EMA-Session 6

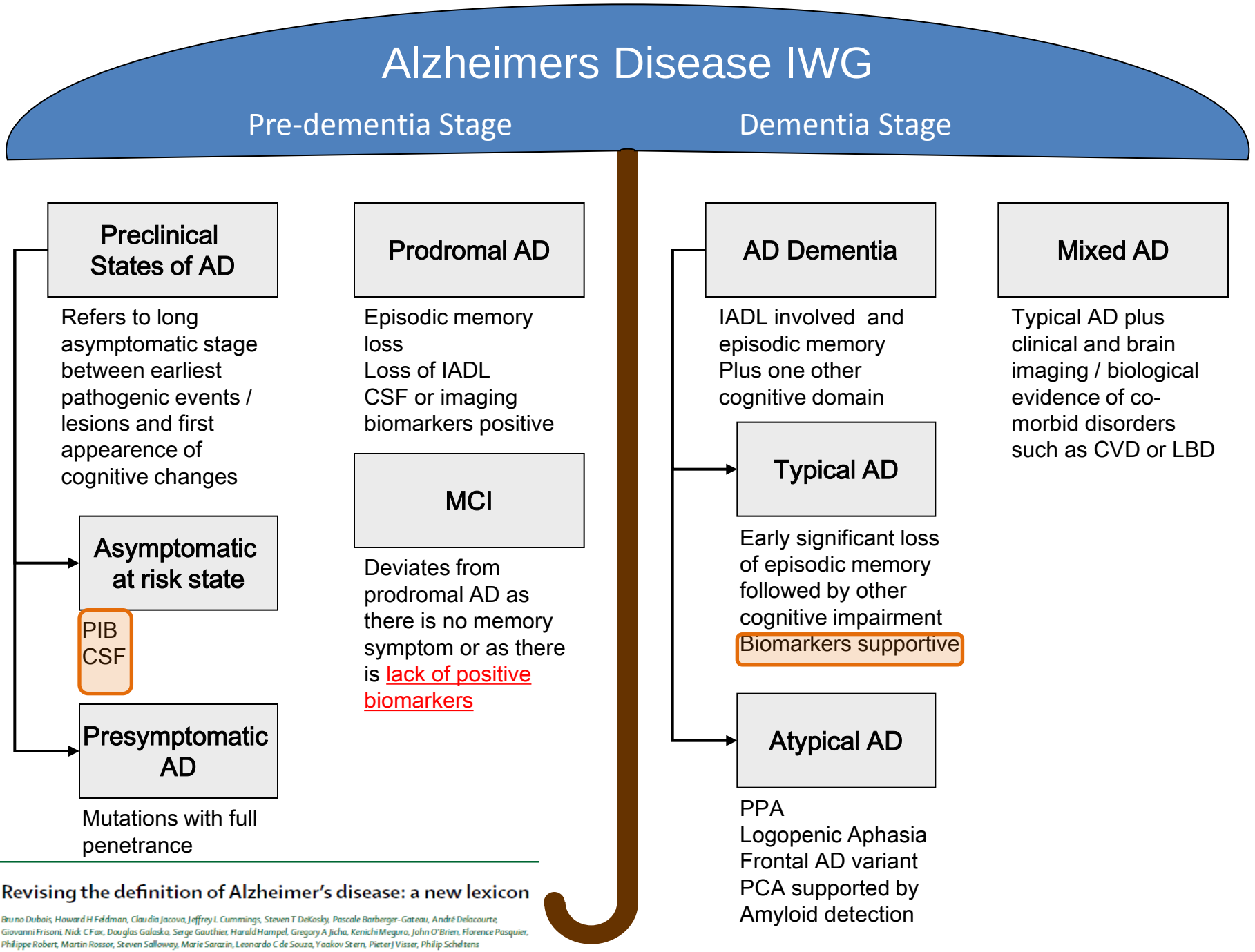
The place for treatments of associated neuropsychiatric and other symptoms

Focus on Challenges of the Clinical Diagnosis of AD

Reinhold Schmidt
Department of Neurology
Medical University Graz, Austria

Declaration of Conflicts of Interest

- I am currently advising Axon Neuroscience in a Tau directed vaccination trial in which I am also the coordinating investigator. I am also advising Avraham Pharmaceuticals in a phase 2 study on ladostigil in mild cognitive impairment, I am also member of an advisory board for Pfizer
- Over the last 5 years I received honoraria for lectures from Novartis,Pfizer,Merz and Takeda


