I nuovi criteri diagnostici della malattia di Alzheimer, quale utilizzo nella pratica clinica.

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Clinical diagnosis of Alzheimer’s disease: Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer’s Disease

Guy McKhann, MD; David Drachman, MD; Marshall Folstein, MD; Robert Katzman, MD; Donald Price, MD; and Emanuel M. Stadlan, MD

Research criteria for the diagnosis of Alzheimer’s disease: revising the NINCDS–ADRDA criteria


Revising the definition of Alzheimer’s disease: a new lexicon


The diagnosis of dementia due to Alzheimer’s disease: Recommendations from the National Institute on Aging and the Alzheimer’s Association workgroup

Position paper of the Italian Society for the study of Dementias (Sindem) on the proposal of a new Lexicon on Alzheimer disease

Massimo Musicco · Alessandro Padovani · Sandro Sorbi · Elio Scarpini · Paolo Caffarra · Stefano Cappa · Francesca Clerici · Massimo Tabaton · Carlo Caltagirone · Vincenzo Bonavita · Amalia C. Bruni · Giuseppe Bruno · Antonio Federico · Carlo Ferrarese · Camillo Marra · Benedetta Naemias · Lucilla Parnetti · Carla Pettenati · Giuseppe Sorrentino · Fabrizio Tagliavini · Claudio Mariani
Clinical diagnosis of probable Alzheimer’s disease. NINCSD-ADRDA Work Group 1984

First step

- No disturbance of consciousness
- Onset between the ages of 40 and 90, most often after age 65
- Absence of diseases or disorders that could account for deficits in cognition

Dementia Established by clinical evaluation

Documented by neuropsychological test

Deficits in two or more areas of cognition

Second step

memory and other cognitive functions
La demenza - DSM-IV TR

Demenza

Criterio A

1 Compromissione della memoria

Una o più tra: afasia, aprassia, agnosia, ...

Criterio B

I deficit del criterio A

Interferiscono significativamente nel lavoro, attività e relazioni sociali

rappresentano un peggioramento significativo rispetto al precedente livello funzionale
Per la malattia di Alzheimer come per molte altre malattie neurodegenerative con compromissione cognitiva, la demenza si presenta solo nelle fasi più avanzate di malattia.

Per le malattie neurodegenerative non Alzheimer la demenza spesso non è un aspetto caratterizzante.

La definizione di demenza è costruita sul paradigma della malattia di Alzheimer (tipica) dove la compromissione della memoria è il sintomo più precoce e più caratterizzante. Nelle demenze non Alzheimer la compromissione della memoria è spesso non prominente e talvolta addirittura assente.
Tracking atrophy progression in familial Alzheimer’s disease: a serial MRI study

Basil H Ridha, Josephine Barnes, Jonathan W Bartlett, Alison Godbolt, Tracey Peppe, Martin N Rossor, Nick C Fox

Lancet Neurol 2006; 5: 828–34
The new criteria of diagnosis and the new proposed lexicon reflect the widely agreed opinion that Alzheimer’s disease preexists prior to the clinical manifestation of dementia.
La malattia di Alzheimer è caratterizzata da uno specifico processo fisiopatologico (aggregazione della beta amiloide) che causa danno sinaptico e neurodegenerazione (neurofibrillare) con uno specifico pattern di progressione temporale.
Fig. 5. Graphic representation of the proposed staging framework for preclinical AD. Note that some individuals will not progress beyond Stage 1 or Stage 2. Individuals in Stage 3 are postulated to be more likely to progress to MCI and AD dementia. Abbreviations: AD, Alzheimer’s disease; Ab, amyloid beta; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose, fMRI, functional magnetic resonance imaging, sMRI, structural magnetic resonance imaging.
The availability of in-vivo biomarkers and their correspondence with Alzheimer's pathology form the basis of the new research criteria, which were founded on a clinicobiological definition. AD is now defined in vivo with a diagnostic algorithm that begins with a characteristic pattern of episodic memory impairment and then requires supportive biomarkers that indicate the pathophysiology or the topography of Alzheimer's pathology. The presence of dementia itself—the more severe form of AD—is not required. The diagnosis of AD is made on the basis of both clinical and biological evidence, with a very high level of specificity and predictive validity. Within this framework, the designation of "probable" and "possible" AD is no longer meaningful because of the use of reliable biomarkers and the designation of "typical" and "atypical" AD.

The argument for defining AD as a clinicobiological entity with a specified clinical phenotype and in-vivo evidence of the footprint of pathological changes has the major advantage that there is no longer a reason to wait until patients have developed full-blown dementia or to exclude from diagnosis and treatment a large number of patients who lack functional disability yet express the disease. The diagnosis in turn can be uncoupled from a particular threshold of severity, and there is no longer a need to anchor the diagnosis of AD to a dementia syndrome as is done today. Here, it is useful to refer to
Revising the definition of Alzheimer’s disease: a new lexicon


Lancet Neurol 2010; 9: 1118-27

<table>
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<tr>
<td>Total tau, phospho-tau</td>
<td>Yes</td>
<td>No</td>
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<td><strong>PET</strong></td>
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<tr>
<td>Amyloid tracer uptake</td>
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<td>Fluorodeoxyglucose</td>
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<td>Yes</td>
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<td><strong>Structural MRI</strong></td>
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<tr>
<td>Medial temporal atrophy</td>
<td>No</td>
<td>Yes</td>
</tr>
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</table>

AD=Alzheimer’s disease.

