AD Statistics

5,200,000
Associated Costs: $148 Billion

- Medicare: $91 billion
- Medicaid: $36.5 billion
- Indirect Costs: $21 billion

Epidemiology of AD

- Accounts for 60-70% of cases of progressive cognitive impairment
- Prevalence of AD doubles approximately every 5 years after age 60
- Prevalence of 1% among those aged 60-64 years, up to 40% among those age 85+
- Given aging of global population, if effective treatment of AD is not identified, population of AD patients will quadruple in next 50 years
Projected Outcomes

Criteria for Diagnosis of Probable Alzheimer’s Disease (NINCDS-ADRDA)

- Dementia established by clinical examination
- Deficit in 2+ areas of cognition (memory required) of at least 12 months in duration
- Gradual onset and progression
- Absence of other systemic disorder or brain disease that can account for the cognitive deficits
Amyloid Plaques and Neurofibrillary Tangles
The Amyloid Cascade

APP

β-secretase

β-APP

γ-secretase

Aβ

monomer

oligomer

plaque
Neurofibrillary Tangles

Tau bound to microtubule

Microtubule

Hyperphosphorylated tau subunits

PHF composed of tau subunits
Tau Destabilization
Mild Cognitive Impairment

- Normal
- Declining Cognition
- Dementia
- Treatment

Time
Mild Cognitive Impairment

- Normal
- MCI
- Dementia

Declining Cognition over Time

Treatment
Mild Cognitive Impairment

Secondary Prevention:
MCI=>/=AD

Time

Normal

Declining Cognition

Dementia

Treatment

MCI

Treated
Petersen’s Criteria for Mild Cognitive Impairment (MCI)\(^1\)

- Memory concerns, preferably corroborated by a reliable informant
- Cognitive performance significantly worse than same age- and education-matched peers on objective testing
- Normal activities of daily living
- Normal global cognitive function
- Not demented

\(^1\)Petersen et al. *Arch Neurol*, 1999
• Most individuals with amnestic MCI will progress to AD at a rate of 10-15% per year compared with healthy controls who convert at 1-2% per year.

• Conversion to AD of up to 80% over approximately 6 years.
Problems with MCI Diagnosis

- Lack of operational definition
- High reversion rates, depending on study
- Many do not develop AD
- Need to identify who benefit most from treatment
DuBois Criteria: Preclinical AD

- Gradual progressive change in memory >6 months
- Objective evidence of impaired memory on testing
- Memory impairment can be isolated or associated with additional cognitive changes
- Biological Marker associated with AD

Biomarkers Associated with AD

**Structural Neuroimaging (CT, MRI)**
- Hippocampal atrophy
- Changes in entorhinal cortex may enhance sensitivity of early diagnosis

**Functional Neuroimaging (PET, SPECT)**
- Early metabolic deficits in temporoparietal regions
- Greater impairment in posterior cingulate gyrus for MCI patients who convert to AD

**CSF markers**
- Low amyloid beta$_{1-42}$
- Increased total tau or phospho-tau
CSF Biomarker

Cerebrospinal fluid (CSF) is a clear fluid that circulates in the space surrounding the spinal cord and brain. CSF protects the brain and spinal cord from injury by acting like a liquid cushion. CSF is usually obtained through a lumbar puncture (spinal tap). During the procedure, a needle is inserted usually between the 3rd and 4th lumbar vertebrae and the CSF fluid is collected for testing.

A lumbar puncture, or spinal tap, is a procedure to collect cerebrospinal fluid to check for the presence of disease or injury. A spinal needle is inserted, usually between the 3rd and 4th lumbar vertebrae in the lower spine. Once the needle is properly positioned in the subarachnoid space (the space between the spinal cord and its covering, the meninges), pressures can be measured and fluid can be collected for testing.
Medial Temporal Lobe Atrophy: MRI as a Biological Marker for MCI

Normal

MCI
FDG-PET

Small et al., NEJM 2006
Comparing predictors of conversion and decline in mild cognitive impairment