Alzheimers Disease IWG
Pre-dementia Stage
Dementia Stage
Preclinical States of AD
Refers to long asymptomatic stage between earliest pathogenic events / lesions and first appearence of cognitive changes
Asymptomatic at risk state
PIB
CSF
Presymptomatic AD
Mutations with full penetrance
Prodromal AD
Episodic memory loss
Loss of IADL
CSF or imaging biomarkers positive
MCI
Deviates from prodromal AD as there is no memory symptom or as there is lack of positive biomarkers
AD Dementia
IADL involved and episodic memory
Plus one other cognitive domain
Typical AD
Early significant loss of episodic memory followed by other cognitive impairment
Biomarkers supportive
Atypical AD
PPA
Logopenic Aphasia
Frontal AD variant
PCA supported by Amyloid detection
Mixed AD
Typical AD plus clinical and brain imaging / biological evidence of co-morbid disorders such as CVD or LBD
Revising the definition of Alzheimer's disease: a new lexicon
Bruno Dubois, Howard H Feldman, Claudia Jacova, Jeffrey L Cummings, Steven T DeKosky, Pascale Barberger-Gateau, André Delacourte, Giovanni Frisoni, Nick C Fox, Douglas Galasko, Serge Gauthier, Harald Hampel, Gregory A Jicha, Kenichi Meguro, John O'Brien, Florence Pasquier, Philippe Robert, Martin Rossor, Steven Salloway, Marie Sarazin, Leonardo C de Souza, Yaakov Stern, Pieter J Visser, Philip Scheltens

Key elements of the IWG new Lexicon

Dubois B, Feldman H, Jacova C et al. Revising the definition of Alzheimer's disease: a new lexicon. Lancet Neurol 2010; 9: 1118–27

- **The term AD refers only to the clinically expressed disorder that features cognitive, behavioural and neuropsychiatric changes that interfere with daily life. The spectrum of clinically manifest AD is subdivided into predementia and dementia phases**
- **Additional terms are proposed for variations in the clinical phenotype (typical versus atypical AD) or when comorbid disorders with the potential to cause or exacerbate cognitive and neuropsychiatric symptoms are present in an individual who also fulfils diagnostic criteria for AD (mixed AD).**
- **Predementia AD is represented by prodromal AD, with episodic memory impairment that is insufficient to disrupt the performance of accustomed instrumental activities of daily living**
- **Preclinical AD refers to the stage of AD that is not clinically expressed; that is, although the molecular pathology of AD is present in the brain, symptoms are absent. The use of preclinical signifies that this stage can only be detected by AD biomarkers, and not by currently available clinical methods. (Asymptomatic at risk and pre-symptomatic AD)**
- **Future consideration that AD alone might replace prodromal AD and AD dementia so as to unify the symptomatic phase of AD under one diagnostic label is proposed**

ELSEVIER

Alzheimer's & Dementia 7 (2011) 257–262

Alzheimer's & Dementia

Featured Articles

Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease

Clifford R. Jack Jr.[a,*], Marilyn S. Albert[b], David S. Knopman[a], Guy M. McKhann[b], Reisa A. Sperling[c], Maria C. Carrillo[d], Bill Thies[d], Creighton H. Phelps[e]

[a]Department of Radiology, Mayo Clinic, Rochester, MN, USA
[b]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[c]Center for Alzheimer Research and Treatment, Brigham and Women's Hosptial, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[d]Alzheimer's Association, Chicago, IL, USA
[e]Division of Neuroscience, National Institute on Aging, Bethesda, MD, USA

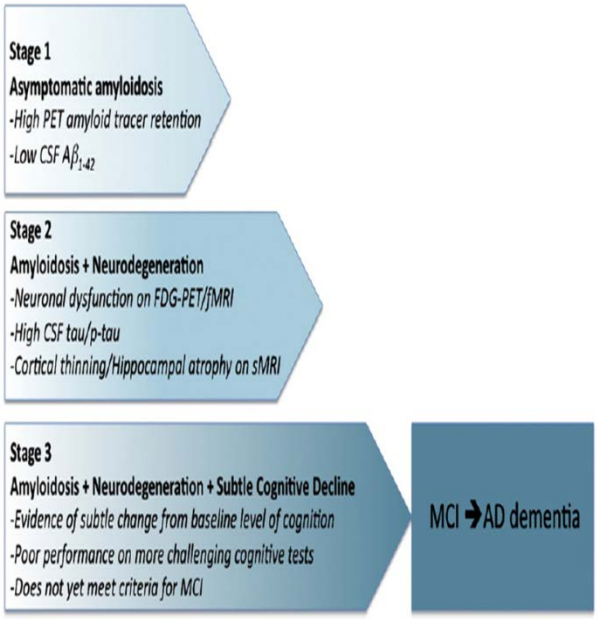
McKhann GM, Knopman DS, Chertkow H et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the national institute on aging and the Alzheimer's association workgroup. Alzheimers Dement 2011; 7:263–9.

