Focal neurological signs or symptoms
• History of cerebrovascular disease and risk factors
• Cognitive: Impaired executive functions; Spotty deficits

Criteria for diagnosis:
1. Dementia
2. Cerebrovascular disease
3. A relationship between the above two disorders

Alzheimer’s disease (AD)
✓ Most common cause of dementia (?)
✓ Pathogenesis not yet clear
✓ 3 neuropathological hallmarks:
  Amyloid-rich senile plaques
  Neurofibrillary tangles
  Loss of neurons and synapses
✓ These changes begin years before the onset of symptoms
Alzheimer’s disease (AD)

Amyloid-hypothesis: neuritic plaques

1. Aβ production
2. Aβ aggregation
3. Aβ accumulation

Neuritic plaques (Senile plaques)

APP: Amyloid Precursor Protein

Non-Amyloidogenic Pathway

γ-secretase

α-secretase

β-secretase (BACE1)

sAPPα

sAPPβ

Aβ

Aβ

Aβ

Alzheimer’s disease (AD)

Tau hypothesis: Neurofibrillary tangles

Neurofibrillary tangles (NFTs)
Alzheimer’s disease (AD)

Early
- Learning and memory
- Thinking and planning

Mild-Moderate
- Speaking and understanding speech
- Your sense of where your body is in relation to objects

Severe
- Severe impairment of different cognitive functions

The Progress of Alzheimer’s Disease

How do we diagnose Alzheimer’s disease?

- Personal history (subject and proxy)
- Physical examination (neurological examination)
- Neuropsychological testing
- Functional status
- Blood test (vitamin B12, folic acid, thyroid function)
- Neuroimaging (morphological, functional)
- CSF

AD – DSM-IV criteria

A. Multiple cognitive deficits manifested by both:
   1. Memory Impairment
   2. One (or more) of the following cognitive disturbances:
      Aphasia, apraxia, agnosia, and disturbances in executive functioning (e.g., planning, abstracting, organizing, sequencing)

B. Cognitive deficits cause significant decline in social or occupational functioning and represent a decline from previous levels of functioning.

C. The course is characterized by gradual onset and continuing cognitive decline.

D. The cognitive deficits are not due to other CNS conditions or systemic conditions known to cause dementia.

2 STEPS, EXCLUSION DIAGNOSIS!

American Psychiatric Association, 1994
In-vivo diagnosis of Alzheimer disease

Presence of Dementia (a syndrome) +

Exclusion of other causes of the dementia syndrome

Brain Imaging

AD – clinical diagnostic criteria

✓ Clinical atypical presentation
✓ Extensive AD neuropathology in asymptomatic subjects
Cortical atrophy and athrophy in the medial temporal lobes (T1-weighted MRI).

Images from Westman E
In AD patients the affected brain regions include:
- Hippocampus,
- Posterior cingulate cortex
- Temporoparietal regions
- Frontal cortex

Positron emission tomography (PET): $^{18}$ fluorodeoxyglucose

↓ $^{18}$ FDG uptake: biomarkers of neuronal degeneration

Image from Westman E

Diagnosis of Alzheimer disease: functional neuroimaging

Positron emission tomography (PET): $[^{11}C]$ Pittsburgh Compound B (PIB)

↑ $[^{11}C]$ PIB uptake: biomarkers of brain $\beta$-amyloid deposition

HC: healthy control; AD: Alzheimer’s disease

Rowe et al., Neurology 2007
Brain imaging in prognosis:
PIB retention in MCI converter and non-converter

AD: Alzheimer’s disease; HC: healthy control; MCI: mild cognitive impairment

Forsberg et al Neurobiology of Aging 2007

AD Treatment
Disease modifying drugs: work in progress

Mangialasche et al., Lancet Neurol 2010
**AD Treatment**

Disease modifying drugs: role of functional neuroimaging

- **Anti-amyloid drug**

![C-PiB PET images](image)

¹¹C-PiB PET images from patients treated with bapineuzumab (A, B) and placebo (C, D) in a RCT. Changes from screening (baseline) to week 78. *(Mean ¹¹C-PiB PET changes are shown at the top centre of each panel for each patient).*

*Rinne et al., Lancet Neurol 2010*

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**Conclusions**

- Dementia is among the most common chronic disorders in older adults

- AD and VaD are the most common causes of dementia, with mixed dementia (AD+VaD) being common in very advanced age

- Brain morphological and functional imaging can support diagnosis, prognosis and treatment monitoring in AD

- Further development and standardization of neuroimaging techniques is needed to validate their application for diagnostic and prognostic purposes in AD
Thank you for your attention!