Table 1: Categorisation of the current, most-validated AD biomarkers
Objective evidence of significantly impaired episodic memory on testing: this generally consists of recall deficit that does not improve significantly or does not normalise with cueing or recognition testing and after effective encoding of information has been previously controlled.

This diagnostic label is applied if there is no disease to which MCI can be attributed. It remains a term of exclusion for individuals who are suspected to have but do not meet the proposed new research criteria for AD, in that they deviate from the clinicobiological phenotype of prodromal AD because they have memory symptoms that are not characteristic of AD or because they are biomarker negative.
Preclinical states of AD (including both “asymptomatic at-risk state for AD” and “presymptomatic AD”)

These terms refer to the long asymptomatic stage between the earliest pathogenic events/brain lesions of AD and the first appearance of specific cognitive changes. Traditionally, a preclinical or asymptomatic phase was recognised post mortem by evidence of histological changes typical of Alzheimer’s pathology in individuals considered as cognitively normal before death. Today, two preclinical states can be isolated in vivo:

- **Asymptomatic at-risk state for AD**—this state can be identified in vivo by evidence of amyloidosis in the brain (with retention of specific PET amyloid tracers) or in the CSF (with changes in amyloid β, tau, and phospho-tau concentrations). In the absence of knowledge about the value of these biological changes to predict the further development of the disease, the asymptomatic phase of AD should still be referred to as an “at-risk state for AD”.

- **Presymptomatic AD**—this state applies to individuals who will develop AD. This can be ascertained only in families that are affected by rare autosomal dominant monogenic AD mutations (monogenetic AD).
Presymptomatic AD
Rilevanza clinica
Alzheimer's disease phenotypes and genotypes associated with mutations in presenilin 2

Suman Jayadev,¹ James B. Leverenz,¹,²,³ Ellen Steinbart,¹,⁴ Justin Stahl,⁵ William Klunk,⁶ Cheng-En Yu⁴ and Thomas D. Bird¹,⁴

Table 2 Clinical phenotype of Volga German families with N141I PSEN2 mutation

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<tr>
<th>Family</th>
<th>Number affected*</th>
<th>Confirmed PSEN2 mutation</th>
<th>Mean age onset ± SD (range)</th>
<th>Mean age death ± SD (range)</th>
<th>Mean duration (years) ± SD (range)</th>
<th>Autopsy¹</th>
<th>Medical records available</th>
<th>First signs and symptoms</th>
<th>Psychosis</th>
<th>Seizures</th>
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<tr>
<td>BDR</td>
<td>5</td>
<td>1</td>
<td>40 ± 1.4 (39–41)</td>
<td>50.8 ± 2.3 (47–53)</td>
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<td>2</td>
<td>1 memory problems</td>
<td>1 psychosis</td>
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<tr>
<td>BE</td>
<td>2</td>
<td>2</td>
<td>61.0 ± 1.4 (60–62)</td>
<td>69</td>
<td>7</td>
<td>1</td>
<td>2</td>
<td>1 memory problems</td>
<td>na</td>
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<tr>
<td>E</td>
<td>8</td>
<td>3</td>
<td>55.0 ± 3.9 (50–60)</td>
<td>67.2 ± 5.9 (58–76)</td>
<td>10.0 ± 3.1 (6–14)</td>
<td>3</td>
<td>7</td>
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<tr>
<td>H</td>
<td>7</td>
<td>5</td>
<td>60.3 ± 5.3 (56–68)</td>
<td>72.3 ± 9.3 (60–80)</td>
<td>16.5 ± 7.8 (11–22)</td>
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<tr>
<td>HB</td>
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<td>72.3 ± 9.0 (58–88)</td>
<td>10.9 ± 3.8 (4–19)</td>
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<td>13</td>
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<td>HD</td>
<td>17</td>
<td>8</td>
<td>52.2 ± 6.2 (45–70)</td>
<td>62.6 ± 7.1 (53–77)</td>
<td>92. ± 3.8 (3–15)</td>
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<td>10 memory problems 4 cognitive problems 1 memory problems 4 cognitive problems 1 memory problems 3 memory problems 1 depression</td>
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<td>57.5 ± 3.5 (55–60)</td>
<td>73.0 ± 5.7 (69–77)</td>
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<td>57.4 ± 7.6 (43–74)</td>
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<tr>
<td>W</td>
<td>6</td>
<td>4</td>
<td>52.0 ± 4.9 (47–58)</td>
<td>67.4 ± 4.9 (62–73)</td>
<td>14.6 ± 8.1 (5–25)</td>
<td>2</td>
<td>5</td>
<td>5 memory problems 2 cognitive problems 53 memory problems 15 cognitive problems 3 vision problems 2 personality changes 1 behavioural change 1 depression 1 seizures</td>
<td>1 hallucinations</td>
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<tr>
<td>Total</td>
<td>11</td>
<td>101</td>
<td>53.7 ± 7.8 (39–75)</td>
<td>64.2 ± 9.8 (43–88)</td>
<td>10.6 ± 4.8 (3–25)</td>
<td>35</td>
<td>64</td>
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<td>21/64 20%</td>
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</table>

na = not applicable. *Number affected: demented persons with the N141I mutation by genotyping or who had a child with the mutation.
¹ Autopsy: total autopsies in families of demented persons with and without genotyping.
Worldwide distribution of PSEN1 Met146Leu mutation

