110 years of diagnosing AD

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A diagnosis post mortem

1907: Alois Alzheimer
Über eine eigenartige Erkrankung der Hirnrinde

Auguste D
51 year old
forgetful, but also
severe aphasia
and behavioural changes

Diagnosis: post mortem
Senile plaques (amyloid-beta)
Neurofibrillary tangles (tau)
A clinical diagnosis of AD

1984: NINCDS-ADRDA criteria

- Memory impairment
- + Other cognitive impairment
- Decline from previous
- Impact on daily living
- Progressive
- Not due to other disorder

- Concept of probable AD during life
- (Senile) dementia is now disease
- Pathological characteristics not taken into account

McKahn et al. Neurology 1984
The first biomarker

MTA visual rating scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Width of choroid fissure</th>
<th>Width of temporal horn</th>
<th>Height of hippocampal formation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>1</td>
<td>↑</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>2</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↓</td>
</tr>
<tr>
<td>3</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↓↓</td>
</tr>
<tr>
<td>4</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↓↓↓</td>
</tr>
</tbody>
</table>
Mid 90’s concept of MCI

- State between normal aging and dementia
- No functional impairment
- Amnestic or non-amnestic
- Multidomain
- Increased risk for dementia

Petersen et al. 1997
MTL atrophy as predictor for decline in subjects with MCI

Visser et al J Neurol 1999
MTA score in MCI

DeCarli, Arch Neurol 2007

MTA predictive of progression to AD in MCI

190 MCI
3 yrs follow-up
HR: 2.3 (1.1-4.9)
[\textsuperscript{\textit{11}}C]PIB: Amyloid in vivo!

Klunk, Nordberg et al, Ann Neurol, 2004
CSF markers

Hansson, Lancet Neurol 2006
Probable AD: A + ≥1 supportive features B, C, D or E

A episodic memory impairment

**Supportive features:**
B medial temporal lobe atrophy (MRI)
C abnormal CSF biomarkers abeta↓; tau↑; ptau↑
D abnormal glucose metabolism (FDG PET) or evidence of amyloid (PIB PET)
E autosomal dominant mutation in immediate family
Revising the definition of Alzheimer’s disease: a new lexicon


<table>
<thead>
<tr>
<th>AD diagnosis</th>
<th>Presence of impairment on specified memory tests</th>
<th>Evidence of biomarkers in vivo</th>
<th>Additional requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical AD</td>
<td>Yes</td>
<td>Required</td>
<td>None</td>
</tr>
<tr>
<td>Atypical AD</td>
<td>Yes</td>
<td>Not required</td>
<td>Specific clinical presentation</td>
</tr>
<tr>
<td>Prodromal AD</td>
<td>Yes</td>
<td>Required</td>
<td>Absence of dementia</td>
</tr>
<tr>
<td>AD dementia</td>
<td>Yes</td>
<td>Required</td>
<td>Presence of dementia</td>
</tr>
<tr>
<td>Mixed AD</td>
<td>Yes</td>
<td>Required</td>
<td>Evidence of comorbid disorders</td>
</tr>
<tr>
<td>Prediagnostic AD</td>
<td>Asymptomatic at risk for AD</td>
<td>No</td>
<td>Absence of symptoms of AD</td>
</tr>
<tr>
<td></td>
<td>Presymptomatic AD</td>
<td>No</td>
<td>Absence of symptoms of AD and presence of monogenic AD mutation</td>
</tr>
<tr>
<td>Mild cognitive impairment</td>
<td>No</td>
<td>Not required</td>
<td>Absence of symptoms or biomarkers specific for AD</td>
</tr>
</tbody>
</table>

AD=Alzheimer’s disease.

Table 2: Comparative features of the different conditions described in the new lexicon according to the new research criteria framework.
The diagnosis of mild cognitive impairment due to Alzheimer’s disease: Recommendations from the National Institute on Aging and Alzheimer’s Association workgroup

Marilyn S. Albert, Steven T. DeKosky, Dennis Dickson, Bruno Dubois, Howard H. Feldman, Nick C. Fox, Anthony Gamst, David M. Holtzman, William J. Jagust, Ronald C. Petersen, Peter J. Snyder, Maria C. Carrillo, Bill Thies, Creighton H. Phelps
Visser et al. Alzheim&Dem 2012
Advancing research diagnostic criteria for Alzheimer’s disease: the IWG-2 criteria

Clinical phenotypes
Typical
• Amnestic syndrome of the hippocampal type
Atypical
• Posterior cortical atrophy
• Logopenic variant
• Frontal variant

Preclinical states
Asymptomatic at risk
• No AD phenotype (typical or atypical)
Presymptomatic (autosomal dominant mutation)
• No AD phenotype (typical or atypical)

Required pathophysiological marker
• CSF (low amyloid $\beta_{1-42}$ and high T-tau or P-tau) or
• Amyloid PET (high retention of amyloid tracer)

Figure: AD is defined as a clinicobiological entity

Dubois et al. Lancet Neurol 2014
Preclinical Alzheimer’s disease: Definition, natural history, and diagnostic criteria

Editorial
Toward a consensus recommendation for defining the asymptomatic-preclinical phases of putative Alzheimer’s disease?

