Pittsburgh Compound B Imaging and Prediction of Progression From Cognitive Normality to Symptomatic Alzheimer Disease

John C. Morris, MD; Catherine M. Roe, PhD; Elizabeth A. Grant, PhD; Denise Head, PhD; Martha Storandt, PhD; Alison M. Goate, DPhil; Anne M. Fagan, PhD; David M. Holtzman, MD; Mark A. Mintun, MD

**Objective:** To determine whether preclinical Alzheimer disease (AD), as detected by the amyloid-imaging agent Pittsburgh Compound B (PiB) in cognitively normal older adults, is associated with risk of symptomatic AD.

**Design:** A longitudinal cohort study of cognitively normal older adults assessed with positron emission tomography (PET) to determine the mean cortical binding potential for PiB and followed up with annual clinical and cognitive assessments for progression to very mild dementia of the Alzheimer type (DAT).

**Setting:** The Alzheimer’s Disease Research Center, Washington University, St Louis, Missouri.

**Participants:** One hundred fifty-nine participants with a mean age of 71.5 years with a Clinical Dementia Rating (CDR) of 0 on a PET PiB scan at baseline.

**Main Outcome Measure:** Progression from CDR 0 to CDR 0.5 status (very mild dementia).

**Results:** Twenty-three participants progressed to CDR 0.5 at follow-up assessment (range, 1-5 assessments after PET PiB). Of these, 9 also were diagnosed with DAT. Higher mean cortical binding potential values for PiB (hazard ratio, 4.85; 95% confidence interval, 1.22-19.01; *P* = .02) and age (hazard ratio, 1.14; 95% confidence interval, 1.02-1.28; *P* = .03) predicted progression to CDR 0.5 DAT. The CDR 0.5 DAT group showed decline in 3 cognitive domains (episodic memory, semantic memory, and visuospatial performance) and had volume loss in the parahippocampal gyrus (includes entorhinal cortex) compared with individuals who remained at CDR 0.

**Conclusion:** Preclinical AD as detected by PET PiB is not benign, as it is associated with progression to symptomatic AD.

**Arch Neurol. 2009;66(12):1469-1475**

The concept of preclinical Alzheimer disease (AD) holds that the Alzheimer pathologic process operates for many years before producing a clinically detectable impairment.1 A key corollary of this concept is that preclinical AD is not benign and will eventually produce sufficient synaptic and neuronal damage to cause cognitive decline and other symptoms of AD.2 Support for preclinical AD comes from postmortem observations showing that the neuropathology of AD, including cerebral deposits of amyloid-β (Aβ) and neurofibrillary changes associated with hyperphosphorylated tau, is present in an age-dependent manner in a substantial proportion of cognitively normal older adults.1,3-5 Autopsy studies, however, are by nature cross-sectional in design and thus cannot predict whether these individuals would have developed symptomatic AD had they lived longer.

Cerebrospinal fluid (CSF) biomarkers of AD, antecedent to the symptomatic stages of the illness, may identify older adults who are predestined to develop mild cognitive impairment (MCI) or dementia.6-8 Our group, for example, reported that the ratio of CSF tau to Aβ42 in cognitively normal individuals with a mean age of about 75 years predicted the development of symptoms of AD within 3 to 4 years.9 To our knowledge, however, there have been no...
studies to show that nondemented persons with Aβ cerebral deposits, as imaged by positron emission tomography (PET) using amyloid tracers such as [11C] Pittsburgh Compound B (PiB), is associated with a greater risk of symptomatic AD.

METHODS

PARTICIPANTS

Individuals living independently in the community volunteered to participate in longitudinal studies of memory and aging at Washington University’s Alzheimer’s Disease Research Center and its affiliated programs. The recruitment protocol and assessment methods for these studies have been described. All participants were assessed annually with identical instruments and procedures with 2 exceptions: (1) the Alzheimer’s Disease Research Center psychometric battery was modified for younger individuals (age, 45-74 years) enrolled in the affiliated Adult Children Study, and (2) these younger participants were assessed every 3 years until they were aged older than 65 years, when they were evaluated annually.

