Alzheimer's Disease
An update on diagnostic criteria
&
Neuropsychiatric symptoms
State of the art lecture
March 4 - 2012

Philippe Robert

- The diagnosis of AD
- Neuropsychiatric symptoms
- Place of the ICT

Diagnosis Starting points

<table>
<thead>
<tr>
<th>Diagnosis criteria for AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>The NINCDS-ADRDA criteria</td>
</tr>
</tbody>
</table>

The rules
1. The diagnosis of AD cannot be certified clinically and needs a post-mortem confirmation to be ascertained.
2. The diagnosis of AD can only be 'probable'.
3. The diagnosis of AD can only be made when the disease is advanced and reaches the threshold of dementia.
Rethinking the diagnosis of degenerative and vascular cases

New starting point

IWG & NIA AA

- International Working group for New Research Criteria for the diagnosis of AD
  *Lancet N, 2007, 2010*

- National Institute on Aging and Alzheimer’s Association Workgroup
  *Alzheimer’s & Dementia, 2011 (4)*
Research criteria for the diagnosis of Alzheimer’s disease: revising the NINCDS-ADRDA criteria

1 major clinical criterion

A. Amnestic syndrome of the ‘hippocampal type’ (that can be isolated or associated to other cognitive / behavioral changes)

+ 1 or more biomarker present

B. Structural: atrophy of medial temporal lobe (MRI)

C. Biological: changes in biomarkers (CSF)

D. Functional/molecular: neuro-imaging pattern/amyloid ligand retention on PET

FCSRT (cued recall measures) is the best predictor of AD pathology

<table>
<thead>
<tr>
<th>memory measures</th>
<th>CSF (+)</th>
<th>CSF (-)</th>
<th>effect size (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCSRT Total Recall</td>
<td>13.4</td>
<td>15.4</td>
<td>0.97</td>
</tr>
<tr>
<td>Logical Memory Delayed Recall</td>
<td>8.1</td>
<td>13.5</td>
<td>0.74</td>
</tr>
<tr>
<td>CERAD verbal Delayed recall</td>
<td>4.2</td>
<td>5.6</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Wagner M et al, Neurology 2012
Biomarkers Enable Specificity Even at the Prodromal Stage of AD

<table>
<thead>
<tr>
<th></th>
<th>Memory</th>
<th>CSF</th>
<th>MRI</th>
<th>PET-FDG</th>
<th>PET-ligand</th>
</tr>
</thead>
<tbody>
<tr>
<td>NINCDS - ADRDA</td>
<td>Not specified</td>
<td>Exclusion</td>
<td>Exclusion</td>
<td>Not specified</td>
<td>Not known</td>
</tr>
</tbody>
</table>

| Specificity for Prodromal AD | >90% Sarazin 2007 | >90% Hansson 2006 | >85% Colliot 2008 | >80% Mosconi 2004 | >95% Rowe 2007 |


International Working group for New Research Criteria for the diagnosis of AD

- Preclinical states
  - Asymptomatic at-risk state for AD
  - Presymptomatic AD

Prodromal AD

AD dementia

Typical

Atypical

Mixed

National Institute on Aging and Alzheimer’s Association Workgroup

Introduction to the recommendations from the National Institute on Aging and the Alzheimer’s Association for revised research criteria for Alzheimer’s disease.

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

Toward defining the preclinical stages of Alzheimer’s disease: Recommendations from the National Institute on Aging and the Alzheimer’s Association workgroup.

Alzheimer’s Disease

- Alzheimer’s Disease
- AD
- Dementia
From a clinico-pathological entity...

The rules

1) The diagnosis of AD cannot be certified clinically and needs a post-mortem confirmation to be ascertained.
2) The diagnosis of AD can only be 'probable'.
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... to a clinico-biological entity

The new rules

As biomarkers can be considered as surrogate markers of the histopathological changes, → the clinical diagnosis can be established in vivo → and no more reference to dementia is needed.
Discussion

National Institute on Aging and Alzheimer’s Association Workgroup
International Working group for New Research Criteria for the diagnosis of AD

Better assessment needed about soft functional signs

2.1.3. Preservation of independence in functional abilities
Persons with MCI commonly have mild problems performing complex functional tasks which they used to perform

Functional Impairment in Elderly Patients With Mild Cognitive Impairment and Mild Alzheimer Disease

Discussion

National Institute on Aging and Alzheimer’s Association Workgroup
International Working group for New Research Criteria for the diagnosis of AD

What about neuropsychiatric symptoms?

