Inverse Relation between In Vivo Amyloid Imaging Load and Cerebrospinal Fluid $A\beta_{42}$ in Humans

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Objectives: **Amyloid-β_{42} ($A\beta_{42}$) appears central to Alzheimer's disease (AD) pathogenesis and is a major component of amyloid plaques. Mean cerebrospinal fluid (CSF) $A\beta_{42}$ is decreased in dementia of the Alzheimer's type. This decrease may reflect plaques acting as an $A\beta_{42}$ "sink," hindering transport of soluble $A\beta_{42}$ between brain and CSF. We investigated this hypothesis.** ***Methods:*** **We compared the in vivo brain amyloid load (via positron emission tomography imaging of the amyloid-binding agent, Pittsburgh Compound-B [PIB]) with CSF $A\beta_{42}$ and other measures (via enzyme-linked immunosorbent assay) in clinically characterized research subjects.** ***Results:*** **Subjects fell into two nonoverlapping groups: those with positive PIB binding had the lowest CSF $A\beta_{42}$ level, and those with negative PIB binding had the highest CSF $A\beta_{42}$ level. No relation was observed between PIB binding and CSF $A\beta_{40}$, tau, phospho-tau_{181}, plasma $A\beta_{40}$, or plasma $A\beta_{42}$. Importantly, PIB binding and CSF $A\beta_{42}$ did not consistently correspond with clinical diagnosis; three cognitively normal subjects were PIB-positive with low CSF $A\beta_{42}$, suggesting the presence of amyloid in the absence of cognitive impairment (ie, preclinical AD).** ***Interpretation:*** **These observations suggest that brain amyloid deposition results in low CSF $A\beta_{42}$, and that amyloid imaging and CSF $A\beta_{42}$ may potentially serve as antecedent biomarkers of (preclinical) AD.**

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Amyloid-β (Aβ) plaque deposition in the brain is a hallmark of Alzheimer's disease (AD), and its histological quantification (together with tangle formation) at autopsy is currently the only tool for definitive diagnosis of AD. Although much is known about the synthesis of Aβ,[1] surprisingly little is known about its metabolism. There is strong clinicopathological evidence that Aβ deposition in plaques precedes any sign of dementia caused by AD by many years, perhaps a decade or longer (ie, preclinical AD).[2,3] This suggests that if a consistent relation between Aβ metabolism and plaque deposition in individual subjects is found, such measures may be useful as potential antecedent biomarkers of AD that would assist in the design of future therapeutic trials to prevent or delay onset of disease. This study was designed to investigate whether there is a relation between in vivo amyloid plaque burden and levels of cerebrospinal fluid (CSF) $A\beta_{42}$, as well as other CSF measures in living humans.

Subjects and Methods

Subjects

Research subjects were participants at the Alzheimer's Disease Research Center (ADRC) at the Washington University School of Medicine (WUSM) and were recruited by the ADRC to this study. Study investigators were blind to the cognitive status of the participants, which was determined by ADRC clinicians in accordance with standard protocols and criteria, as described previously.[4,5] All subjects were assessed on clinical grounds to be cognitively normal in accordance with a Clinical Dementia Rating (CDR)[6] of 0 (n = 18) or to have very mild (CDR 0.5; n = 3), mild (CDR 1; n = 2), or moderate (CDR 2; n = 1) dementia. Demented subjects were diagnosed, again in accordance with standard criteria, as

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having dementia of the Alzheimer's type (DAT; n = 4) or a non-AD dementia (n = 2). The rate of postmortem confirmation of the clinical diagnosis of DAT from our center is 93%,[5] including the CDR 0.5 stage, which elsewhere may be considered to represent "mild cognitive impairment."[7] All subjects in the study underwent lumbar puncture (LP) for the collection of CSF and imaging with positron emission tomography (PET) and Pittsburgh Compound-B (PIB)[8] ({N-methyl-[^{11}C]}2-(4′-methylaminophenyl)-6-hydroxybenzothiazole) for calculation of in vivo amyloid burden. LP and PIB imaging were performed within 1 (n = 18) or 2 (n = 6) years of each other, both within approximately 1 year of clinical assessment. Subjects were between 48 and 83 years old and were in good general health, having no other neurological, psychiatric, or systemic medical illness that could contribute importantly to dementia (eg, head trauma, stroke, chronic liver or kidney disease) and no medical contraindication to LP (eg, bleeding diathesis or taking anticoagulants) or magnetic resonance imaging (MRI; eg, claustrophobia, pregnancy, or presence of a pacemaker or any paramagnetic material in the body). All studies were approved by the WUSM Human Studies Committee, and informed consent was obtained from all subjects. Apolipoprotein E genotypes were kindly provided by the WUSM ADRC Genetics Core (Dr Alison Goate, Core Leader).