Table 1
AD dementia criteria incorporating biomarkers

Diagnostic category	Biomarker probability of AD etiology	Aβ (PET or CSF)	Neuronal injury (CSF tau, FDG-PET, structural MRI)
Probable AD dementia			
Based on clinical criteria	Uninformative	Unavailable, conflicting, or indeterminate	Unavailable, conflicting, or indeterminate
With three levels of evidence of AD pathophysiological process	Intermediate	Unavailable or indeterminate	Positive
	Intermediate	Positive	Unavailable or indeterminate
	High	Positive	Positive
Possible AD dementia (atypical clinical presentation)			
Based on clinical criteria	Uninformative	Unavailable, conflicting, or indeterminate	Unavailable, conflicting, or indeterminate
With evidence of AD pathophysiological process	High but does not rule out second etiology	Positive	Positive
Dementia-unlikely due to AD	Lowest	Negative	Negative

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid-beta; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, ^{18}fluorodeoxyglucose; MRI, magnetic resonance imaging.

**Sperling RA, Aisen PS, Beckett LA et al. 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.
Alzheimers Dement 2011; 7: 280–92**



Key concepts

- ***AD is conceptualized as a continuum in which the initially asymptomatic AD pathophysiological cascade eventually results in symptoms***
- ***Preclinical AD* (Sperling et al., 2011)**
- Establish that AD has a long asymptomatic stage
- Can only be identified with in vivo AD biomarkers
- **AD Dementia (McKhann et al., 2011)**
- Key criteria remain unchanged from the 1984 McKhann et al. criteria for 'probable AD' except now allow nonamnestic presentations of AD dementia
- Identify intra-individual decline in cognition and function as the salient clinical features
- AD biomarkers **may increase the certainty that the basis of the clinical dementia syndrome is the AD pathophysiological process**
- Do not advocate the use of AD biomarker tests **for routine diagnostic purposes** at the present time

Terminology in NIA-AA and IWG Lexicon

- AD dementia refers to dementia caused by the pathophysiology of AD and encompasses the mildest to the most severe *dementia* stages. (AD dementia by IWG)
- Atypical presentations are addressed with the term possible AD dementia. Etiologically mixed presentations refer to the presence of comorbid disorders that could affect cognition when criteria for AD dementia also are met (atypical dementia and mixed AD by IWG)
- MCI due to AD is defined as the symptomatic predementia phase of AD (prodromal AD by IWG)
- Preclinical AD refers to the pathophysiological stage when in vivo molecular biomarkers of AD are present, but symptoms are absent (asymptomatic at risk state by IWG)

Journal of INTERNAL MEDICINE
Click here for more articles from the symposium
doi: 10.1111/joim.12199

Harmonized diagnostic criteria for Alzheimer's disease: recommendations

J. C. Morris[1], K. Blennow[2], L. Froelich[3], A. Nordberg[4], H. Soininen[5,6], G. Waldemar[7], L.-O. Wahlund[8] & B. Dubois[9,10]

