NEW DEVELOPMENT OF DSM5
NEUROCOGNITIVE DISORDER

--- AN UPDATE ON DSM 5 MINOR
NEUROCOGNITIVE DISORDER

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Outline

- Four major changes for the cognitive disorders in DSM5
- Historical background of MND
- Empirical evidence to establish a diagnosis of MND
- Proposed diagnostic criteria for MND
- Pros and cons
- Conclusions
DSM

- Widely used by practitioners and insurance companies
- Have major social-economical implications
Four major changes for the cognitive disorders

- DSM-IV-TR (delirium, dementia, and amnestic disorders)
- (1) dropping the term “dementia”
- (2) adding a new diagnostic category titled “minor neurocognitive disorder (MND)"
- (3) explicitly categorizing the syndromes of psychosis and depression for Alzheimer’s disease
- (4) provision of assessment techniques for the specific cognitive domains of impairment in great details.
Historical background of MND

- mild cognitive deficits as a variant of normal aging
  - benign senescent forgetfulness (Kral, 1962)
  - age-associated memory impairment (Crook, 1986)
  - age-associated cognitive decline (Levy, 1994)
  - age-related cognitive decline
Historical background of MND

- mild cognitive deficits as a subclinical abnormal state
  - amnestic MCI
  - mild cognitive disorder (ICD-10)
  - mild neurocognitive disorder (DSM-4)
  - cognitive impairment, no dementia
Amnestic MCI-- Petersen’s Criteria

- Subjective memory loss (preferably corroborated by witness)
- Objective memory deficits > 1.5 SD below those of comparable peers
- Normal cognitive function aside from memory (IQ < 0.5 SD of those of the comparable peers)
- Ability to carry out ADLs independently.
- Not demented
FIGURE 1. Conceptual Model of the Cognitive Continuum From Normal Aging to Dementia

Nosological Categories

- AAMI: memory 1 SD below young norms
- MCIa: memory 1.5 SD below peer norms
- AACD: 1 cognitive domain 1 SD below peer norms
- CIND: ≥1 cognitive domain(s) impaired
Empirical evidence to establish a diagnosis of MND

- Clinical, epidemiological, radiological, pathological, and biomarker research data suggesting that such a syndrome is a valid clinical entity with prognostic and potentially therapeutic implications.
<table>
<thead>
<tr>
<th>Patient</th>
<th>C-8</th>
<th>C-2</th>
<th>MCI-2</th>
<th>MCI-10</th>
<th>MCI-4</th>
<th>AD-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVR</td>
<td>1.06</td>
<td>1.64</td>
<td>1.04</td>
<td>1.62</td>
<td>2.59</td>
<td>2.48</td>
</tr>
</tbody>
</table>

**Frontal DVR**
CSF in MCI: \( \uparrow \) tau, \( \downarrow \) \( \beta \)-amyloid

- A combination of CSF T-tau and A42 at baseline yielded a sensitivity of 95% and a specificity of 83% for detection of incipient AD inpatients with MCI
- hazard ratio 17.7

The association between pathological CSF and progression to AD was much stronger than age, sex, education, APOE genotype, and plasma homocysteine.

Hansson et al., 2006
PET in evaluation of dementia

146 patients undergoing evaluation for dementia with at least 2 years' follow-up for disease progression at the University of California, Los Angeles, from 1991 to 2000

138 patients undergoing evaluation for dementia at an international consortium of facilities, with histopathological diagnoses an average of 2.9 years later
PET in evaluation of dementia

- Progressive dementia was detected by PET with a sensitivity of 93% (191/206) and a specificity of 76% (59/78).
- Among 138 patients with neuropathologically based diagnoses, PET identified patients with AD with a sensitivity of 94% and specificities of 73%.
Use of MRI to predict who will get Alzheimer’s disease (Killiany RJ et al. Ann Neurol 2000;47:430-39)

- 79 subjects with mild memory difficulty; follow up 3 yrs
- Hippocampus/ Sup. Temporal area/ Ant. Cingulate
- N > MCI (questionable) > MCI (converter) > AD
- Discriminant functional analysis
- Accuracy between groups: 75-100%
AD Progression