Lumbar Puncture and Cerebrospinal Fluid Processing

CSF (20–35ml) was collected at 8:00 AM after overnight fasting, as described previously.[9] LPs (L4/L5) were performed by a trained neurologist using a 22-gauge Sprotte spinal needle. No subjects experienced a post-LP headache requiring intervention. CSF samples were free from any blood contamination. Samples were gently inverted to avoid gradient effects, briefly centrifuged at low speed to pellet any cellular elements, and aliquoted (500μl) into polypropylene tubes before freezing at −84°C.

Cerebrospinal Fluid Biomarker Assessment

CSF samples were analyzed for total tau, phospho-tau$_{181}$, and Aβ_{42} by commercial enzyme-linked immunosorbent assay (Innotest; Innogenetics, Ghent, Belgium), and Aβ_{40} by enzyme-linked immunosorbent assay.[10] For all biomarker measures, samples were kept continuously on ice, and assays were performed on sample aliquots after a single thaw after initial freezing.

Plasma Collection and Biomarker Assessment

Fasted blood (10–15ml) was obtained from each subject just before LP, and plasma was prepared by centrifugation (2,000*g*, 15 minutes, 4°C). Plasma samples were aliquoted (500μl) into polypropylene tubes before freezing at −84°C. Plasma was analyzed for Aβ_{40} and Aβ_{42} by enzyme-linked immunosorbent assay.[10] Assays were performed on sample aliquots after a single thaw after initial freezing.

Pittsburgh Compound-B Synthesis and Positron Emission Tomography Imaging

PIB was synthesized according to published methods.[11] PET imaging was performed using a Siemens 961 HR ECAT PET scanner (CTI, Knoxville, TN). After positioning with the lowest slice 1cm above the canthomeatal line, a transmission scan was collected for attenuation correction. Ten millicurie PIB (range, 4.0–16.8; specific activity > 1,200Ci/mmol) was then injected via an antecubital vein, and a 60-minute, three-dimensional (septa withdrawn), dynamic PET scan was collected. Images were reconstructed as 5-minute frames using scatter correction and a ramp filter. Frames were corrected for any head motion (using in-house software[12]) and registered to the subject's MRI scan to allow for region of interest (ROI) placement. The data from 30 to 60 minutes after PIB injection were also summed for visual inspection.

Defining Regions of Interest

Three-dimensional ROIs were created for each subject based on their individual MRI scans. Brain regions were selected to demonstrate the contrasting levels of PIB uptake based on the average 30- to 60-minute PIB uptake seen in subjects with DAT. Five ROIs were created for each subject and included the prefrontal cortex, lateral temporal cortex, precuneus, cerebellar cortex, and gyrus rectus. The cerebellum was chosen as a region with low specific binding of PIB for use as a reference region. Specific criteria were as follows: In the *prefrontal cortex,* the cortical gray matter of the superior and middle frontal gyri (Brodmann area 10 [BA 10]) was manually traced in transverse sections, starting at the beginning of the genu of the corpus callosum and continuing rostrally for 2cm. The anterior cingulate gyrus was excluded. In the *lateral temporal cortex,* the cortical gray matter of the superior and middle temporal gyri (BAs 22 and 21) was manually traced in coronal sections, starting at 24mm and ending at 46mm (*y*-axis) in Talairach atlas coordinates. In sagittal sections, the *precuneus* was manually traced beginning in each hemisphere as close to the midline as the region was visible and continuing 1cm laterally. The posterior boundary of the region was the parietooccipital sulcus, and the region included the posterior portion of BAs 7 and 31. The posterior cingulate gyrus was excluded. In the *cerebellar cortex,* each hemisphere of the cerebellum was traced in coronal sections between −10 and 4mm (*y*-axis) in Talairach atlas coordinates, excluding the cerebellum caudal to −10mm. The boundaries used were the edge of the cerebellum on the outside and the cerebellar white matter on the inside, excluding CSF and visible streaks of white matter. The *gyrus rectus* was manually traced in transverse sections from the caudal boundary of the gyrus rectus rostrally until the sulcus in the middle of one of the gyri closed and became completely filled with white matter (BAs 11 and 47).