S.M. Landau, PhD
D. Harvey, PhD
C.M. Madison, MS
E.M. Reiman, MD
N.L. Foster, MD
P.S. Aisen, MD
R.C. Petersen, MD, PhD
L.M. Shaw, PhD
J.Q. Trojanowski, MD, PhD
C.R. Jack, Jr., MD
M.W. Weiner, MD
W.J. Jagust, MD
On behalf of the Alzheimer’s Disease Neuroimaging Initiative

ABSTRACT

Objective: A variety of measurements have been individually linked to decline in mild cognitive impairment (MCI), but the identification of optimal markers for predicting disease progression remains unresolved. The goal of this study was to evaluate the prognostic ability of genetic, CSF, neuroimaging, and cognitive measurements obtained in the same participants.

Methods: APOE ε4 allele frequency, CSF proteins (Aβ₁₋₄₂, total tau, hyperphosphorylated tau [p-tau₁₈₁₉₆]), glucose metabolism (FDG-PET), hippocampal volume, and episodic memory performance were evaluated at baseline in patients with amnestic MCI (n = 85), using data from a large multisite study (Alzheimer’s Disease Neuroimaging Initiative). Patients were classified as normal or abnormal on each predictor variable based on externally derived cutoffs, and then variables were evaluated as predictors of subsequent conversion to Alzheimer disease (AD) and cognitive decline (Alzheimer’s Disease Assessment Scale–Cognitive Subscale) during a variable follow-up period (1.9 ± 0.4 years).

Results: Patients with MCI converted to AD at an annual rate of 17.2%. Subjects with MCI who had abnormal results on both FDG-PET and episodic memory were 11.7 times more likely to convert to AD than subjects who had normal results on both measures (p ≤ 0.02). In addition, the CSF ratio p-tau₁₈₁₉₆/Aβ₁₋₄₂ (β = 1.10 ± 0.53; p = 0.04) and, marginally, FDG-PET predicted cognitive decline.

Conclusions: Baseline FDG-PET and episodic memory predict conversion to AD, whereas p-tau₁₈₁₉₆/Aβ₁₋₄₂ and, marginally, FDG-PET predict longitudinal cognitive decline. Complementary information provided by these biomarkers may aid in future selection of patients for clinical trials or identification of patients likely to benefit from a therapeutic intervention. Neurology® 2010;75:230–238

Address correspondence and reprint requests to Dr. Susan M. Landau, 118 Barker Hall MC #3190, UC Berkeley, Berkeley, CA 94720-3190
Subjects

- Recruited from ADNI database of 200 AD, 400 MCI, and 200 Normal Control subjects with serial imaging and neuropsychological evaluations
- Of the 400, 85 MCI had all four measures of interest
- Approximately 2-year follow up
MCI Subjects

- Age 55 to 90 years
- Clinical Dementia Rating (CDR) Scale scores of 0.5
- MMSE of 24-30 (inclusive)
- Abnormal memory function documented by scoring below education-adjusted cutoff on a paragraph recall test
Measures of Interest

- Episodic memory: total words recalled on 5 learning trials of a word list learning and memory task
- Structural imaging: hippocampal volume
- CSF biomarker: $\text{p-tau/AB}_{1-42}$ ratio
- PET: temporoparietal hypometabolism
Data Analysis

• ROC analyses with AD and Normal Controls to establish optimal cutoff scores for each measure.
• The cutoffs were then used to categorize MCI as AD+ or AD- on each measure and derive the positive predictive value (PPV; number of converters correctly classified as AD+/all MCI converters) and negative predictive value (NPV; # non-converter correctly classified as AD-/all MCI non-converters)
• Cox proportional hazards regression model to predict conversion to AD diagnosis
## Cox Proportional Hazard Models