A large variability for a founder mutation

ABSTRACT

Objective: Large kindreds segregating familial Alzheimer disease (FAD) offer the opportunity of studying clinical variability as observed for presenilin 1 (PSEN1) mutations. Two early-onset FAD (EOFAD) Calabrian families with PSEN1 Met146Leu (ATG/CTG) mutation constitute a unique population descending from a remote common ancestor. Recently, several other EOFAD families with the same mutation have been described worldwide.

Methods: We searched for a common founder of the PSEN1 Met146Leu mutation in families with different geographic origins by genealogic and molecular analyses. We also investigated the phenotypic variability at onset in a group of 50 patients (mean age at onset 40.0 ± 4.8 years) by clinical, neuropsychological, and molecular methodologies.

Results: EOFAD Met146Leu families from around the world resulted to be related and constitute a single kindred originating from Southern Italy before the 17th century. Phenotypic variability at onset is broad: 4 different clinical presentations may be recognized, 2 classic for AD (memory deficits and spatial and temporal disorientation), whereas the others are expressions of frontal impairment. The apathetic and dysexecutive subgroups could be related to orbital-medial prefrontal cortex and dorsolateral prefrontal cortex dysfunction.

Conclusions: Genealogic and molecular findings provided evidence that the PSEN1 Met146Leu families from around the world analyzed in this study are related and represent a single kindred originating from Southern Italy. The marked phenotypic variability might reflect early involvement by the pathologic process of different cortical areas. Although the clinical phenotype is quite variable, the neuropathologic and biochemical characteristics of the lesions account for neurodegenerative processes unmistakably of Alzheimer nature. Neurology® 2010:74:798-806

GLOSSARY

AD = Alzheimer disease; EOFAD = early-onset familial Alzheimer disease; FAD = familial Alzheimer disease; H-E = hematoxylin-eosin.

Alzheimer disease (AD) is a common degenerative disorder of unknown etiology, believed to involve a combination of genetic and environmental factors. About 47% of families with the disease has a common genetic cause, affecting presenilin 1 (PSEN1).
Asymptomatic at-risk state for AD
Cerebrospinal Fluid tau/β-Amyloid$_{42}$ Ratio as a Prediction of Cognitive Decline in Nondemented Older Adults

Anne M. Fagan, PhD; Catherine M. Roe, PhD; Chenglie Xiong, PhD; Mark A. Mintun, MD; John C. Morris, MD; David M. Holtzman, MD

Figure 3. Cerebrospinal fluid (CSF) tau/Ab$_{42}$ and ptau$_{181}$/Ab$_{42}$ as predictors of conversion from Clinical Dementia Rating (CDR) 0 to CDR greater than 0. Kaplan-Meier estimates of rate of conversion from CDR 0 to CDR greater than 0 using cut-off values of 1.15 for tau/Ab$_{42}$ and 0.214 for ptau$_{181}$/Ab$_{42}$ (representing the top 15% of distribution values). ptau indicates phosphorylated tau; Ab, β-amyloid.
Pittsburgh Compound B Imaging and Prediction of Progression From Cognitive Normality to Symptomatic Alzheimer Disease

John C. Morris, MD; Catherine M. Roe, PhD; Elizabeth A. Grant, PhD; Denise Head, PhD; Martha Storandt, PhD; Alison M. Goate, DPhil; Anne M. Fagan, PhD; David M. Holtzman, MD; Mark A. Mintun, MD

Table 2. Cox Proportional Hazards Model Testing MCBP for PiB as a Predictor of Time to DAT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HR (95% CI)</th>
<th>P Value</th>
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<tbody>
<tr>
<td>MCBP</td>
<td>4.82 (1.22-19.01)</td>
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</tr>
<tr>
<td>Age, y</td>
<td>1.14 (1.02-1.28)</td>
<td>.03</td>
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<tr>
<td>Education, y</td>
<td>0.91 (0.69-1.19)</td>
<td>.49</td>
</tr>
<tr>
<td>APOE ε4 carrier</td>
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<td>.98</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.54 (0.10-2.90)</td>
<td>.48</td>
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Table 3. Cox Proportional Hazards Model Testing MCBP as a Predictor of Time to CDR 0.5

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<th>HR (95% CI)</th>
<th>P Value</th>
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<td>MCBP</td>
<td>2.74 (0.59-12.78)</td>
<td>.20</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.11 (1.04-1.18)</td>
<td>.002</td>
</tr>
<tr>
<td>Education, y</td>
<td>0.99 (0.84-1.16)</td>
<td>.88</td>
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<tr>
<td>APOE ε4 carrier</td>
<td>1.49 (0.56-3.94)</td>
<td>.42</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.26 (0.50-3.15)</td>
<td>.62</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; DAT, dementia of the Alzheimer type; HR, hazard ratio; MCBP, mean cortical binding potential; PiB, Pittsburgh Compound B.
Asymptomatic at-risk state for AD
Rilevanza clinica

