An update on Alzheimer disease

Prof Dr Murat Emre
Istanbul Faculty of Medicine
Department of Neurology
muratemre@superonline.com

Disclosures

No relevant disclosures or mention of off-label content

Learning Objectives

- At the end of this talk, the attendees should be informed on the:
  - New diagnostic criteria for dementia and Alzheimer's disease dementia
  - Novel diagnostic methods for Alzheimer disease
  - Current concepts on disease mechanisms

New definition, new diagnostic criteria (NIA-AA; McKhann et al, 2011)

Diagnosis of dementia

There are cognitive or behavioral symptoms that:

1. Interfere with the ability to function at work or at usual activities; and

2. Represent a decline from previous levels of functioning and performing; and

3. Are not explained by delirium or major psychiatric disorder

Diagnosis of dementia

4. Cognitive impairment is detected and diagnosed through a combination of

(1) history-taking from the patient and a knowledgeable informant and

(2) an objective cognitive assessment, a “bedside” mental status examination or neuropsychological testing.

Diagnosis of dementia

5. The cognitive or behavioral impairment involves a **minimum of two** of the following domains:

a. **Impaired ability to acquire and remember new information**
b. **Impaired reasoning and handling of complex tasks, poor judgment**
c. Impaired visuospatial abilities
d. Impaired language functions (speaking, reading, writing)
e. Changes in personality, behavior, or comportment

Probable AD dementia

1. Meets criteria for dementia, and in addition, has the following characteristics:

A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;

B. Clear-cut history of worsening of cognition by report or observation;

C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories.

a. Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain

Probable AD dementia

b. Non-amnestic presentations:

Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present.

Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present.

Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.

Probable AD Dementia

D. The diagnosis of probable AD dementia should not be applied when there is evidence of:

(a) Substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or

(b) core features of DLB other than dementia itself; or

(c) prominent features of behavioral variant frontotemporal dementia; or

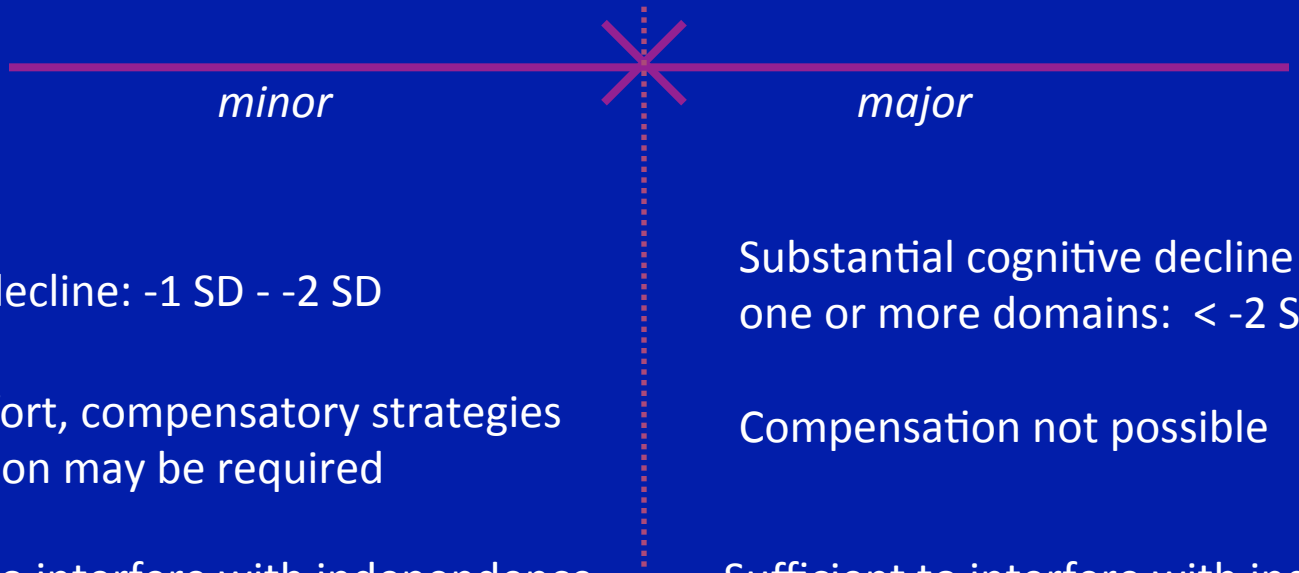
(d) prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or

(e) evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

New diagnostic criteria: DSM

DSM-5 (May 2013)

Minor Neurocognitive Disorder (MCI)
Major Neurocognitive Disorder (Dementia)



New diagnostic methods

Molecular imaging

- Beta-amyloid deposition can be imaged in vivo using PET
- Three compounds ar commercialized: florbetapir, flutemetamol and florbetaben
- Used to estimate beta-amyloid plaque density
- A positive scan does not establish a diagnosis of AD, a negative scan is inconsitent with a pathological diagnosis of AD
- Tau imaging also in development

rs-fcMRI in cognitively normal elderly (Brier et al, 2014)