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>HR</strong> (95% CI)</td>
<td><strong>p</strong></td>
</tr>
<tr>
<td>FDG-PET</td>
<td>2.94 (1.23-7.04)</td>
<td>.02</td>
</tr>
<tr>
<td>Hippocampal Volume</td>
<td>2.49 (1.02-5.96)</td>
<td>.04</td>
</tr>
<tr>
<td>CSF</td>
<td>3.99 (1.19-13.21)</td>
<td>.03</td>
</tr>
<tr>
<td>AVLT</td>
<td>4.68 (1.37-15.98)</td>
<td>.01</td>
</tr>
</tbody>
</table>
### Results – Classification Accuracy

Table 2: Normal, MCI, and AD subjects with available data for all measures of interest and ROC analysis results

<table>
<thead>
<tr>
<th>Sample sizes a</th>
<th>Genetic: APOE ε4</th>
<th>Neuroimaging</th>
<th>CSF biomarkers</th>
<th>ROC curve analyses (AD and normal) b</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>193</td>
<td>97</td>
<td>146</td>
<td>102</td>
</tr>
<tr>
<td>MCI</td>
<td>85</td>
<td>85</td>
<td>85</td>
<td>85</td>
</tr>
<tr>
<td>Normal</td>
<td>227</td>
<td>102</td>
<td>198</td>
<td>114</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>FDG-PET</th>
<th>Hippocampal volume</th>
<th>Aβ_{1-42}</th>
<th>p-tau_{181p}</th>
<th>t-tau</th>
<th>p-tau_{181p}/Aβ_{1-42}</th>
<th>t-tau/Aβ_{1-42}</th>
<th>Memory: AVLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROC AUC</td>
<td>0.88</td>
<td>0.89</td>
<td>0.81</td>
<td>0.80</td>
<td>0.80</td>
<td>0.80</td>
<td>0.84</td>
<td>0.85</td>
</tr>
<tr>
<td>Threshold value</td>
<td>1.21</td>
<td>3.260.40</td>
<td>165.50</td>
<td>26.10</td>
<td>86.80</td>
<td>0.14</td>
<td>0.46</td>
<td>33.50</td>
</tr>
<tr>
<td>Sensitivity, %</td>
<td>82</td>
<td>79</td>
<td>82</td>
<td>80</td>
<td>71</td>
<td>87</td>
<td>85</td>
<td>93</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>70</td>
<td>82</td>
<td>70</td>
<td>70</td>
<td>77</td>
<td>70</td>
<td>78</td>
<td>88</td>
</tr>
<tr>
<td>Overall accuracy, %</td>
<td>76</td>
<td>81</td>
<td>76</td>
<td>75</td>
<td>74</td>
<td>78</td>
<td>81</td>
<td>90</td>
</tr>
<tr>
<td>Positive/negative predictive value (MCI), %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>40</td>
<td>41</td>
<td>41</td>
<td>38</td>
<td>42</td>
<td>42</td>
<td>42</td>
<td>39</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>74</td>
<td>79</td>
<td>78</td>
<td>76</td>
<td>83</td>
<td>73</td>
<td>87</td>
<td>76</td>
</tr>
</tbody>
</table>
Predicted survival curves based on Cox proportional hazards models (table 3) illustrate the univariate results for (A) FDG-PET and (B) AVLT, which were the 2 variables that remained significant in the multivariate model. Both curves show that for each variable, a higher proportion of AD+ subjects (solid black line) remained dementia-free over time compared to AD+ subjects (dotted line). Age, education, and sex were included as control covariates. Proportion of subjects remaining dementia-free is shown on the y-axis.
Study Conclusions

• All biomarkers were significant predictors of conversion or decline
• In multivariate models, FDG-PET and AVLT were significant predictors
• Individuals with abnormal PET and AVLT were 11.7 times more likely to convert to AD
## Results – Classification Accuracy