• “the evidence derived from these studies appears sufficient to consider that normal persons with amyloid brain deposition detected in vivo with PIB–PET imaging, and/or CSF abnormal concentrations in Aβ42 and P-tau have a higher risk of having AD. However, since it is not yet possible to predict who will develop dementia, and since specific preventive strategies suitable for this group are not available, the panel believes that PIB-PET imaging and CSF examination for Aβ42 and T-tau/P-tau should not be performed in asymptomatic persons.”
Prodromal AD (also called “predementia stage of AD”)  
This term refers to the early symptomatic, predementia phase of AD in which (1) clinical symptoms including episodic memory loss of the hippocampal type (characterised by a free recall deficit on testing not normalised with cueing) are present, but not sufficiently severe to affect instrumental activities of daily living and do not warrant a diagnosis of dementia; and in which (2) biomarker evidence from CSF or imaging is supportive of the presence of AD pathological changes. This phase is now included in the new definition of AD. The term of prodromal AD might disappear in the future if AD is considered to encompass both the predementia and dementia stages.
Amnestic syndrome of the medial temporal type identifies prodromal AD
A longitudinal study

M. Sarazin, PhD*
C. Berr, PhD*
J. De Rotrou, PhD
C. Fabrigoule, PhD
F. Pasquier, PhD
S. Legrain, MD
B. Michel, MD
M. Puel, MD
M. Volteau, PhD
J. Touchon, MD
M. Verny, PhD
B. Dubois, MD

Kaplan-Meier survival curves for the development of Alzheimer disease (AD) dementia in patients with mild cognitive impairment for subjects with or without amnestic syndrome of the medial temporal type

The curves show the dramatic difference in the development of AD dementia between groups, according to the initial performance on Free and Cued Selective Recall Reminding Test total recall. Receiver operating characteristic analysis was performed on the whole sample (n = 251 patients).
Abstract  Aim of the present review paper was to evaluate the hypothesis (included in the proposal of new research criteria for Alzheimer’s disease; Dubois et al., Lancet Neurology, 6, 734–746, 2007) that a neuropsychological tool which provides support for the semantic encoding of memorandum at the time of study and supplies category cues at the time of retrieval (i.e. the Grober-Buschke paradigm) is more effective than traditional measures of free recall in 1) differentiating patients affected by the amnestic form of Mild Cognitive Impairment (MCI) or by mild to moderate forms of Alzheimer’s disease (AD) from healthy matches, 2) predicting the conversion of individuals with MCI to AD, and 3) differentiating AD patients from individuals affected by other forms of dementia. Results of the review are controversial regarding the superiority of the Grober-Buschke procedure in differentiating individuals affected by AD or MCI from healthy individuals. The only study that evaluated this issue directly found that the Grober-Buschke procedure was more sensitive and specific than more traditional memory tests in predicting the conversion of MCI patients to AD. Finally, two studies reported that patients affected by AD or other forms of dementia showed different performance patterns in the free and cued recall tasks of the Grober-Buschke procedure. In conclusion, although encouraging results are reported in the few studies that investigated the ability of this procedure to predict the evolution of individuals with amnestic MCI and to differentiate AD patients from patients with other forms of cortical and subcortical dementia, more experimental work is needed to confirm these positive findings.

Keywords  Dementia · Alzheimer · Memory · Grober-Buschke procedure · Neuropsychology

Introduction

The feasibility of using a neuropsychological approach in the early diagnosis of Alzheimer’s disease (AD) and the differential diagnosis between AD and other forms of dementia rests on the assumption of “selective regional vulnerability” of degenerative diseases affecting the central nervous system. According to Cummings (2003, p. 148), “...the molecular biology of neurodegenerative diseases is
Table 2

<table>
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<tr>
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<th>Number of controls</th>
<th>Number of cases</th>
<th>d</th>
<th>99% CI</th>
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<td>6,509</td>
<td>868</td>
<td>1.19*</td>
<td>1.15–1.24</td>
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<td>6,694</td>
<td>704</td>
<td>1.03*</td>
<td>0.98–1.08</td>
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<td>Verbal Ability</td>
<td>15</td>
<td>3,625</td>
<td>438</td>
<td>0.79*</td>
<td>0.73–0.85</td>
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<td>Visuospatial Skill</td>
<td>9</td>
<td>3,159</td>
<td>363</td>
<td>0.64*</td>
<td>0.58–0.71</td>
</tr>
<tr>
<td>Primary Memory</td>
<td>8</td>
<td>1,567</td>
<td>205</td>
<td>0.00</td>
<td>-0.09–0.09</td>
</tr>
<tr>
<td>Attention</td>
<td>5</td>
<td>2,969</td>
<td>289</td>
<td>0.62*</td>
<td>0.55–0.68</td>
</tr>
<tr>
<td>Perceptual Speed</td>
<td>4</td>
<td>1,274</td>
<td>65</td>
<td>1.11*</td>
<td>1.00–1.22</td>
</tr>
<tr>
<td>Executive Functioning</td>
<td>3</td>
<td>547</td>
<td>166</td>
<td>1.07*</td>
<td>0.92–1.21</td>
</tr>
</tbody>
</table>

*Note. CI = confidence interval; O/L% = overlap statistic.