Results

All subjects underwent PET imaging with PIB for calculation of in vivo amyloid plaque binding.[8] Visual inspection of the radiolabeled tracer on PET images showed early and rapid uptake of PIB into all brain regions of all subjects, followed by prolonged retention in several cortical and subcortical regions in some subjects. Figure 1 shows the PET images from two subjects exhibiting positive PIB binding (PIB-positive; see Figs 1A, C) and a subject without increased PIB bind-

ing (PIB-negative; see Fig 1B). In positive cases, prominent binding of PIB was observed in several regions including the prefrontal cortex, precuneus, and temporal cortex, whereas the cerebellar cortex and brainstem white matter showed little to no specific binding, a pattern consistent with the initial PIB study in AD brain.[8]

For quantitative analysis of PIB binding, three-dimensional ROIs were created for each subject based on their MRI and were applied to all PIB PET scans. ROIs included prefrontal cortex, lateral temporal cortex, precuneus, cerebellar cortex, and gyrus rectus. Because the cerebellar cortex has been demonstrated to have minimal PIB binding in ex vivo preparations, even in subjects with AD,[11] and did not exhibit PIB retention in any of the subjects in this study, Logan[13] graphical analysis using this region as the input function was performed on the ROI data to calculate the PIB distribution volume. The validity of Logan analysis of PIB data and its comparison with other methods of pharmacokinetic analysis have been reported.[14,15] PIB binding potential (binding potential = distribution volume −1) in each ROI was then calculated for each subject. To simplify the display of the data, we averaged binding potential values for the prefrontal cortex, precuneus, lateral temporal cortex, and gyrus rectus to yield the mean cortical binding potential for each subject. The majority of subjects in this cohort (17/24) exhibited a lack of PIB binding, as indicated by visual inspection of PET images, as well as mean cortical binding potentials not different from zero (Table). Seven of the 24 subjects displayed positive mean cortical PIB binding, indicating the presumed presence of PIB-detectable amyloid in the cortical ROIs.

Lumbar CSF and plasma samples were also obtained from the same cohort of subjects. Levels of the AD-related markers $A\beta_{40}$, $A\beta_{42}$, tau (the primary component of neurofibrillary tangles), and phospho-tau_{181} in CSF and $A\beta_{40}$ and $A\beta_{42}$ in plasma were measured in each subject and plotted as a function of their mean cortical PIB binding potential. Subjects with positive cortical PIB binding had the lowest levels of CSF $A\beta_{42}$ (Fig 2A). In contrast, visual inspection of the plotted data suggested no apparent relation between PIB binding and CSF levels of the other AD-related markers (see Figs 2B–D). Interestingly, in this small cohort, those subjects with positive cortical PIB binding had lower CSF $A\beta_{42}$ levels than those with negative PIB binding, with no overlap between the groups. Levels of plasma $A\beta_{40}$ and $A\beta_{42}$ did not correlate with PIB binding (see Figs 2E, F). Thus, we observed an inverse relation between in vivo brain amyloid load and the level of CSF $A\beta_{42}$, but not plasma $A\beta_{42}$.

We next compared the PIB binding and CSF measures with the clinical diagnoses made by independent, experienced clinicians blind to the biomarker data. Some important discrepancies were observed. Of the seven subjects exhibiting positive PIB binding and low CSF $A\beta_{42}$ values, three were diagnosed as having mild or moderate DAT (CDR 1 or 2; see filled squares in Fig 2 and also Fig 1A) and one was diagnosed with very mild DAT (CDR 0.5; see open triangles in Fig 2). Importantly, however, the remaining three PIB-positive subjects with low CSF $A\beta_{42}$ values were diagnosed as being cognitively normal (CDR 0; see open circles in Fig 2), suggesting the presence of cortical amyloid and low CSF $A\beta_{42}$ in these subjects in the absence of cognitive impairment. The PET images of one of these subjects are shown in Figure 1C. These subjects all scored within the lower reference range on the Logical Memory component of the Wechsler Memory Scale, with the mean value intermediate to those of nondemented PIB-negative subjects and demented PIB-positive subjects with DAT (Fig 3). Also notable is that two additional subjects in our cohort had very mild dementia (CDR 0.5; see solid triangles in Fig 2), but with impairments considered *not* to be caused by AD. One subject was diagnosed with frontotemporal lobar degeneration, a group of disorders characterized, in part, by the absence of cerebral amyloid deposition.[16] The other subject had received a CDR score of 0.5, but clinical notation indicated a questionable impairment that was perhaps attributable to hypnotic drug therapy initiated for a chronic sleep disorder. These two non-DAT subjects with a CDR score of 0.5 exhibited negative PIB binding and a high CSF $A\beta_{42}$ value, a pattern different from the subjects whose cognitive impairments were believed to be due to AD. Our finding of an absence of PIB binding and high CSF $A\beta_{42}$ values in these two non-DAT subjects with a CDR score of 0.5 suggests that these biological measures may be useful for excluding brain Aβ amyloidosis as an underlying contributor to cognitive impairment.