<table>
<thead>
<tr>
<th>Sample sizes</th>
<th>Genetic: APOE ε4</th>
<th>Neuroimaging</th>
<th>CSF biomarkers</th>
<th>ROC curve analyses (AD and normal)</th>
<th>Memory: AVLT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>FDG-PET</td>
<td>Hippocampal volume</td>
<td>Aβ₁-₄₂</td>
<td>p-tau₁₈₁₃</td>
</tr>
<tr>
<td>AD</td>
<td>193</td>
<td>97</td>
<td>146</td>
<td>102</td>
<td>102</td>
</tr>
<tr>
<td>MCI</td>
<td>85</td>
<td>85</td>
<td>85</td>
<td>85</td>
<td>84</td>
</tr>
<tr>
<td>Normal</td>
<td>227</td>
<td>102</td>
<td>198</td>
<td>114</td>
<td>114</td>
</tr>
</tbody>
</table>

### ROC curve analyses (AD and normal)

<table>
<thead>
<tr>
<th></th>
<th>ROC AUC</th>
<th>Threshold value</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Overall accuracy, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.88</td>
<td>1.21</td>
<td>82</td>
<td>70</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>0.89</td>
<td>3,260.40</td>
<td>79</td>
<td>82</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>0.81</td>
<td>165.50</td>
<td>82</td>
<td>70</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>0.80</td>
<td>26.10</td>
<td>80</td>
<td>70</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>0.80</td>
<td>86.80</td>
<td>71</td>
<td>77</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>0.84</td>
<td>0.14</td>
<td>87</td>
<td>70</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>0.85</td>
<td>0.46</td>
<td>85</td>
<td>78</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>0.95</td>
<td>33.50</td>
<td>93</td>
<td>88</td>
<td>90</td>
</tr>
</tbody>
</table>

### Positive/negative predictive value (MCI), %

<table>
<thead>
<tr>
<th></th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>38</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>88</td>
</tr>
</tbody>
</table>
Implications

Tapping into an accurate diagnosis of Alzheimer's disease

August 09, 2010

It may soon be possible to obtain a highly accurate diagnosis of Alzheimer's disease by analyzing a sample of spinal fluid. A study released Monday found that a constellation of three substances in the cerebrospinal fluid was present in 90% of people who had been diagnosed with Alzheimer's.

The test also showed the same markers were found in 72% of people with mild cognitive impairment, considered an early stage of the disease, and in one-third of adults who had no cognitive problems.

Many experts believe that biomarkers in spinal fluid may emerge as the most accurate diagnosis of Alzheimer's disease. At present, the disease is diagnosed using pencil-and-paper cognitive tests, which are subjective and may be inaccurate. The diagnosis can only be confirmed by examining brain tissue at an autopsy.
Correction: September 16, 2010

An article on Aug. 10 about spinal fluid tests in Alzheimer’s research left the incorrect impression that the test can predict the disease with 100 percent accuracy in all patients. (That impression was reinforced by the headline.) In fact, the test was found to be as much as 100 percent accurate in identifying a signature level of abnormal proteins in patients with memory loss who went on to develop Alzheimer’s — not in identifying patients who “are on their way” to developing the disease.

The article also misinterpreted an element of the researchers’ findings. Among a group of patients who had memory loss and developed Alzheimer’s within five years, every one had protein levels associated with the disease five years before; it was not the case that “every one of those patients with the proteins developed Alzheimer’s within five years.”

And the article misstated the source from which the finding of 100 percent accuracy was drawn. It came from a separate set of patients that the researchers examined to validate the protein signature they had identified in an initial group. (In the initial group, as the article noted, nearly every person with Alzheimer’s had the signature protein levels.)
In Spinal-Fluid Test, an Early Warning on Alzheimer’s

By GINA KOLATA
Published: August 9, 2010

Researchers report that a spinal fluid test can be 100 percent accurate in identifying a signature level of abnormal proteins in patients with significant memory loss who went on to develop Alzheimer’s disease.

Although there has been increasing evidence of the value of this and other tests in finding signs of Alzheimer’s, the study, which will appear Tuesday in the Archives of Neurology, shows how accurate they can be. The new result is one of a number of remarkable recent findings about Alzheimer’s.
Critiques

• While the study boasts large sample sizes, number of subjects with all biomarkers on xx% of total sample
• Validation not established on sample of interest
• Wrong description of PPV and NPV
• PPV = number of converters with AD+/total AD+
• Sensitivity = number of AD+/total