Is Mild Cognitive Impairment a Useful Concept?

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10th PICAD and the 2nd MeCoND
Thessaloniki, Greece, 04.02.17
The overlap

Ferris et al. 1996

AD, Alzheimer’s disease
MCI, mild cognitive impairment
AAMI, age-associated memory impairment
• The presymptomatic phase of AD is quite long (5-10 years)
• Early interventions may slow the process or prevent the development of dementia
• Who is at risk and what to do about it?
Mild Cognitive Impairment

- Benign senescent forgetfulness (Kral)
- Age-associated memory impairment (AAMI)
- Age-associated cognitive impairment
- Subjective complaints of memory deficit (GDS 2/3)
- Cognitive impairment, not demented (CIND)
- Questionable dementia (CDR 0.5)
- Minimally impaired
- Incipient dementia
- Very mild dementia
- Borderline cases
Mild Cognitive Impairment: Petersen’s diagnostic criteria

• Complaints of memory problems
• Memory performance below age-based reference norms
• Normal performance in other cognitive domains
• Absence of impairment in instrumental and basic activities of daily living
Mild Cognitive Impairment

- Acquired memory complaints
- Persistent complaints
- Objective cognitive impairment
- Normal ADL
- Otherwise normal cognitive findings

Exclude: Depression

- Psychosocial stress
- Drug/alcohol abuse, etc.
What is Mild Cognitive Impairment (MCI)?

- Is MCI a true disease entity?
  - Up to 75% have hippocampal atrophy
  - 70% convert to AD within 5 to 6 years
  - Most have AD pathology at autopsy

- Is MCI a heterogeneous clinical entity?
  - At least 30% never convert to AD
Subtypes of MCI

Several subtypes have been identified:

- Prodromal phase of AD
- Prodromal phase of vascular dementia (VaD)
- Prodromal phase of mixed AD and VaD
- Nonprogressive changes in cognition
  - within limits of normal aging
  - same concept as age-associated memory impairment (AAMI)
- Secondary to treatable causes
# Etiology: Heterogeneity of MCI

<table>
<thead>
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Preludes of dementia

- Memory → AD
- Language → PPA
- Executive → FTD, PD dem
- Praxis → CBGD
- RSBD → DLBD
MCI

- Mental retardation
- Depression
- Anxiety
- Metabolic impairment
- Brain aging

Potentially improving

Stable

Progressing

AD
VaD
Others

Brain aging

MCI

AD
VaD
Others
Is MCI really incipient dementia?

Not always!
White Matter Lesions (WML):

- Cardiovascular risk factors (HT, CAD, CVD) are associated with WML.
- WML are associated with dysfunction of the blood brain barrier, causing plasma components extravasation and brain cells reaction.
- Subcortical WML interact with AD pathology to produce dementia.

Is WML predictive of cognitive decline?
MCI is not a single clinical entity. The term includes many forms, many etiologies, and different rates of evolution. Some people may not progress or even improve.
Conclusions

The presence of unaccounted-for MCI predicts the development of dementia, particularly if associated with gait disturbances. Patients with MCI should be recognized and monitored for cognitive and functional decline due to their increased risk for subsequent dementia.
What can be done?

• Risk factors modification
• Social interaction
• Physical activity
• Cognitive stimulation
• Treatment of coexistent depression
Take home message

• The term MCI is of limited clinical usefulness
• Its diagnosis is arbitrary and it does not have a uniform underlying pathology
• The use of the term as a diagnosis is not productive, except for research purposes
Is MCI really incipient dementia?
Early impairments in AD

- Encoding new episodic memories
- Deficits in attention
- Deficits in semantic memory
- Language difficulties
- Verbal short-term memory impairment

Perry, Watson, Hodges

*Neuropsychologia* 38:252, 2000
Age-associated memory decline

Limited to hippocampal functions:

• Decline in acquisition and retrieval of new information
• No decline in language, abstract reasoning or visuospatial ability

Small et al., Neurology 52:1392,1999
Limitations of the MCI definition

• Based on complaints, which are subjective, depending on personality and psychological state
• Dependence on cognitive tests, which do not include reference to premorbid state
• Lack of consensus about the test used
Heterogeneity of MCI

- Overlap with “worrying-well”
- Overlap with early dementia
## Etiological heterogeneity of MCI

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Can the MCI concept, as heralding AD, be extended to other disorders?
Drugs which may prevent dementia

- Antihypertensive therapy
- Lipid lowering drugs
- Antioxidants
- Folic acid/vitamin B₁₂
- NSAID’s
Cocktail recommendation

Folic acid
Statin

NSAID?
ACE-Inhibitor?
Lifestyle changes

- Smoking cessation
- “Healthy” diet
- Overweight reduction
- Physical activity
- Cognitive activity
- Mild/moderate alcohol use
Several neuropsychological tools

- MMSE
- MoCA
- Addenbrook
  and others
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Dementia Program

Section Heads:
Lefkos Middleton, UK & Magda Tsolaki, Greece
Debates

Debate: Is SNAP a preclinical state of Alzheimer’s disease (AD)?
Host: Lefkos T Middleton, UK
Yes: Kurt Jellinger, Austria
No: Lea Grinberg, USA / Brazil

Proposition: Animal models for AD have led us nowhere.
Host: Magda Tsolaki, Greece
Agree: Marwan N Sabbagh, USA
Disagree: Spiros Georgopoulos, Greece

Debate: Diet and dementia: Still an unsolved issue requiring further nutrient mechanism-based research
Host: Nikolas Scarmeas, Greece
Pro: Roger Bullock, UK
Con: Evangelos Evangelou, UK

Debate: Does cognitive reserve prevent neurodegeneration?
Host: Robert Perneczky, UK
Neuroprotective: Panos Alexopoulos, Greece
Purely symptomatic: Eider Arenaza-Urquijo, USA
Debates

Proposition: GWAS in AD are a waste of time and money
Host: S. Efthimiopoulos, Greece
Yes: George Koutsis, Greece
No: Andreas Papassotiropoulos, Switzerland

Debate: Can sleep measurements tell us about the neuropathology underlying dementia?
Host: Elissaios Karagiorgiou, USA
Yes: Lea Grinberg, USA / Brazil
No: Roger Bullock, UK

Debate: Is mild cognitive impairment (MCI) a useful concept?
Host: Panteleimon Giannakopoulos, Switzerland
Yes: Magda Tzolaki, Greece
No: Morris Freedman, Canada

Debate: Which is the main factor responsible for the reduction of dementia incidence?
Host: Marwan N Sabbagh, USA
Mainly Cardiornascular and diabetes: Ioanna Tzoulaki, UK
Other factors: Evangelos Evangelou, UK
Debates

Are low-risk genes for AD really important?
Cornelia M. van Duijn, Netherlands

The tau connection
Lea Grinberg, USA / Brazil

What can genetics teach us about human memory?
Andreas Papassotriopoulos, Switzerland

Why have we failed to cure AD?
Amos Korczyn, Israel

Nonpharmacological Interventions in dementia
Magda Tsolaki, Greece

Innovative technology for cognitively impaired people
Luiza Spiru, Romania
Dementia Roundtable: Research, Innovation and Social Support In Greece

Dementia prevalence in Greece

- Dementia genetics in Greece: Insights from a large community-based cohort on the island of Crete
- Classic and novel CSF biomarkers in Dementia
- New technologies for supporting patients and caregivers
- Greek National Action Plan for Dementia and Alzheimer's Disease