Inclusion criteria for this study were (1) age 50 years or older; (2) cognitive normality (including the absence of MCI) at the index clinical assessment, which was within 2 years prior or 1 month after their PET PiB scan, completed between April 2004 and November 2008; and (3) at least 1 assessment subsequent to the index assessment. Exclusion criteria included the presence at baseline of a clinically meaningful disorder (eg, disabling stroke) that could interfere with longitudinal follow-up or contraindicate the assessment protocol (eg, cardiac pacemaker precluding magnetic resonance imaging (MRI)).

All procedures were approved by the University’s Human Research Protection Office. Written informed consent was obtained from each participant and their collateral source (informant).

CLINICAL ASSESSMENT

At baseline and each follow-up, experienced clinicians conducted semistructured interviews with the informant and separately with the participant to determine whether there had been decline in the participant’s cognitive abilities that were sufficient to interfere with his or her accustomed activities. The assessment protocol included demographic information, health history, an aphasia battery, medication history, a depression assessment protocol included demographic information, health history, an aphasia battery, medication history, a depression assessment protocol included demographic information, health history, an aphasia battery, medication history, a depression assessment, and the Mini-Mental State Examination. After a neurological examination of the participant, the clinician synthesized all information to determine whether dementia was present or absent based on the principle of intraindividual cognitive decline relative to previously attained function. The clinician’s judgment was operationalized with the Clinical Dementia Rating (CDR), in which CDR 0, 0.5, 1, 2, and 3 correspond to no dementia (ie, cognitively normal), very mild, mild, moderate, and severe dementia, respectively. An etiologic diagnosis of dementia (ie, CDR=0.5) is made by the clinician in accordance with standard criteria.

The CDR determination and dementia diagnosis were made without reference to the participant’s performance on the psychometric battery. The independence of the clinical and psychometric assessments allows the cognitive test results to be assessed longitudinally without the confounding that occurs when psychometric performance is used both to classify participants and to evaluate outcomes. The clinical assessment alone permits the detection of very mild cognitive decline at the CDR 0.5 stage, even when cognitive test deficits are too minimal to meet criteria for MCI (eg, pre-MCI). Participants meeting the clinical phenotype for AD (eg, gradual onset and progression of cognitive dysfunction and interference with conduct of accustomed activities) were diagnosed with dementia of the Alzheimer type (DAT). The accuracy of the diagnosis of DAT as confirmed by postmortem examination is 93% for our study overall and 92% for our participants with CDR 0.5 who might be classified elsewhere as having MCI or pre-MCI. Participants at the CDR 0.5 stage who did not fulfill the DAT phenotype were diagnosed with a non-AD disorder as appropriate or as having uncertain dementia if no etiologic condition was readily apparent; for this study, both categories together are considered to be non-DAT.

PSYCHOMETRIC ASSESSMENT

Within a few weeks of the clinical assessment, psychometricians who were unaware of the results of any prior psychometric assessments administered a 1.5-hour neuropsychological test battery. Individual measures in the test battery include Logical Memory and Associate Learning from the Wechsler Memory Scale and the free and Selective Reminding Test (sum of 3 free recall trials) to evaluate episodic memory; Information from the Wechsler Adult Intelligence Scale and the Boston Naming Test to evaluate semantic memory; Mental Control and Digit Span (forward and backward) from the Wechsler Memory Scale and Word Fluency for the letters s and p to evaluate working memory; and Block Design and Digit Symbol from the Wechsler Adult Intelligence Scale and the Trail-Making Test A to measure visuospatial ability and speeded psychomotor performance. Scores are converted to z scores using means and standard deviations (SDs) from the initial assessment of a reference group of 310 participants who had a CDR of 0 at enrollment and throughout follow-up and had at least 2 follow-up assessments. These z scores were then averaged to form composites that represented the 4 cognitive domains.