At risk or ill?
Prevalence of amyloid positivity

- Subject-level meta-analysis
  - Non-demented subjects (Jansen et al. JAMA 2015)
    - Normal cognition, subjective cognitive impairment, mild cognitive impairment
    - Amyloid assessed in CSF or by PET imaging
    - Data from 55 studies
  - Demented subjects (Ossenkoppele et al. JAMA 2015)
    - AD and other dementias
    - Amyloid assessed by PET imaging
    - Data from 29 studies
Prevalence amyloid positivity in non-demented subjects

53%

23%
Prevalence amyloid positivity in non-demented subjects: effect of APOE
Prevalence amyloid positivity in non-demented subjects: effect of APOE

**C** APOE genotypes in normal cognition

**D** APOE genotypes in mild cognitive impairment
Comparison prevalence amyloid positivity and AD-type dementia

![Graph showing prevalence of Alzheimer disease and amyloid positivity over age.](image)

- Prevalence of amyloid positivity in normal cognition.
- Prevalence of AD-type dementia.
- 25 years difference between the two curves.
Relation with memory score

1a. normal cognition

- Abnormal amyloid
- Normal amyloid

1b. mild cognitive impairment

1a Frequency of memory impairment (z-score <= -1.28) in participants with normal cognition, n=2544
1b Frequency of memory impairment in participants with MCI, n=2960

Jansen et al in preparation
2a. normal cognition

- Abnormal amyloid
- Normal amyloid

2b. mild cognitive impairment

Frequency of low MMSE (MMSE <= 27) in participants with normal cognition, n=2885
Frequency of low MMSE in participants with MCI, n=4126

Jansen et al in preparation
Summary prevalence amyloid positivity in non-demented subjects

- Higher in MCI than in cognitively normal and SCI
- Strongly dependent on age and APOE genotype
- Amyloid positivity in cognitively normal subjects precedes AD-type dementia by >25 years
- Relation with memory score in normal individuals
Injury markers predict time to dementia in subjects with MCI and amyloid pathology

Figure 2
Decline in Mini-Mental State Examination (MMSE) score in subjects with mild cognitive impairment (MCI) and abnormal CSF Aβ₁₋₄₂ according to CSF total tau (t-tau) and hippocampal volume

A CSF t-tau

B Hippocampal atrophy

C Combination of CSF t-tau and hippocampal atrophy
Prognosis preclinical AD (n=311): progression to MCI

NIA-AA stage 0
Normal amyloid and tau

NIA-AA stage 1
Abnormal amyloid and normal tau

NIA-AA stage 2/3
Abnormal amyloid and abnormal tau

Vos et al Lancet Neurology 2013
Defeating Alzheimer’s disease and other dementias: a priority for European science and society

Panel 4: Putative risk and protective factors for late-onset dementia and Alzheimer’s disease

**Risk factors**
- Older age
- Genetic factors
  - Familial aggregation (two or more family members with the disease)
  - APOE ε4 allele
  - Other susceptibility genes (e.g., CR1, PICALM, CLU, TREM2, TOMM40)
- Vascular risk and metabolic factors
  - Atherosclerosis
  - Cerebral macrovascular and microvascular lesions
  - Cardiovascular diseases
  - Diabetes mellitus and pre-diabetes
  - Midlife hypertension
  - Midlife overweight and obesity
  - Midlife high serum cholesterol
- Lifestyle factors
  - Sedentary lifestyle
  - Smoking
  - Heavy alcohol consumption
- Diet and nutritional factors
  - Saturated fats
  - Hyperhomocysteinaemia
  - Deficiencies in vitamin B6, B12, and folate
- Other factors
  - Depression
  - Traumatic brain injury
  - Occupational exposure (e.g., heavy metals, extremely-low-frequency electromagnetic fields)
  - Infectious agents (e.g., herpes simplex virus type I, *Chlamydia pneumoniae*, spirochetes)

**Protective factors**
- Genetic factors
  - Some genes proposed (e.g., APP, APOE ε2 allele)
- Psychosocial factors
  - High education and socioeconomic status
  - High work complexity
  - Rich social network and social engagement
  - Mentally stimulating activity
- Lifestyle factors
  - Physical activity
  - Light-to-moderate alcohol intake
- Diet and nutritional factors
  - Mediterranean diet
  - Polyunsaturated fatty acid and fish-related fats
  - Vitamin B6, vitamin B12, and folate
  - Antioxidant vitamins (A, C, E)
  - Vitamin D
- Drugs
  - Antihypertensive drugs
  - Statins
  - Hormone replacement therapy
  - Non-steroidal anti-inflammatory drugs

Many risk and protective factors for dementia and Alzheimer’s disease have been proposed and investigated; however, the evidence to support the factors listed here is variable, and the relevance of several proposed factors is open to debate. The most pronounced risk factors are advancing age and carrying one or two APOE ε4 alleles.

APOE = apolipoprotein E; CR1 = complement component receptor 1; PICALM = phosphatidylinositol-binding clathrin assembly protein; CLU = clusterin; TREM2 = triggering receptor expressed on myeloid cells 2; TOMM40 = translocase of outer mitochondrial membrane 40 homologue; APP = amyloid precursor protein.
Figure 4: From genetic and genomic discoveries to precision medicine
Figure 5: Pathways to Alzheimer's disease
Summary of diagnostic definitions and development of therapies for AD

Scheltens et al. Lancet 2016
Crucial tipping point in research

- Prodromal AD: diagnosing AD before dementia
- Preclinical AD: Amyloid presence without symptoms
- Additional biomarkers help to identify progressors
- Clinical trials include earlier populations using biomarkers instead of clinical phenotype
- Major breakthroughs in basic and clinical science will yield new targets and biomarkers
- Dementia field follows the oncology pathway: earlier detection and personalized / precision medicine

Scheltens et al. Lancet 2016