- Two groups of cognitively normal elderly 1) preclinical AD: AD biomarkers in CSF 2) CSF normal
- In the first group significant interaction between age and deterioration of functional connectivity
- The reported effects of aging on fcMRI are mainly due to preclinical AD

Biomarkers

Diagnosis in CSF

- Beta-amyloid, tau and phospho-tau levels
- **Aβ42 ↓, t-Tau ↑, p-Tau ↑**
- Sensitivity 90%
  - Standardization on-going
- Specificity
  - p-Tau: AD vs FTD %92, AD vs DLB **%68**
  - Mixed dementias?
- In 512 patients 92% correct classification with the CSF profile (Schoonenboom et al, 2012)

A blood based miRNA test for AD

- Next-generation sequencing of miRNAs from blood samples of 48 AD patients and 22 controls
- A total of 140 unique mature miRNAs with significantly changed expression levels.
- A panel of 12 miRNAs selected for further analysis on a larger cohort of 202 samples, comprising AD patients, healthy controls and patients with other CNS illnesses.
- Using this 12-miRNA signature, AD and controls differentiated with an accuracy of 93%, a specificity of 95% and a sensitivity of 92%.
- Differentiation of AD from other neurological diseases with accuracies between 74% and 78%.

Leidinger et al, 2013

Olfactory deficits to predict AD?

- 1,037 participants without dementia evaluated with the 40-item UPSIT. In 757, follow-up at 2 and 4 years
- Lower baseline UPSIT scores associated with cognitive decline, remained significant after including covariates.
- UPSIT, but not Selective Reminding Test predicted cognitive decline in those without baseline cognitive impairment.
- 101 participants transitioned to AD dementia. Lower baseline UPSIT scores associated with transition to AD dementia, highly significant ($p < 0.0001$) after including demographic, cognitive, and functional covariates.

Devanand et al, 2015

New mechanistic concept

Clinical and biomarker changes in ad-AD (Bateman et al, NEJM, July 2012)

- 128 participants; age at baseline and age of disease onset in the parent to calculate the years from expected onset
- A-beta42 in CSF declines 25 years
- Amyloid deposition (PIB-PET) 15 years
- CSF tau increases, atrophy starts 15 years
- Cerebral hypometabolism, impaired episodic memory 10 years
- Global cognitive impiarment (MMSE; CDR) 5 years before expected symptom onset
- Criteria for dementia met 3 years after

New Genetic finding (Jonsson et al, Nature, Aug 2012)

- Coding variants in APP gene studied in whole genome data of 1795 Icelanders
- Those over 85 years with/without AD compared
- A coding mutation (A673T) in APP gene found which protects against AD and age-related cognitive decline
- This mutation results in 40% reduction in the formation of amyloidogenic peptides in vitro
- Rare mutation: 1 in 10 000 in North America
- Proof of principle that reducing beta-cleavage of APP may protect against AD

Biological markers and conversion to dementia

- 73 patients with MCI; CSF Aβ42, cortical metabolism (FDG-PET) and hippocampal volume assessed
- Patients divided into 5 groups: 1) Aβ42− FDG-PET− Hippo−, 2) Aβ42+ FDG-PET− Hippo−, 3) Aβ42 + FDG-PET + Hippo−, 4) Aβ42 + FDG-PET+ Hippo+, and 5) any other combination.
- **In** follow-up, 29 progressed to dementia. Incident dementia increased with greater biological severity in groups 1 to 5 from 4% to 27%, 64%, and 100% (*p* for trend < 0.0001), and occurred increasingly earlier (*p* for trend = 0.024).
- “The core biomarker pattern is in line with the current pathophysiologic model of AD. Fully normal and fully abnormal pattern is associated with exceptional and universal development of dementia”.

Prestia et al 2013

Multi-domaine interventions: FINGER study

- DB, RCT; individuals aged 60-77 years with CAIDE (Cardiovascular Risk Factors, Aging and Dementia) Risk Score of at least 6 points and cognition at mean level or slightly lower
- Randomly assigned to a 2 year multidomain intervention (n=631) (diet, exercise, cognitive training, vascular risk monitoring), or a control group (n=629) (general health advice).
- Estimated mean change in NTB total Z score at 2 years was 0·20 in the intervention group and 0·16 in the control group (p= 0.030)
- A multidomain intervention could improve or maintain cognitive functioning in at-risk elderly people from the general population.

Ngandu et al, 2015

Conclusions

- New definitions, new diagnostic criteria for dementia and AD dementia
- Molecular imaging and CSF biomarkers as diagnostic tools
- Role of amyloid deposition as initial pathophysiological event suggested
- Studies in advanced disease failed, studies in preclinical and early stages on-going

References

- McKhann et al, 2011
- DSM-5, 2013
- Brier et al, 2014
- Sperling et al, 2011
- Bateman et al, NEJM, 2012
- Jonsson et al, 2012
- Prestia et al, 2013
- Dysken et al, 2014
- Devanand et al, 2015
- Ngandu et al, 2015