IMAGING ASSESSMENT

For MRI, 1 to 4 MPRAGE T1-weighted images were acquired (1×1×1.25 mm3) in 1 scanning session on a Sonata 1.5T (n=3), Vision 1.5T (n=48), or Trio 3T (n=67) scanner. Image processing was conducted as described and included motion correction, averaging across scans, atlas transformation, and inhomogeneity correction. Regional volume estimates were obtained with the FreeSurfer image analysis suite (Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, Massachusetts), in which each voxel in an image is assigned a neuroanatomical label based on probabilistic information from a manually labeled training set that included cognitively normal older adults and those with symptomatic AD. This technique generates volumes that correspond well to manually generated regions. Regions of interest (ROIs) included the prefrontal cortex (combined superior, middle, and inferior frontal gyri), lateral parietal (combined inferior and superior parietal and supramarginal regions), temporal neocortical (combined superior, middle, and inferior temporal gyri), anterior cingulate, posterior cingulate, precuneus, hippocampal, and parahippocampal (including entorhinal cortex) regions. Intracranial volume was used to adjust ROI for head-size variation based on a covariance approach. FreeSurfer-derived quantitative estimates have been shown to be reliable despite biases across different scanners. Volume data were not included for 40 participants owing to processing errors (n=39) and protracted delay between PET PiB and MRI scans (n=1).

The PET PiB imaging has also been described in detail. The PET imaging was conducted with a Siemens 961 HR ECAT scan.
ner or a Siemens 962 HR+ ECAT scanner (CTI, Knoxville, Kentucky). Participants kept their eyes closed during scanning and a mask was used to minimize head motion. After radiochemical synthesis of [11C] PiB, approximately 12 mCi of the tracer was administered intravenously with simultaneous initiation of a 60-minute dynamic PET scan. The PiB image analysis was achieved by registering each participant’s PET PiB image set to the MPRAGE MRI that was registered to a standard atlas target designed to minimize bias due to atrophy. The ROIs for PET (detailed information on the boundaries for the ROIs is available) were individually drawn on the MRI and applied to unblurred images of the PET dynamic data, yielding high-resolution regional time-activity curves. These curves were analyzed for PiB-specific binding using the Logan graphical analysis, with the cerebellum as a reference tissue input function. The Logan analysis yielded a tracer distribution volume ratio, which was then converted to an estimate of the binding potential (BP) for each ROI: BP = distribution volume ratio × 1. The BP expresses regional PiB binding values in a manner directly proportional to the number of binding sites. The BP values from the prefrontal cortex, gyrus rectus, lateral temporal cortex, and precuneus ROIs were averaged in each participant to calculate the mean cortical BP (MCBP); these ROIs have high PiB uptake in participants with symptomatic AD.

**GENOTYPING**

Using DNA extracted from peripheral blood samples in each participant, genotyping for apolipoprotein E (APOE) was performed using standard procedures as previously described.

**STATISTICAL ANALYSIS**

A Cox proportional hazard model was used to examine associations between levels of fibrillar Aβ cerebral deposits as estimated by the MCBP and time to first diagnosis of DAT. The models were adjusted for age at PET PiB scan, education, sex, and whether the participant was an APOE ε4 carrier. Data from participants who did not receive a DAT diagnosis during the follow-up period (including those who did not receive a diagnosis for non-DAT dementia) were censored at the date of their most recent clinical assessment. A similar analysis was conducted, testing time to any diagnosis of dementia (ie, a CDR ≥ 0) rather than time to a diagnosis of DAT specifically. In this analysis, data from participants who did not develop dementia were censored at the date of their most recent clinical assessment. Mixed linear models (PROC MIXED; SAS Institute Inc, Cary, North Carolina) controlling for age, sex, education, and APOE ε4 carrier status were used to determine whether there were differences in the slope of the cognitive domain composite scores for participants who (1) remained cognitively normal, (2) developed non-DAT dementia, and (3) developed DAT during the follow-up period.