Abnormal

CSF Abeta42

Amyloid Imaging

Pre-Symptomatic
eMCI
LMCI
Dementia

TIME

Function (ADL)
FDG PET
MRI Hippocampal Volume
Cog Perf
CSF Tau

Normal

CSF abeta42
Amyloid Imaging
CSF Tau
FDG PET
MRI Hippocampal Volume
Cognitive Performance
Function (ADL)
MND: proposed diagnostic criteria

- Evidence of modest cognitive decline from a previous level of performance in one or more of the domains (executive ability, learning and memory, language, visuoconstruction, etc)
  - Concerns of the individual, a knowledgeable informant, or the clinician

AND

- A decline in neurocognitive performance on formal testing or equivalent clinical evaluation
  - Typically 1 and 2 standard deviations below appropriate norms (i.e., between the 2.5 and 16 percentile)
cognitive deficits are insufficient to interfere with independence (IADL), but greater effort may be required to maintain independence

Exclude delirium, major mental disorder
Pros

- These conditions are increasingly seen in clinical practice
- Such a syndrome is a valid clinical entity with prognostic and potentially therapeutic implications
- Clinicians have a pressing need for reliable and valid diagnostic criteria in order to assess them and provide services
  - Further investigation of brain function
  - Identification of treatable causes and progressive disorders
  - Appropriate early interventions
    - Current treatment for dementia is inefficacious
Cons

- Criteria have unacceptably high false positive rates (>50 percent?)
Progression and reversion rate

Varied considerably across subtypes and settings

<table>
<thead>
<tr>
<th>Rate of progression to dementia</th>
<th>Rate of reversion to NORMAL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AAMI</strong></td>
<td>9.1%</td>
</tr>
<tr>
<td><strong>AACD</strong></td>
<td>29%</td>
</tr>
<tr>
<td><strong>aMCI</strong></td>
<td>10-15%</td>
</tr>
<tr>
<td></td>
<td>80%</td>
</tr>
<tr>
<td><strong>CIND</strong></td>
<td>45%</td>
</tr>
<tr>
<td>AAMI</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>~34.5%</td>
</tr>
<tr>
<td>aMCI</td>
<td>&gt;40%</td>
</tr>
<tr>
<td></td>
<td>4-8%</td>
</tr>
</tbody>
</table>
Cons

- Criteria have unacceptably high false positive rates (>50 percent?)
  - Not include biological markers
  - Why scare half the people with false positive?
- No effective treatment even for those who are true positives
- Accurate biological tests are within reach
  - Although need to establish standardized procedure and cutoff point
Similar examples

- DSM5 dropped 2 proposed diagnoses
  - attenuated psychosis syndrome
  - mixed anxiety depressive disorder
- these diagnoses may lead to unnecessary overprescription of drugs for many subjects who have the diagnosis but never develop into major mental illness
The diagnosis of mild cognitive impairment due to Alzheimer’s disease: Recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease

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

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Institute of Memory and Alzheimer’s Disease, INSERM Unit Cognition, Neuro-imagerie et maladies du Cerveau, Groupe Hospitalier Pitie-Salpetriere, Paris, France
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
Mild cognitive impairment due to AD

- **MCI due to AD (high likelihood)**
  - Positive A-beta biomarker (amyloid imaging/CSF) and
  - Positive biomarkers for neuronal injury (MRI, FDG PET, CSF tau)

- **MCI due to AD (intermediate likelihood)**
  - Positive A-beta biomarker (amyloid imaging/CSF) or
  - Positive biomarkers for neuronal injury (MRI, FDG PET, CSF tau)

- **MCI unlikely due to AD**
  - All biomarkers negative
Conclusions

- MND has been proposed as a clinical diagnosis
- It is with relatively stringent clinical criteria, but without criteria based on biological markers
- False positive rate can not be overlooked
  - Potential harm should be considered
- No effective treatment for most MNDs
- Facilitate clinical awareness? Research? Futile pharmacological treatment?
Thank you.