Teng A et al. Neuropsychiatric symptoms are associated with progression from mild cognitive impairment to AD. Dementia, 2007
Vicini Chilovi B. et al. Differential impact of apathy and depression in the development of dementia in mild cognitive impairment patients. Dementia, 2009
Ramakers & al. Affective symptoms as predictors of AD in subjects with MCI. Psychol Med 2010

The diagnosis of AD
Neuropsychiatric symptoms
Place of the ICT
ICTUS
A longitudinal observational study of AD patients

- Delusions
- Hallucinations
- Agitation
- Depression
- Anxiety
- Euphoria
- Apathy
- Disinhibition
- Irritability
- Aberrant motor behaviour
- Sleep problems
- Eating problems

NPI domain score >4
Range 0–12 for each domain

Reynish et al. Neurology, 2007
Robert et al. JNHA, 2007

PHRC PREAL: 245 Amnestic MCI
Conversion MCI → MA at 3 years n = 59 (27.6%)

Lack of interest

Conversion MCI → MA at 2 years

24% for MCI without depression & apathy
8% for MCI with depression
19% for MCI with depression & apathy
60% for MCI with apathy

Chilovi & al, Dementia, 2009

Recommendations for the analysis of NPI scores
1. Single MCI: if present at the start of treatment, should be reassessed for improvement
2. Single MCI later, single or sequential in a group patient population or showing response to an intervention, may help define the symptoms most responsive to a given treatment or management.
3. The NPI-C: A Clinician-Rated Assessment of Neuropsychiatric Symptoms in Dementia

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The diagnosis of AD
- Place of Neuropsychiatric symptoms
- Place of the ICT

Original article
Proposed diagnostic criteria for apathy in Alzheimer’s disease and other neuropsychiatric disorders


Loss of or diminished motivation in comparison to the patient’s previous level of functioning and which is not consistent with his age or culture. These changes in motivation may be reported by the patient himself or by the observations of others.
Ambulatory actigraphy correlates with apathy in mild AD

- Locomotor activity was assessed using a wrist-worn actigraph for 75 minutes, during which a neuropsychological and behavioral examination were performed (60 minutes) followed by 15 minutes of free activity.

Day time activity with & without Apathy - 7 days

- AD - No Apathy
- AD - Apathy

Cognitive symptoms
- Memory
- Language
- Attention
- Apraxia

ASSESSMENT

NeuroPsychiatric Symptoms
- Agitation
- Psychotic symptoms
- Apathy
- Depression

Loss of Autonomy in Activities of Daily Living

Controls (N=15)

AD with apathy (N=17)

AD without apathy (N=15)

- Sex ratio (M/F)
  - Controls: 0.60 ± 0.51
  - AD with apathy: 0.29 ± 0.47
  - AD without apathy: 0.27 ± 0.46

- Age (yrs)
  - Controls: 73.13 ± 6.01
  - AD with apathy: 78.65 ± 7.36
  - AD without apathy: 80.20 ± 4.96

- MMSE
  - Controls: 30.00 ± 0.00
  - AD with apathy: 22.59 ± 2.72
  - AD without apathy: 20.40 ± 3.16

- MADRS
  - Controls: 3.33 ± 3.08
  - AD with apathy: 5.29 ± 4.48
  - AD without apathy: 4.73 ± 4.93
**SWEET-Home project**

- ANR TecSan – 2009 program
- Nice CMRR
- INRIA Pulsar
- CNRS MICA center
- LinCare Service

**Aims to build an innovative framework for modeling behavior and activities of daily living of patient presenting AD and whether they are involved in goal directed behaviors.**

**A place for Behavioral assessment**

- Set up the 2 video cameras according to the activities planned during the video tape recording.
- Give global explanations of the session and have the participant sign the informed consent (Cf. information review, informed consent).
- Fix on the actigraphs (MotionPod®, Actiwatch®, MotionLogger®) and explain the participant the video tape recording script including the activities list and their achievement order.
- For the equipment calibration, the participant will be asked to stand still for 10 seconds.