* p < .01.
I marker biologi della “prodromal AD”

• The diagnostic validity of each marker can be established by well-designed longitudinal studies.
• The panelists have considered a sensitivity of 80% or higher with a specificity of 85% or higher as cut-off values of validity of the marker as a predictor of conversion.
Atrofia corticale alla MRI
Prediction of conversion from mild cognitive impairment to Alzheimer’s disease dementia based upon biomarkers and neuropsychological test performance

Michael Ewers\textsuperscript{a,b,*}, Cathal Walsh\textsuperscript{c}, John Q. Trojanowski\textsuperscript{d}, Leslie M. Shaw\textsuperscript{d}, Ronald C. Petersen\textsuperscript{e}, Clifford R. Jack Jr.\textsuperscript{f}, Howard H. Feldman\textsuperscript{g}, Arun L.W. Bokde\textsuperscript{h}, Gene E. Alexander\textsuperscript{i}, Philip Scheltens\textsuperscript{j}, Bruno Vellas\textsuperscript{k}, Bruno Dubois\textsuperscript{l}, Michael Weiner\textsuperscript{a,b}, Harald Hampel\textsuperscript{m}, in collaboration with the North American Alzheimer’s Disease Neuroimaging Initiative (ADNI)

<table>
<thead>
<tr>
<th></th>
<th>Se</th>
<th>Sp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right entorhinal cortex thickness (%)</td>
<td>67.9</td>
<td>86.1</td>
</tr>
<tr>
<td>Left entorhinal cortex thickness (%)</td>
<td>74.1</td>
<td>84.2</td>
</tr>
<tr>
<td>Left hippocampus volume (%)</td>
<td>66.7</td>
<td>79.2</td>
</tr>
<tr>
<td>Right hippocampus volume (%)</td>
<td>65.4</td>
<td>85.1</td>
</tr>
</tbody>
</table>
Ridotto metabolismo glucidico e imaging dell’amilode alla PET
Sensibilità e specificità nel predire la conversione da MCI ad AD della FDG-PET

<table>
<thead>
<tr>
<th>Author(s) &amp; Co.</th>
<th>Year</th>
<th>Journal</th>
<th>Sensibilità</th>
<th>Specificità</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chetelat G, &amp; Co.</td>
<td>2003</td>
<td>Neurology 60:1374–137</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Anchisi D, &amp; Co.</td>
<td>2005</td>
<td>Arch Neurol 62:1728–1733</td>
<td>93</td>
<td>84</td>
</tr>
</tbody>
</table>
Conversion of amyloid positive and negative MCI to AD over 3 years
An $^{11}$C-PIB PET study

Se 93% SP 81%
31 soggetti
Marker liquorali
The effects of normal aging and ApoE genotype on the levels of CSF biomarkers for Alzheimer’s disease

Lidia Glodzik-Sobanska\textsuperscript{a}, Elizabeth Pirraglia\textsuperscript{a}, Miroslaw Brys\textsuperscript{a}, Susan de Santi\textsuperscript{a}, Lisa Mosconi\textsuperscript{a}, Kenneth E. Rich\textsuperscript{a}, Remigiusz Switalski\textsuperscript{a}, Leslie Saint Louis\textsuperscript{a}, Martin J. Sadowski\textsuperscript{a}, Frank Martiniuk\textsuperscript{a}, Pankaj Mehta\textsuperscript{b}, Domenico Pratico\textsuperscript{c}, Raymond P. Zinkowski\textsuperscript{d}, Kaj Blennow\textsuperscript{e}, and Mony J. de Leon\textsuperscript{a, f, *}

CSF Biomarkers and Incipient Alzheimer Disease in Patients With Mild Cognitive Impairment

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Oskar Hansson, MD, PhD
Niels Andreasen, MD, PhD
Lucilla Parmenti, MD, PhD
Michael Jonsson, MD
Sanna-Kaisa Herukka, PhD
Wiesje M. van der Flier, PhD
Marinus A. Blankenstein, PhD
Michael Ewers, PhD
Kenneth Rich, MD
Elmar Kaiser, MD
Marcel Verbeek, PhD
Magda Tsolaki, MD, PhD
Ezra Mulugeta, PhD
Erik Rosén, PhD
Dag Aarsland, MD, PhD
Pieter Jelle Visser, MD, PhD
Johannes Schröder, MD, PhD
Jan Marcusson, MD, PhD
Mony de Leon, MD, PhD
Harald Hampel, MD, PhD
Philip Scheltens, MD, PhD
Tuula Pirttilä, MD, PhD
Anders Wallin, MD, PhD
Maria Eriksdotter Jönsson, MD
Lennart Minthon, MD, PhD
Bengt Winblad, MD, PhD
Kaj Blennow, MD, PhD

Context Small single-center studies have shown that cerebrospinal fluid (CSF) biomarkers may be useful to identify incipient Alzheimer disease (AD) in patients with mild cognitive impairment (MCI), but large-scale multicenter studies have not been conducted.

Objective To determine the diagnostic accuracy of CSF β-amyloid_1-42 (Aβ42), total tau protein (T-tau), and tau phosphorylated at threonine 181 (P-tau) for predicting incipient AD in patients with MCI.