A series of analyses of covariance—with regional volume (eg, hippocampus) as a continuous dependent variable and longitudinal cognitive status (ie, remained cognitively normal, developed non-DAT dementia, or developed DAT) as a categorical independent variable, and age at PET PiB scan, education, sex, and APOE ε4 status as covariates—was conducted to examine whether there were group differences in structural brain integrity at the time of the PET PiB scan.

**RESULTS**

One hundred fifty-nine participants met the inclusion criteria. Data from many of the 159 participants have appeared in other reports from our Alzheimer’s Disease Research Center. In particular, one of the participants is the subject of a case report; this man, aged 85 years at CDR 0 at baseline, declined in episodic memory and in working memory at age 88 years and was diagnosed as CDR 0.5 and DAT at age 89 years. Although PET PiB imaging results at age 88.5 years were negative, at age 89.5 years, he had low CSF Aβ42 and elevated CSF tau levels. Neuropathologic examination at age 91 years showed numerous neocortical diffuse Aβ plaques; postmortem biochemical analysis showed that PiB abnormalities in binding was below the level needed for in vivo detection. This case suggests that CSF abnormalities indicative of AD may precede, in some individuals, the detection of fibrillar Aβ by amyloid imaging.

In the 159 participants, the mean interval between the clinical assessment and PET PiB scan was 0.56 years (SD, 0.42 years) and between the clinical assessment and MRI was 0.44 years (SD, 0.41 years). The mean interval between PET PiB and MRI scans was 0.40 years (SD, 0.40 years). Table 1 presents demographic information for the participants at the time of their PET PiB scans or index clinical assessment. Participants ranged in age from 51.2 to 88.9 years; the follow-up duration from PET PiB to most recent clinical assessment ranged from 0.8 to 5.5 years; and the number of assessments (including the index assessment) ranged from 2 to 6.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDR</td>
<td>0.5</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>DAT</td>
</tr>
<tr>
<td>Age, y</td>
<td>89.5</td>
</tr>
<tr>
<td>Sex, %</td>
<td>Male</td>
</tr>
<tr>
<td>Race, %</td>
<td>African American 10.7</td>
</tr>
<tr>
<td>Education, y</td>
<td>15.6</td>
</tr>
<tr>
<td>APOE ε4 carrier, %</td>
<td>31.5</td>
</tr>
<tr>
<td>MMSE scorea</td>
<td>29.8</td>
</tr>
<tr>
<td>Follow-up time, y</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; DAT, dementia of the Alzheimer type; HR, hazard ratio; MCBP, mean cortical binding potential; PiB, Pittsburgh Compound B.

Table 1. Characteristics of 159 Cognitively Normal Individuals

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>71.5 (8.6)</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>69.8</td>
</tr>
<tr>
<td>African American race, %</td>
<td>10.7</td>
</tr>
<tr>
<td>Education, y</td>
<td>15.6 (2.5)</td>
</tr>
<tr>
<td>APOE ε4 carrier, %</td>
<td>31.5</td>
</tr>
<tr>
<td>MMSE scorea</td>
<td>29.8 (1.2)</td>
</tr>
<tr>
<td>Follow-up time, y</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Abbreviation: MMSE, Mini-Mental State Examination. Range of possible scores, 30 (best) to 0 (worst).

