Neuro-Imaging in dementia:
using MRI in routine work-up

Prof. Philip Scheltens
Alzheimer Center
VU University Medical Center
Amsterdam
The Netherlands

Outline of talk

• Current guidelines
• Imaging used to exclude disease
• Specific patterns in disease
  ▪ Medial temporal lobe atrophy in AD
• Prediction of AD in MCI patients
• Summary
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Practical recommendations:
- Cerebral atrophy is a key element in the routine work-up of patients with dementia
- Volumetric MR or CT measurement strategies for the diagnosis of AD and are not recommended for routine use at this time
- PET imaging is not recommended for routine use in the diagnostic evaluation of dementia at this time

Table 1: Potentially reversible primary pathologies for cognitive symptoms in 1000 memory clinic patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients with potentially reversible cause (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td>25</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>10</td>
</tr>
<tr>
<td>Alcohol</td>
<td>5</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>6</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6</td>
</tr>
<tr>
<td>Parkinson</td>
<td>5</td>
</tr>
<tr>
<td>Depression</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 2: Potentially reversible secondary pathologies for cognitive symptoms in 1000 memory clinic patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients with potentially reversible cause (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism</td>
<td>6</td>
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<td>Diabetes</td>
<td>5</td>
</tr>
<tr>
<td>Depression</td>
<td>4</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>3</td>
</tr>
<tr>
<td>Alcohol</td>
<td>2</td>
</tr>
<tr>
<td>Vascular</td>
<td>1</td>
</tr>
</tbody>
</table>

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The decreasing prevalence of reversible dementias

- Updated meta-analysis
- 39 studies; 7042 patients
- 2.2% 'required neuroimaging'
- Potentially reversible causes in 9%
- 0.6% actually reversed

Clarfield, Arch Intern Med 2003

“Treatable Cause” (?)
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“Treatable causes” with imaging

- Low yield:
  - Farina (1999): 7.2%, but none that had not been discovered clinically
  - Chui (1997): 5% clinically significant, undetected lesion
  - Foster (1999): scanning each patient <65 y, and treating only subdural hematomas cost-effective
  - Waldemar (2003): 4% (1% tumours, 3% hydrocephalus) in demented patients

The ‘exclusionary’ approach to dementia

- Has ended
- Was based on concept of “most dementias are AD”
- AD being non treatable
- No need for early detection
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The ‘inclusionary’ approach

- Has entered the clinic
- Based on ‘new’ concepts such as
  - Wider availability of MRI
  - Early detection
  - Mixed cases, specific therapy directed at AD component
  - Insights into treatment of vascular risk factors
  - Recognition of MCI as risk state
  - Increasing prevalence of younger cases (AD, FTD)
  - Increasing demands of carers for certainty

Changing indications for imaging

- Neuroimaging at least once during work-up
- Changing attitude in era of medically treatable disease
- Rule out surgically treatable cause (rare!)
  - Subdural hematoma, mass lesion, hydrocephalus
  - Exclusionary approach (CT era)
- Demonstrate specific pathology
  - E.g. MTA in AD, focal atrophy in FTD, ischemia in VaD, concomitant vascular disease
- Possibilities to monitor disease
- Standard protocol

Basic MRI protocol

- Coronal 3D MP-RAGE 8'
  - 1.5 mm slices, 148 partitions, 1 mm pixels
- Axial FLAIR 4'
  - 5 mm slices, inferior sat, 1 mm pixels
- Axial / coronal T2 TSE 512 7'
  - 4 mm slices, turbofactor 15, 0.5 mm pixels
- Axial T2* gradient-echo 4'
  - 5 mm slices, TE=22 ms, 1 mm pixels
- Total examination time (incl. scouts) ~ 12’ / 25’
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The spectrum of FTLD

FTD  SD
PA

The need to look at all slices....

Subcortical vascular cognitive impairment
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Caveat
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Alzheimer’s disease: Braak stages

Hippocampal volume as an index of Alzheimer neuropathology
Findings from the Nun Study
K.M. Gela, PhD, J.A. Bertiniot, PhD, C.D. Smith, MD, W.B. Markesbery, MD, and D.A. Sadow, PhD
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The ‘fingerprint’ of AD

MTL atrophy: visual rating

- Widening of choroidal fissure
  - Distance MTL to brainstem not relevant
- Loss of height of hippocampus/MTL
- Widening of temporal horn
  - Pitfall:hydrocephalus, atrophy BG
- Widening of (collateral) sulcus


Visual rating of MTA

<table>
<thead>
<tr>
<th>Score</th>
<th>Width of choroid fissure</th>
<th>Width of temporal horn</th>
<th>Height of hippocampus</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>1</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>2</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↓↓</td>
</tr>
<tr>
<td>3</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↓↓↓</td>
</tr>
</tbody>
</table>


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Visual rating of MTA
Examples

Visual rating of MTA
Reliability
- Scheltens et al. 1995
  - 4 raters (1 radiologist)
  - 2 sessions
  - templates
  - mean inter-rater reliability: 0.50
  - mean intra-rater reliability: 0.70
- De Carli et al.
  - 4 raters (neurologists, 2 US, 2 EU)
  - inter-rater against 1 (PhS): 0.60-0.70

Correlation between visually and volumetrically estimated MTA

<table>
<thead>
<tr>
<th>Visual MTA</th>
<th>N Left MTL</th>
<th>p</th>
<th>N Right MTL</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>139</td>
<td>6.48±0.07</td>
<td>&lt;0.0000</td>
<td>141</td>
</tr>
<tr>
<td>1</td>
<td>55</td>
<td>5.63±0.12</td>
<td></td>
<td>53</td>
</tr>
</tbody>
</table>

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Correlation with pathology

- VANTAA 85+ study
- 145 postmortem MRI’s; digitally stored
- 94 demented
- Rated in coronal slices 0-4
- Pathology done independently CERAD + NIA-RIA
- MTA 0-1: 1/94 demented
- MTA 2-8: 93/94 demented
- Highest MTA scores in HS and high probability AD

Bankhof et al. unpublished data.