Design, Setting, and Participants The study had 2 parts: a cross-sectional study involving patients with AD and controls to identify cut points, followed by a prospective cohort study involving patients with MCI, conducted 1990-2007. A total of 750 individuals with MCI, 529 with AD, and 304 controls were recruited by 12 centers in Europe and the United States. Individuals with MCI were followed up for at least 2 years or until symptoms had progressed to clinical dementia.

Main Outcome Measures Sensitivity, specificity, positive and negative likelihood ratios (LRs) of CSF Aβ42, T-tau, and P-tau for identifying incipient AD.

Results During follow-up, 271 participants with MCI were diagnosed with AD and 59 with other dementias. The Aβ42 assay in particular had considerable intersite variability. Patients who developed AD had lower median Aβ42 (356; range, 96-1075 ng/L) and higher P-tau (81; range, 15-183 ng/L) and T-tau (582; range, 83-2174 ng/L) levels than MCI patients who did not develop AD during follow-up (579; range, 121-1420 ng/L for Aβ42; 53; range, 15-163 ng/L for P-tau; and 294; range, 31-2483 ng/L for T-tau, P < .001). The area under the receiver operating characteristic curve was 0.78 (95% confidence interval [CI], 0.75-0.82) for Aβ42, 0.76 (95% CI, 0.72-0.80) for P-tau, and 0.79 (95% CI, 0.76-0.83) for T-tau. Cut-offs with sensitivity set to 85% were defined in the AD and control groups and tested in the MCI group, where the combination of Aβ42/P-tau ratio and T-tau identified incipient AD with a sensitivity of 83% (95% CI, 78%-88%), specificity 72% (95% CI, 68%-76%), positive LR, 3.0 (95% CI, 2.5-3.4), and negative LR, 0.24 (95% CI, 0.21-0.28). The positive predictive value was 62% and the negative predictive value was 88%.

Conclusions This multicenter study found that CSF Aβ42, T-tau, and P-tau identify incipient AD with good accuracy, but less accurately than reported from single-center studies. Intersite assay variability highlights a need for standardization of analytical techniques and clinical procedures.

JAMA. 2009;302(4):385-393

Tangles consisting of the protein tau and extracellular deposits of synaptotoxic β-amyloid (Aβ) peptides in fibril structures, which will be developed raise a need for methods enabling early diagnosis. Further, treatments would need to be initiated.
“The combination of Aβ42/P-tau ratio and T-tau identified incipient AD with a sensitivity of 83% and a specificity of 72%. Considering that 271 individuals with MCI had AD and 59 other dementias, we can calculate that the “a priori” probability of AD in the studied sample was 40% (271/691) and the post-test improvement in the positive predictive value (62%) was really poor. The reasons for these unsatisfactory results were individuated in the large variability and thus in the insufficient accuracy of the determinations of the CSF concentrations of Aβ42, T-tau and P-tau. A recent study that adopted strictly standardized procedures of evaluation of CSF parameters and found satisfactory intra laboratory coefficients of variation around 5% [47 ]. Unfortunately, in that study the inter laboratory coefficients of variation confirmed the high inter laboratory variability of CSF determinations.”
“The proposed new diagnostic criteria and the new proposed lexicon for AD are conceptually attractive. However the evidence about the instrumental and laboratory markers for the diagnosis of the preclinical and asymptomatic states of the disease are, until to now, insufficient to support the routine clinical use of these investigations.”
“Although not specifically evaluated in this position paper, it is panelists' opinion that selected dementia centers, with recognized expertise, may provide CSF analysis and morphological and functional imaging in selected patients both for differential diagnosis in dementia with atypical presentations and for population enrichment in clinical trials.”
“The limited usefulness of present laboratory and instrumental markers in clinical practice does not extend to the field of research where, the markers maintain huge interest for the purpose of improving human health.”
The diagnosis of dementia due to Alzheimer’s disease: Recommendations from the National Institute on Aging and the Alzheimer’s Association workgroup

Guy M. McKhann a,b,*, David S. Knopman c, Howard Chertkow d,e, Bradley T. Hyman f, Clifford R. Jack, Jr. g, Claudia H. Kawas h,i,j, William E. Klunk k, Walter J. Koroshetz l, Jennifer J. Manly m,n,o, Richard Mayeux m,n,o, Richard C. Mohs p, John C. Morris q, Martin N. Rossor r, Philip Scheltens s, Maria C. Carillo t, Bill Thies t, Sandra Weintraub u,v, Creighton H. Phelps w

Our knowledge of the clinical manifestations and biology of AD has increased vastly. The features of the original criteria that required revision include the following:

1. The fact that the histological pathology of AD (or surrogates for this pathology) may be found across a broad clinical spectrum (including individuals who are cognitively normal, those with MCI, and those with dementia) [6,7]. Therefore, throughout this article, we

3. No inclusion of results of magnetic resonance imaging, positron emission tomography (PET) imaging and cerebrospinal fluid (CSF) assays (that we will refer to subsequently as biomarkers) in decision-making. Initial efforts to incorporate biomarkers into

4. The implication that memory impairment is always the primary cognitive deficit in all patients with AD dementia. Experience has shown that there are several nonamnestic presentations of the pathophysiological process of AD, the most common ones being the syn-