Table 2. Cox Proportional Hazards Model Testing MCBP for PiB as a Predictor of Time to DAT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCBP</td>
<td>4.82 (1.22-19.01)</td>
<td>.02</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.14 (1.02-1.28)</td>
<td>.03</td>
</tr>
<tr>
<td>Education, y</td>
<td>0.91 (0.69-1.19)</td>
<td>.49</td>
</tr>
<tr>
<td>APOE ε4 carrier</td>
<td>0.98 (0.20-4.90)</td>
<td>.98</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.54 (0.10-2.90)</td>
<td>.48</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; DAT, dementia of the Alzheimer type; HR, hazard ratio; MCBP, mean cortical binding potential; PiB, Pittsburgh Compound B.
An additional 14 participants were staged at CDR 0.5 subsequent to PET PiB scan but were not diagnosed with DAT. In these individuals, 2 were diagnosed with vascular dementia and no etiological diagnosis could be made for the remaining 12 (uncertain). As shown in Table 3, for all 23 individuals with CDR 0.5 subsequent to PET PiB (9 diagnosed with DAT and 14 non-DAT), only age predicted progression to CDR 0.5.

There were significant differences in parahippocampal volume (P = .008) across the 3 groups. (Forty participants did not have volume data.) The cognitively normal group (n=101) had larger parahippocampal volumes compared with individuals (n=7) who progressed to DAT (P = .03 for adjusted means) and individual (n=10) who progressed to non-DAT (P = .05 for adjusted means). The 2 dementia groups did not differ (P > .63). Group differences in hippocampal volume did not reach significance (P = .09), and there were no significant group differences in any other regional volumes (P > .22).

Data from participants in the Adult Children Study who received a different set of psychometric tests and for whom cognitive composite scores could therefore not be generated were not included in the mixed linear models, leaving a sample of 116 participants for the slope analyses. There were significant differences in longitudinal cognitive performance across the 3 groups (97 who maintained nondemented cognition, 11 who developed non-DAT, and 8 who developed DAT) in the slope of episodic memory (P = .01), semantic memory (P < .001), and visuospatial (P = .004) composite scores during the follow-up period. There was no difference in the slope of working memory composite scores across the groups (P = .84). The adjusted mean slopes and intercepts for each group on each composite score are plotted in the Figure. The decline across 3 cognitive domains for both CDR 0.5 groups (DAT and non-DAT) is consistent with the independent clinical determination of very mild dementia.

### Table 3. Cox Proportional Hazards Model Testing MCBP as a Predictor of Time to CDR 0.5

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCBP</td>
<td>2.74 (0.59-12.78)</td>
<td>.20</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.11 (1.04-1.18)</td>
<td>.002</td>
</tr>
<tr>
<td>Education, y</td>
<td>0.99 (0.84-1.16)</td>
<td>.88</td>
</tr>
<tr>
<td>APOE ε4 carrier</td>
<td>1.49 (0.56-3.94)</td>
<td>.42</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.26 (0.50-3.15)</td>
<td>.62</td>
</tr>
</tbody>
</table>

Abbreviations: CDR, Clinical Dementia Rating; CI, confidence interval; HR, hazard ratio; MCBP, mean cortical binding potential.

Increasing evidence suggests that preclinical AD has deleterious consequences for brain structure and function. Reduced levels of CSF Aβ42 in cognitively normal older adults are associated with whole brain atrophy and with hypometabolism in the medial temporal lobe. Non-demented older individuals with elevated PiB binding levels also demonstrate regional brain atrophy and cerebral cortical thinning as well as episodic memory deficits and longitudinal cognitive decline. Higher educational attainment may permit individuals with preclinical AD, as ascertained by PET PiB, to better tolerate AD pathology without obvious cognitive deterioration than those with less education, suggesting that they have a greater reserve against the clinical expression of AD. Similarly, non-demented older adults with preclinical AD who have high occupational status have accelerated rates of brain atrophy.

At least 2 studies suggest that preclinical AD, as detected by the CSF signature for AD in cognitively normal individuals, predicts development of symptomatic AD. Skoog and colleagues reported that 7 of 35 individuals who were nondemented at their baseline assessment at age 85 years when CSF was obtained developed dementia by age 88 years and had lower levels of CSF Aβ42. In 61 cognitively normal individuals with a mean age of 73 years, our group found that the ratio of CSF tau to Aβ42 predicted the 13 individuals who became demented within 3 to 4 years of follow-up after CSF was obtained. The findings from these 2 studies are consis-
tent with reports that CSF biomarkers and PET PiB can predict progression from MCI or early symptomatic AD to more overt DAT.