**Scenario**

- **Step A (directed activities):**
- **Step B (semi directed activities):**
- **Step C (free activities):**
Vision component

Vision component (detection, classification, tracking): detect the person in the scene and to track his different movements over time.

Semi directed activities

<table>
<thead>
<tr>
<th>Activity</th>
<th>Right order</th>
<th>Error of order</th>
<th>Omission</th>
<th>Speed of execution (s/act)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. read</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. warm water</td>
<td>✔</td>
<td></td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>3. compose phone number X</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Plant watering</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Turn on TV</td>
<td>✔</td>
<td></td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>6. Play card</td>
<td>✔</td>
<td></td>
<td>1.06</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
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<tr>
<td>1. read</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. warm water</td>
<td>✔</td>
<td></td>
<td>1.16</td>
<td></td>
</tr>
<tr>
<td>3. compose phone number X</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Plant watering</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Turn on TV</td>
<td>✔</td>
<td></td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>6. Play card</td>
<td>✔</td>
<td></td>
<td>3.24</td>
<td></td>
</tr>
</tbody>
</table>

V 3 - Control activity

<table>
<thead>
<tr>
<th>Activity</th>
<th>Right order</th>
<th>Error of order</th>
<th>Omission</th>
<th>Speed of execution (s/act)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. read</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. warm water</td>
<td>✔</td>
<td></td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>3. compose phone number X</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Plant watering</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Turn on TV</td>
<td>✔</td>
<td></td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>6. Play card</td>
<td>✔</td>
<td></td>
<td>0.05</td>
<td></td>
</tr>
</tbody>
</table>

Development of the index of efficacy:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control subjects (N=30)</th>
<th>All-elderly patients (N=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of efficacy error (X±S)</td>
<td>8.73 [6.08, 8.74]</td>
<td>9.51 [7.96, 8.08]</td>
</tr>
<tr>
<td>Omission of at least one activity, N(%)</td>
<td>8.05%</td>
<td>4.52%</td>
</tr>
<tr>
<td>Repetition of at least one activity, N(%)</td>
<td>8.94%</td>
<td>6.17%</td>
</tr>
<tr>
<td>Incorrect order, N(%)</td>
<td>9.05%</td>
<td>4.20%</td>
</tr>
<tr>
<td>Not least one failure to complete one activity of the first time, N(%)</td>
<td>1.14%</td>
<td>7.48%</td>
</tr>
</tbody>
</table>

Time spent doing activities / total time in the room

Adjusted by coefficient K

Omission
Repetition
Incorrect order
Failure to complete one activity
## Functional impairment score:

<table>
<thead>
<tr>
<th>Measure</th>
<th>Test population (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMSLE vs.</td>
<td></td>
</tr>
<tr>
<td>1) Index = Ratio of effect</td>
<td>0.51 (p)</td>
</tr>
<tr>
<td>2) Index = Ratio of effect log10</td>
<td>0.78 (p)</td>
</tr>
<tr>
<td>3) Index = Ratio of effect log10 log10</td>
<td>0.60 (p)</td>
</tr>
<tr>
<td>4) Index = Ratio of effect log10 log10 log10</td>
<td>0.77 (p)</td>
</tr>
<tr>
<td>5) Functional Impairment Score = f (a, b, c, x, y)</td>
<td>0.81 (p)</td>
</tr>
</tbody>
</table>

| NMSLE-F vs. |                         |
| 1) Index = Ratio of effect | 0.53 (p) |
| 2) Index = Ratio of effect log10 | 0.64 (p) |
| 3) Index = Ratio of effect log10 log10 | 0.68 (p) |
| 4) Index = Ratio of effect log10 log10 log10 | 0.45 (p) |
| 5) Functional Impairment Score = f (a, b, c, x, y) | 0.66 (p) |

*Significance levels (p < 0.05) and the correlation coefficient.*

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## The importance of non-pharmacological approaches

**INTervention**

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“What are you interested in?” A survey on 601 Nursing Homes Residents activities interests

A total of 601 residents from 19 nursing homes have completed the survey from March to May 2011
- F = 484
- Mean age =85.9

Enjoying a good meal (83%)
Dressing up (75.9%)
Watching TV (75.5%)

Summary

- New paradigm for the diagnosis
- Neuropsychiatric symptoms as core features
- ICT, opportunity for better assessment and treatment