6. Proposed age cutoffs for the diagnosis of AD dementia. Work over the past decades has established that AD dementia in those aged <40 years, although rare, does not differ in its pathophysiology from older persons [18]. AD dementia in persons aged ≥90 years is also part of that same spectrum as that of younger
The diagnosis of dementia due to Alzheimer’s disease: Recommendations from the National Institute on Aging and the Alzheimer’s Association workgroup


Fig. 3. Hypothetical model of dynamic biomarkers of the AD expanded to explicate the preclinical phase: Aβ as identified by cerebrospinal fluid Aβ42 assay or PET amyloid imaging. Synaptic dysfunction evidenced by fluorodeoxyglucose (F18) positron emission tomography (FDG-PET) or functional magnetic resonance imaging (fMRI), with a dashed line to indicate that synaptic dysfunction may be detectable in carriers of the ε4 allele of the apolipoprotein E gene before detectable Aβ deposition. Neuronal injury is evidenced by cerebrospinal fluid tau or phospho-tau, brain structure is evidenced by structural magnetic resonance imaging. Biomarkers change from normal to maximally abnormal (y-axis) as a function of disease stage (x-axis). The temporal trajectory of two key indicators used to stage the disease clinically, cognitive and behavioral measures, and clinical function are also illustrated. Figure adapted with permission from Jack et al [22].
We emphasize again that this framework is not intended to serve as diagnostic criteria for clinical purposes. Use of these biomarkers in the clinical setting is currently unwarranted because many individuals who satisfy the proposed research criteria may not develop the clinical features of AD in their lifetime. Inappropriate use of this information in this context could be associated with unwarranted concern because there is currently insufficient information to relate preclinical biomarker evidence of AD to subsequent rates of clinical progression with any certainty.
We propose the terminology for “MCI due to AD” in the following sections, incorporating the use of biomarkers. It is fully recognized that there are limitations in our knowledge about these biomarkers, as noted earlier. These criteria are designed to stimulate the application of biomarkers in clinical research settings, thus permitting refinements in these criteria over time (Table 3).

The National Institute on Aging and the Alzheimer’s Association charged a workgroup with the task of developing criteria for the symptomatic predementia phase of Alzheimer’s disease (AD), referred to in this article as mild cognitive impairment due to AD. The workgroup developed the following two sets of criteria: (1) core clinical criteria that could be used by healthcare providers without access to advanced imaging techniques or cerebrospinal fluid analysis, and (2) research criteria that could be used in clinical research settings, including clinical trials. The second set of criteria incorporate the use of biomarkers based on imaging and cerebrospinal fluid measures. The final set of criteria for mild cognitive impairment due to AD has four levels of certainty, depending on the presence and nature of the biomarker findings. Considerable work is needed to validate the criteria that use biomarkers and to standardize biomarker analysis for use in community settings.
Table 1
Summary of clinical and cognitive evaluation for MCI due to AD

Establish clinical and cognitive criteria
Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (i.e., historical or observed evidence of decline over time)
Objective evidence of Impairment in one or more cognitive domains, typically including memory (i.e., formal or bedside testing to establish level of cognitive function in multiple domains)
Preservation of independence in functional abilities
Not demented
Examine etiology of MCI consistent with AD pathophysiological process
Rule out vascular, traumatic, medical causes of cognitive decline, where possible
Provide evidence of longitudinal decline in cognition, when feasible
Report history consistent with AD genetic factors, where relevant

Abbreviations: AD, Alzheimer’s disease; MCI, mild cognitive impairment.
<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Biomarker probability of AD etiology</th>
<th>Aβ (PET or CSF)</th>
<th>Neuronal injury (tau, FDG, sMRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCI—core clinical criteria</td>
<td>Uninformative</td>
<td>Conflicting/indeterminant/untested</td>
<td>Conflicting/indeterminant/untested</td>
</tr>
<tr>
<td>MCI due to AD—intermediate likelihood</td>
<td>Intermediate</td>
<td>Positive</td>
<td>Untested</td>
</tr>
<tr>
<td>MCI due to AD—high likelihood</td>
<td>Highest</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>MCI—unlikely due to AD</td>
<td>Lowest</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer’s disease; Aβ, amyloid beta peptide; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; sMRI, structural magnetic resonance imaging.
All cause dementia

Specific cognitive impairment

- Interfere with activity of daily living
- Represent a decline from previous level
- Not explained by delirium

Detected by history taking, objective cognitive assessment either bedside or neuropsychological testing
The cognitive or behavioral impairment involves a minimum of two of the following domains:

a. Impaired ability to acquire and remember new information—symptoms include: repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route.

b. Impaired reasoning and handling of complex tasks, poor judgment—symptoms include: poor understanding of safety risks, inability to manage finances, poor decision-making ability, inability to plan complex or sequential activities.

c. Impaired visuospatial abilities—symptoms include: inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements, or orient clothing to the body.

d. Impaired language functions (speaking, reading, writing)—symptoms include: difficulty thinking of common words while speaking, hesitations; speech, spelling, and writing errors.

e. Changes in personality, behavior, or comportment—symptoms include: uncharacteristic mood fluctuations such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, socially unacceptable behaviors.
3. Proposed classification criteria for AD dementia