We now extend these findings by providing, to our knowledge, the first demonstration that elevated MCBP for PiB in cognitively normal older adults predicts the development of symptomatic AD (DAT). This predictive effect appears to be specific to the diagnosis of DAT and does not extend to non-DAT causes of dementia. The diagnosis of DAT was made by experienced clinicians who successfully diagnose the disorder at earlier stages than is typical and was independently supported by decline in multiple cognitive domains and by parahippocampal volume loss. (The parahippocampal region includes the entorhinal cortex, a region that is a sensitive indicator of AD.)

Our study is limited by several factors, including the small number of individuals who developed DAT, the relatively short follow-up period, and the confirmation of the diagnosis of DAT by postmortem examination in only 1 of the 9 cases (the other 8 individuals with DAT are still alive). Another limitation is that the non-DAT group likely has heterogeneous etiologies and it is possible that some of these individuals will later be recognized to have AD. Finally, our psychometric battery was developed in 1979 at the beginning of our studies on memory and aging and has been maintained to allow longitudinal comparisons, but it may lack more sensitive measures that are now available for some domains. Many more individuals, studied for longer intervals and ideally through autopsy, will be needed to confirm or refute our observations. Nonetheless, this study provides support for the premise that preclinical AD, detected either by the CSF signature for AD or here by elevated PiB retention, predicts symptomatic AD.

Accepted for Publication: July 11, 2009.

Correspondence: John C. Morris, MD, Alzheimer’s Disease Research Center, 4488 Forest Park Ave, Ste 160, St Louis, MO 63108 (morrisj@abraxas.wustl.edu).

Author Contributions: Study concept and design: Morris, Roe, and Mintun. Acquisition of data: Morris, Roe, Grant, Head, Storandt, Goate, and Mintun. Analysis and interpretation of data: Morris, Roe, Head, Fagan, Holtzman, and Mintun. Drafting of the manuscript: Morris, Roe, and Storandt. Critical revision of the manuscript for important intellectual content: Morris, Roe, Grant, Head, Goate, Fagan, Holtzman, and Mintun. Statistical analysis: Roe and Storandt. Obtained funding: Morris and Mintun. Administrative, technical, and material support: Morris, Grant, Goate, Fagan, Holtzman, and Mintun. Study supervision: Morris, Head, and Mintun.

Financial Disclosure: Dr Mintun has been a consultant to Avid RP.

Funding/Support: This study was supported by grants P50AG05681, P01AG03991, and P01AG026276 from the
National Institute on Aging (Dr Morris), an anonymous foundation, and the Charles and Joanne Knight Alzheimer’s Research Initiative. Dr Roe is enrolled in the Post-doctoral Program of U1L1RR024992 from the National Center for Research Resources.

Additional Contributions: The authors thank investigators and staff from the Alzheimer’s Disease Research Center’s Clinical and Genetics Cores for clinical and cognitive assessments and genotyping and from the Imaging Core, particularly Lindsay Casmaer and Tessa Mazocco, for data processing. Finally, the authors thank our dedicated participants and their families for their contributions.

REFERENCES


---

Trial Registration Required. As a member of the International Committee of Medical Journal Editors (ICMJE), Archives of Neurology will require, as a condition of consideration for publication, registration of all trials in a public trials registry (such as http://ClinicalTrials.gov). Trials must be registered at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after July 1, 2005. The trial registration number should be supplied at the time of submission.

For details about this new policy, and for information on how the ICMJE defines a clinical trial, see the editorials by DeAngelis et al in the September 8, 2004 (2004;292:1363-1364) and June 15, 2005 (2005;293:2927-2929) issues of JAMA. Also see the Instructions to Authors on our Web site: www.archneur.com.