Cognitive functions and dementia

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What is dementia?

• DE-MENTIA = „without mind“

• acquired memory dysfunction (= set of signs and symptoms) and other cognitive domains beyond normal aging
  → attention
  → language
  → executive functions (decision making)

• duration of at least 6 month (shorter = delirium)
Clinical manifestation of dementia

**Cognitive dysfunction**
- memory, thinking and learning disturbances, visuo-spatial impairment
- executive functions impairment
- failure of symbolic functions

**Behavioral disorders**
- personality changes
- emotional changes, depression and anxiety, hallucinations and delusions
- irritatability, aggressiveness, apathy, sleep disturbances

**Limitation in everyday Activities**
- homework
- grooming, continence, walking
- complex activities (employment, driving, etc.)
Dementia is about forgetting, but forget it!
Incidence of dementia - increases with age

Growdon, 2007
New dementia cases per year in EU compared with other diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Annual Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia</td>
<td>600,000&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stroke</td>
<td>575,000&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diabetes</td>
<td>500,000&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>350,000&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Types of dementias

- Parkinson's disease
- Lewy body
- Alzheimer's Disease
- Mixed dementia
- Frontotemporal dementia
- Vascular dementia
Frontotemporal dementia

- 5-10%
- peak 45-65 years
- neuronal loss changes in frontal and temporal region → mutation of the tau protein

• Frontal variant
  → personality changes, behavioral dysfunctions, failure in executive functions

• Temporal variant
  → semantic dementia, speech impairment, (anomia), failure of understanding
Dementia with Lewy bodies

• 10-20%

• neuronal changes due to synucleopathy → brain stem, diencefalon, anterior cingulum, amygdala, cortex

→ fluctuating cognitive impairment
→ persistent visual hallucinations
→ extrapyramidal symptoms
→ neuroleptic sensitivity
Vascular dementia

- 10-15%
- heterogenous group → cognitive impairment due to vascular changes (ischemia, hemorrhage) with various clinical symptoms

- cortical dementia
- subcortical dementia
- posthemorrhagical dementia
- hereditary dementia
EFNS-ENS Guidelines on the diagnosis and management of disorders associated with dementia

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Alzheimer's Disease (AD)

• progressive neurological disease

• most common type of dementia

• risk factors
  ✓ age
  ✓ apolipoprotein E4 (APOE-4)
  ✓ female
  ✓ low education
  ✓ family history of AD or Down syndrome
  ✓ head trauma
  ✓ cerebrovascular disease (hypertension)
    ✓ diabetes, hyperhomocysteinemia, high fat level in diet

• protecting factors → antioxidants, NSA, hypolipidemics
How was it?

Alois Alzheimer (1864-1915)  
Oskar Fischer (1876 – 1942)
Oskar Fischer and the study of dementia

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The centenary of Alois Alzheimer’s description of the case of Auguste Deter has renewed interest in the early history of dementia research. In his 1907 paper Alzheimer described the presence of plaques and tangles in one case of presenile dementia. In the same year, Oskar Fischer reported neuritic plaques in 12 cases of senile dementia. These were landmark findings in the history of research in dementia because they delineated the clinicopathological entity that is now known as Alzheimer’s disease. Although much has been written about Alzheimer, only little is known about Fischer. The present article discusses Fischer’s work on dementia in the context of his life and time.
37 meeting of psychiatrists from south Germany in Tübingen, 1906

**Alzheimer A.** Über eine eigenartige Erkrankung der Hirnrinde. *Allg Z Psychiat* 1907;64:146-148


1. patient

12 patients

10 controls, 10 psychosis, 45 neurosyphilis
senile plaques

neurofibrillary tangles

Courtesy of doc. Bartos
Beta-Amyloid

α-secretase

β-secretase

γ-secretase

Enzymes
Clinical course in AD

Impairment vs. time

memory only
Clinical course in AD

Impairment

memory +

attention

time
Clinical course in AD

Impairment

memory + attention

aphasia visuospatial

time
Can we diagnose AD before the onset of dementia?