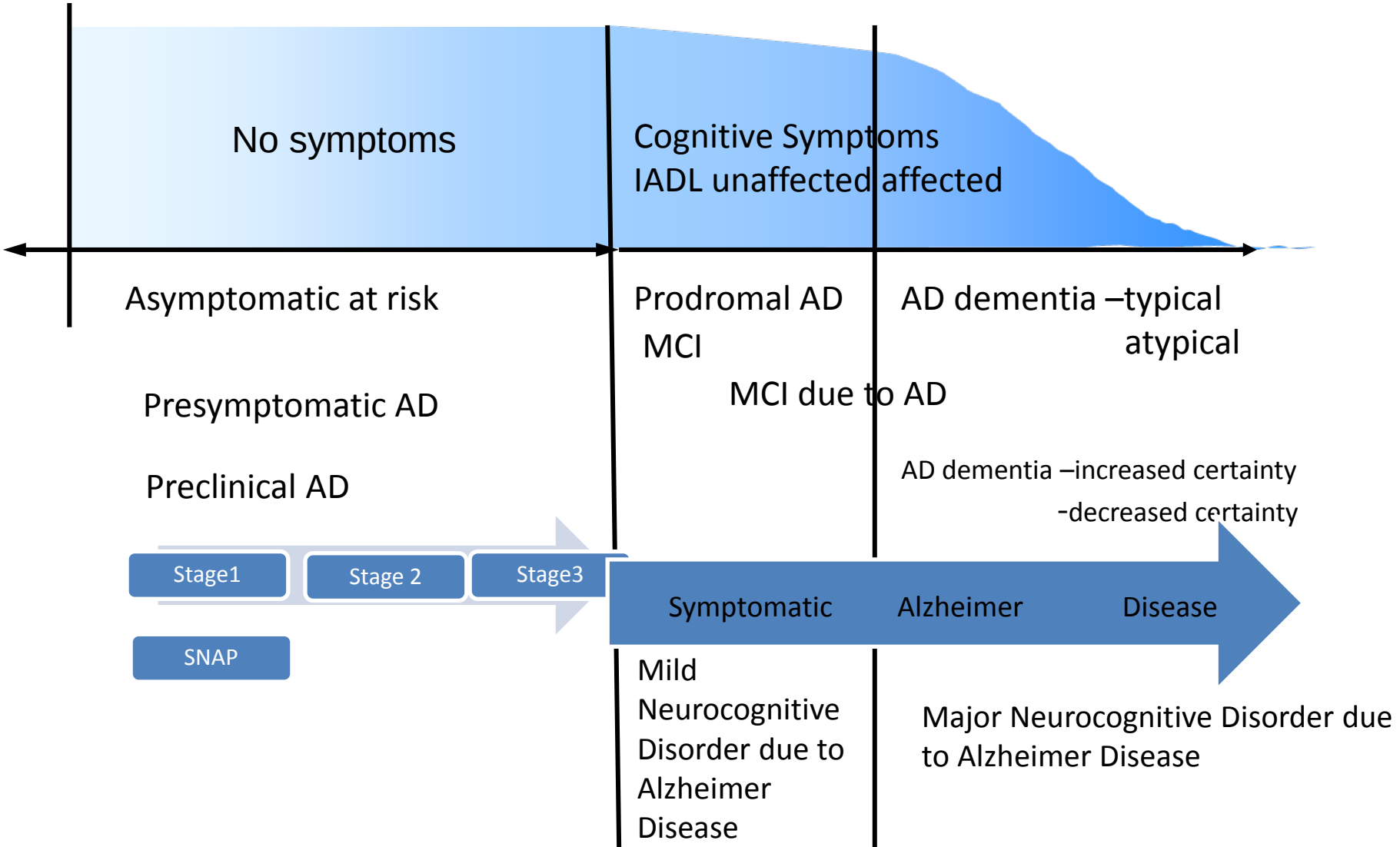
Table 3 *Comparison of international working group criteria and NIA-AA criteria for clinical diagnosis of Alzheimer's disease*

Similarities	
Incorporate biomarkers for AD into the diagnostic process	
Move towards an aetiological diagnosis for MCI	
'Prodromal AD' (IWG)	
'MCI due to AD' (NIA-AA)	
Differences	
IWG	NIA-AA
'AD' refers only to symptomatic stage	'AD' refers to the pathologic process, whether asymptomatic or symptomatic
Replace 'MCI' with 'Prodromal AD'	Retain 'MCI'
Requires objective impairment in memory	Subjective and/or objective impairment in memory and/or nonmemory domains
Biomarker abnormalities required for diagnosis	Biomarker abnormalities support diagnosis but not required