We propose the following terminology for classifying individuals with dementia caused by AD: (1) **Probable AD dementia**, (2) **Possible AD dementia**, and (3) **Probable or possible AD dementia** with evidence of the AD pathophysiological process. The first two are intended for use in all clinical settings. The third is currently intended for research purposes.
In persons who meet the core clinical Criteria for probable AD dementia biomarker evidence may **increase the certainty that the basis of the clinical dementia syndrome is the AD pathophysiological process.** However, we do not advocate the use of AD biomarker tests for routine diagnostic purposes at the present time. There are several reasons for this limitation: (1) the core clinical criteria provide very good diagnostic accuracy and utility in most patients; (2) more research needs to be done to ensure that criteria that include the use of biomarkers have been appropriately designed, (3) there is limited standardization of biomarkers from one locale to another, and (4) access to biomarkers is limited to varying degrees in community settings. Presently, the use of biomarkers to enhance
<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Biomarker probability of AD etiology</th>
<th>Aβ (PET or CSF)</th>
<th>Neuronal injury (CSF tau, FDG-PET, structural MRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable AD dementia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Based on clinical criteria</td>
<td>Uninformative</td>
<td>Unavailable, conflicting, or indeterminate</td>
<td>Unavailable, conflicting, or indeterminate</td>
</tr>
<tr>
<td>With three levels of evidence of AD</td>
<td>Intermediate</td>
<td>Unavailable or indeterminate</td>
<td>Positive</td>
</tr>
<tr>
<td>pathophysiological process</td>
<td>Intermediate</td>
<td>Positive</td>
<td>Unavailable or indeterminate</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Possible AD dementia (atypical clinical presentation)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Based on clinical criteria</td>
<td>Uninformative</td>
<td>Unavailable, conflicting, or indeterminate</td>
<td>Unavailable, conflicting, or indeterminate</td>
</tr>
<tr>
<td>With evidence of AD pathophysiological process</td>
<td>High but does not rule out second etiology</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Dementia-unlikely due to AD</td>
<td>Lowest</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer’s disease; Aβ, amyloid-beta; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, $^{18}$fluorodeoxyglucose; MRI, magnetic resonance imaging.
Application of the National Institute on Aging–Alzheimer’s Association AD criteria to ADNI

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ABSTRACT

Objective: We describe the operationalization of the National Institute on Aging–Alzheimer’s Association (NIA-AA) workgroup diagnostic guidelines pertaining to Alzheimer disease (AD) dementia in a large multicenter group of subjects with AD dementia.

Methods: Subjects with AD dementia from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) with at least 1 amyloid biomarker (n = 211) were included in this report. Biomarker data from CSF Aβ42, amyloid PET, fluorodeoxyglucose-PET, and MRI were examined. The biomarker results were assessed on a per-patient basis and the subject categorization as defined in the NIA-AA workgroup guidelines was determined.

Results: When using a requirement that subjects have a positive amyloid biomarker and single neuronal injury marker having an AD pattern, 87% (48% for both neuronal injury biomarkers) of the subjects could be categorized as “high probability” for AD. Amyloid status of the combined Pittsburgh compound B-PET and CSF results showed an amyloid-negative rate of 10% in the AD group. In the ADNI AD group, 5 of 92 subjects fit the category “dementia unlikely due to AD” when at least one neuronal injury marker was negative.

Conclusions: A large proportion of subjects with AD dementia in ADNI may be categorized more definitively as high-probability AD using the proposed biomarker scheme in the NIA-AA criteria. A minority of subjects may be excluded from the diagnosis of AD by using biomarkers in clinically categorized AD subjects. In a well-defined AD dementia population, significant biomarker inconsistency can be seen on a per-patient basis. Neurology® 2013;80:2130–2137
<table>
<thead>
<tr>
<th>Amyloid</th>
<th>FDG</th>
<th>MRI</th>
<th>Count, n (% in total Aβ sample)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aβ+</td>
<td>AD</td>
<td>Abnormal</td>
<td>44 (48)</td>
</tr>
<tr>
<td></td>
<td>AD</td>
<td>Normal</td>
<td>15 (16)</td>
</tr>
<tr>
<td></td>
<td>FTD</td>
<td>Abnormal</td>
<td>1 (1)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>Abnormal</td>
<td>20 (22)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>Normal</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Aβ−</td>
<td>AD</td>
<td>Abnormal</td>
<td>2 (2)</td>
</tr>
<tr>
<td></td>
<td>AD</td>
<td>Normal</td>
<td>1 (1)</td>
</tr>
<tr>
<td></td>
<td>FTD</td>
<td>Abnormal</td>
<td>1 (1)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>Abnormal</td>
<td>2 (2)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>Normal</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Abbreviations: Aβ = β-amyloid; AD = Alzheimer disease; FDG = fluorodeoxyglucose; FTD = frontotemporal dementia.
Comparison of symptomatic and asymptomatic persons with Alzheimer disease neuropathology

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Walter Kukull, PhD

Neurology® 2013;80:2121-2129

Figure: Distribution of B and C scores among asymptomatic and symptomatic subjects with neuropathologic Alzheimer disease.

CERAD = Consortium to Establish a Registry for Alzheimer’s Disease.