What are the early signs of the disease?
New diagnostic criteria for AD

- Memory impairment combined with
  - typical findings in CSF (beta-amyloid, tau protein)
  - MRI volumometry (hippocampal atrophy)
  - perfusion on SPECT or metabolism on PET
    (hypoperfusion in temporoparietal and frontal brain regions)

Dubois et al, 2007, DSM V - 2011
MRI volumetry


Screening tests in dementia

Senzitivity 80-85% demented vs. non-demented

Specificity 76-80%

Kahle-Wrobleski et al., 2007
## Mini Mental State Examination

<table>
<thead>
<tr>
<th>Temporal orientation (5 points)</th>
<th>What is the approximate time?</th>
<th>What day of the week is it?</th>
<th>What is the date today?</th>
<th>What is the month?</th>
<th>What is the year?</th>
</tr>
</thead>
<tbody>
<tr>
<td>RÉPEAT (1 point)</td>
<td>&quot;NOIFS, ANDS OR BUTS&quot;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage command (3 points)</td>
<td>&quot;Take this piece of paper with your right hand, fold it in half, and put it on the floor&quot;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Writing a complete sentence (1 point)</td>
<td>Write a sentence that makes sense</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reading and obey (1 point)</td>
<td>Close your eyes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copy the diagram (1 point)</td>
<td>Copy two pentagons with an intersection</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Earlier and cheaper diagnosis?

MOCA

sensitivity 90%
specificity 90%

Nasreddine et al., 2005
EFNS guidelines for the diagnosis and management of Alzheimer’s disease

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Keywords: Alzheimer’s disease, dementia, diagnosis, guideline, management, review, treatment

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Background and objectives: In 2008 a task force was set up to develop a revision of the European Federation of the Neurological Societies (EFNS) guideline for the diagnosis and management of Alzheimer’s disease (AD) and other disorders associated with dementia, published in early 2007. The aim of this revised international guideline was to present a peer-reviewed evidence-based statement for the guidance of practice for clinical neurologists, geriatricians, psychiatrists, and other specialist physicians responsible for the care of patients with AD. Mild cognitive impairment and non-Alzheimer dementias are not included in this guideline.
AD – insidiously progressive disease

• Dementia syndrome in AD is preceded by amyloid deposition in the brain (1 decade earlier)

• 20%-30% of cognitively normal elderly persons have brain AD pathology

• 50%-70% of patients with MCI have AD pathology (conversion 15% per year)

Progression of neuropathology in AD (years)

- Neurons/synapses
- Aβ-
- NFT

ageing prodromal MCI AD
The diagnosis of dementia due to Alzheimer’s disease: Recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease


Toward defining the preclinical stages of Alzheimer’s disease: Recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease

Earlier diagnostics

Normal ageing?

Preclinical AD?

MCI

prodromal AD

Who?

dementia
AD – management strategies

• normal ageing – (no symptoms), AD pathology not present
  influencing risk factors +,-

• preclinical AD – (no symptom), AD pathology present
  primary prevention

• prodromal AD (MCI syndrome)
  secondary prevention

• full blown AD (dementia syndrome)
  treatment of established AD
Cholinesterase inhibitors

- **acetylcholinesterase** (brain - neurotransmission) – donepezil, galantamin, rivastigmin

- **butyrylcholinesterase**
  (brain – inflammation, neurodegeneration) **rivastigmin**

**internal organs**
Cholinergic synapse

Presynaptic part

Cholin + acetate

Acetyl CoA + Choline

Cholin acetyltransferase

Postsynaptic part

N = nicotinic ACh receptors
M = muscarinic Ach receptors
Glutamate
Magnesium

NMDA receptor

AMPA receptor

Na^+

Ca^{2+}

Ca^{2+}
Monotherapy - memantine

Combined therapy memantine + IChE

Adherence to therapy – motivation seeing the improvement

- symptomatic (IAChE) - delayed decline
- disease modifying - slowing of the decline

Gauthier S. *Brain Aging* 2002;2:9–22
What improvement is possible today?

- Rivastigmin patch
- Donepezil oro-tabs
- Memantine once daily
- Higher dose of inhibitors - donepezil 23 mg
- Combination therapy ChEI + memantine
- Severe dementia – theory versus practice
- Avoid non-evidence based (nootropics)
Non-evidence based medications

Level A evidence for AD

no Level A evidence
Net cost of care per AD patient over 3 years

Fagnani et al., 2004
Conclusions

• forget dementia

• AD is insidiously progressive disease

• cholinesterase inhibitors, butyrylcholinesterasis
  • don't forget they will hardly ever disappear

• disease modifying therapies

• investment in treatment should go with investments in diagnostics