NIA-AA versus DSM-5

Criteria	NIA-AA	DSM-5
Terminology	**AD Dementia**	**Major Neurocognitive Disorder due to AD**
Cognitive Decline from previous level of performance	At least 2 cognitive domains Patient and informant plus quantified mental status examination	At least 2 domains Patient alone sufficient plus quantified mental status examination
Interference with IADL	applies	applies
Delirum or another mental disorder (psychiatric disorder)	excluded	Excluded (or not exclusively in the context of delirium
Insiduous onset and gradual progression	At least two domains amnestic and non-amnestic possible	Memory and learning required
	No evidence of mixed pathology	applies
	MCI due to AD	**Mild Neurocognitive Disorder due to AD**
Level of independence	Preserved - mild problems allowed	Preserved, greater effort, compensatory strategies or accomodation may be needed
Cognitive dysfunction	At least 1 domain, not necessarily memory	At least 1 domain, memory and learning required

Current Terminology



European Journal of Neurology 2010, 17: 1236–1248 doi:10.1111/j.1468-1331.2010.03040.x

EFNS GUIDELINES/CME ARTICLE

EFNS guidelines for the diagnosis and management of Alzheimer's disease

Plus Biomarkers

	Preclinical AD (BM)	Prodromal AD (BM)	MCI due to AD (BM)	Mild Ncog. Dis. due to AD
Clinical history supplemented by an informant	✓	✓	✓	✓
Neurological and physical examination	✓	✓	✓	✓
ADL assessment by informant based questionnaires		✓	✓	✓
Cognitive assessment by general cognitive measure and detailed testing of the main cognitive domains	✓	✓	✓	✓
Assessment of BPSD				
Assessment of co-morbidity		✓	✓	✓
Folic acid, vitamin B12, TSH, calcium, glucose, complete blood cell count, renal and liver function, syphilis, Borrelia and HIV in atpicaö cases or respective clinical features		✓	✓	✓
Multislice CT or coronal MRI		✓	✓	✓
FDG PET and perfusion SPECT are adjuncts				
EEG in atypical cases and when CJD or transient epileptic amnesia is suspected				
CSF analysis is recommended in differential diagnosis for atypical clinical presentations of AD				
Screening for known pathogenic mutations in patients with appropriate phenotype or a family history of an autosomal dominant dementia possible	✓			✓

European Journal of Neurology 2010, 17: 1236–1248
doi:10.1111/j.1468-1331.2010.03040.x

EFNS GUIDELINES/CME ARTICLE

EFNS guidelines for the diagnosis and management of Alzheimer's disease

Plus Biomarkers

	IWG AD (BM supp)	NIA-AA AD core	NIA-AA Certainty BM	Major Ncog. Dis. due to AD
Clinical history supplemented by an informant	✓	✓	✓	✓
Neurological and physical examination	✓	✓	✓	✓
ADL assessment by informant based questionnaires	✓	✓	✓	✓
Cognitive assessment by general cognitive measure and detailed testing of the main cognitive domains	✓	✓	✓	✓
Assessment of BPSD	✓	✓	✓	✓
Assessment of co-morbidity	✓	✓	✓	✓
Folic acid, vitamin B12, TSH, calcium, glucose, complete blood cell count, renal and liver function, syphilis, Borrelia and HIV in atpicaö cases or respective clinical features	✓	✓	✓	✓
Multislice CT or coronal MRI	✓	✓	✓	✓
FDG PET and perfusion SPECT are adjuncts				
EEG in atypical cases and when CJD or transient epileptic amnesia is suspected		✓		✓
CSF analysis is recommended in differential diagnosis for atypical clinical presentations of AD	✓			
Screening for known pathogenic mutations in patients with appropriate phenotype or a family history of an autosomal dominant dementia possible	✓		✓	✓

Conclusions I

- Despite the development of new AD criteria the diagnostic work up of the dementia stage of AD remained widely unchanged, but additional terms are proposed for variations in the clinical phenotype. Biomarker assessment is recommended for research purposes or as supportive evidence for underlying AD pathophysiology in clinical routine
- Various new definitions for prodromal states of AD have now been proposed. They differ in terms of the specification of cognitive domains affected, in the definitions of involvement of IADL and dependency and in the requirements for biomarker assessment. A unifying terminology which uses the term symptomatic AD for all stages of AD with clinical evidence for the disease has also been proposed

Conclusions II

- Definitions of asymptomatic stages of AD rely on biomarker positivity or carrier status of known mutations.
- The validation status of these concepts is low
- This statement is based on the lack of ability to use biomarker data to provide individuals with an accurate prediction of the likelihood of progression to dementia. These limitations reflect, in part, the need to better define the factors that could increase the risk of rapid decline
- More long-term longitudinal data are required and it is likely that they will continue to alter the definitions of biomarker positivity.