Assessment MTL atrophy: Qualitative rating

Volumetry of MTA

Volumetry on coronal MRI scan at level head of hippocampus

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Diagnostic value of MTA
AD vs. ND (n=107)

<table>
<thead>
<tr>
<th></th>
<th>MMSE</th>
<th>VOLUME</th>
<th>VISUAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>76 (65-84)</td>
<td>78 (70-86)</td>
<td>90 (84-96)</td>
</tr>
<tr>
<td>Specificity</td>
<td>85 (78-92)</td>
<td>91 (86-96)</td>
<td>98 (100-96)</td>
</tr>
<tr>
<td>+LR</td>
<td>8.7</td>
<td>98</td>
<td></td>
</tr>
</tbody>
</table>

Wahlund et al. JNNP 2000;69:630-635

Diagnostic value of MTA in AD vs. C

- Visual rating: all studies: sensitivity 85%, specificity 88%
- Fulfills NIA-Reagan criteria for biological marker
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MTA assessment in routine practice

- Feasible and reliable
- Sensitive to AD
- Specific to normal aging
- Non-specific to other dementias (?)
- Early marker in MCI?

Medial temporal lobe atrophy on MRI in dementia with Lewy bodies and VaD, Barber R, Gholkar A, Scheltens P, Ballard C, McKeith IG, O'Brien JT. Neurology 1999;52:1153-1158

Subjects
n=104
> 60 years
DSMIV dementia

DLB
n=26
age = 76
MMSE* = 13.5

AD
n=28
age = 77
MMSE = 15.4

VaD
n=24
age = 77
MMSE* = 18.0

Normal controls
n=26
age = 76
MMSE = 28.1

Medial temporal lobe atrophy on MRI in dementia with Lewy bodies and VaD, Barber R, Gholkar A, Scheltens P, Ballard C, McKeith IG, O'Brien JT. Neurology 1999;52:1153-1158

Present Absent

<table>
<thead>
<tr>
<th></th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD (n=28)</td>
<td>100%</td>
<td>-</td>
</tr>
<tr>
<td>VaD (n=24)</td>
<td>87%</td>
<td>13%</td>
</tr>
<tr>
<td>DLB (n=26)</td>
<td>62%</td>
<td>38%</td>
</tr>
<tr>
<td>CTR (n=26)</td>
<td>4%</td>
<td>96%</td>
</tr>
</tbody>
</table>
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MRI volumetric study of dementia with
Lewy bodies
A comparison with AD and vascular dementia

Table 1: Difference between subjects with DLB and other dementia subtypes

<table>
<thead>
<tr>
<th>Region of interest</th>
<th>DLB</th>
<th>AD</th>
<th>% SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole brain</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Ventricles</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Frontal lobes</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Temporal lobes</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = no significant volume difference
$\textit{p}$ = significance level

Temporal lobe atrophy on MRI in Parkinson disease with dementia
A comparison with Alzheimer disease and dementia with Lewy bodies

Table 1: Medial temporal lobe atrophy on MRI

<table>
<thead>
<tr>
<th>Medial temporal lobe atrophy</th>
<th>Controls</th>
<th>PD</th>
<th>PD+</th>
<th>DLB</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>1.46 ± 1.49</td>
<td>1.89 ± 0.49</td>
<td>2.03 ± 0.06</td>
<td>2.06 ± 0.06</td>
<td>2.08 ± 0.06</td>
</tr>
<tr>
<td>Left</td>
<td>1.18 ± 0.56</td>
<td>1.65 ± 0.06</td>
<td>2.20 ± 0.75</td>
<td>2.05 ± 0.52</td>
<td>2.08 ± 0.48</td>
</tr>
</tbody>
</table>

Values are means ± SD
*p* < 0.05, PD, DLB, AD, post hoc Bonferroni T test.
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Karas, Scheltens, Barkhof, Rombouts, submitted.

MTA in MCI

Medial temporal lobe atrophy
and memory dysfunction
as predictors for dementia in subjects
with mild cognitive impairment

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Table 3: Logistic regression analysis of clinical outcome

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Estimate</th>
<th>Std. Error</th>
<th>Wald</th>
<th>df</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.07</td>
<td>0.04</td>
<td>4.85</td>
<td>1</td>
<td>0.03</td>
</tr>
<tr>
<td>Education</td>
<td>0.05</td>
<td>0.03</td>
<td>4.03</td>
<td>1</td>
<td>0.05</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.12</td>
<td>0.07</td>
<td>4.32</td>
<td>1</td>
<td>0.04</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.08</td>
<td>0.05</td>
<td>4.03</td>
<td>1</td>
<td>0.04</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.10</td>
<td>0.06</td>
<td>4.80</td>
<td>1</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Figure 1. Medial temporal lobe atrophy on MRI predicts dementia in patients with mild cognitive impairment.

Table 4: Congruence correlation analysis

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Correlation coefficient</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTA</td>
<td>0.45</td>
<td>0.01</td>
</tr>
<tr>
<td>MTA</td>
<td>0.48</td>
<td>0.001</td>
</tr>
<tr>
<td>MTA</td>
<td>0.50</td>
<td>0.001</td>
</tr>
</tbody>
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Conclusions

• The work up of dementia has changed and will continue to change depending on changing insights and changing attitudes towards dementia

• MRI needed, not to exclude, but to diagnose (AD) and help differentiating from other dementias and for early detection

• Standard protocol required!