Discussion

Although results from studies of AD mouse models have provided support for the hypothesis that plaques act as an $A\beta_{42}$ "sink," preventing the transport of soluble $A\beta_{42}$ from the brain to the CSF,[17,18] to our knowledge, this is the first study to investigate the relation between in vivo brain amyloid burden and CSF $A\beta_{42}$ levels in living humans. An inverse association between amyloid burden and CSF $A\beta_{42}$ indicates a relation between these two measures, but does not define the underlying biological mechanism(s). These data support the hypothesis that amyloid deposition in the brain acts as a "sink," resulting in a new equilibrium between soluble and deposited $A\beta_{42}$ in the central nervous system. Another possibility is that low CSF $A\beta_{42}$ is due to neuronal dysfunction and loss with resultant decreased $A\beta_{42}$ production. In fact, it has been shown that individuals with even very mild DAT have signif-

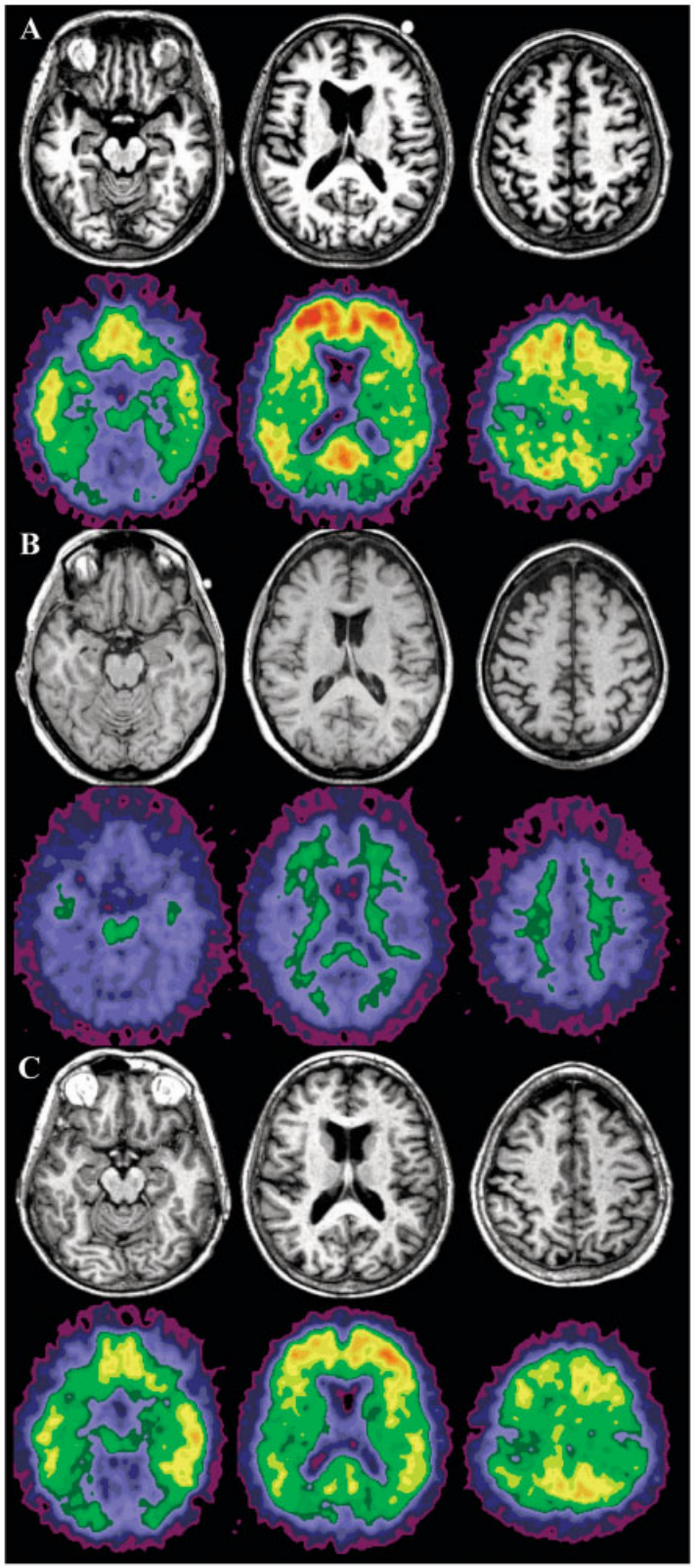

Fig 1. Distribution of Pittsburgh Compound-B (PIB) in three subjects as viewed by positron emission tomography (PET). For each subject, the three magnetic resonance (MR) images (black and white) are at three different levels above the anterior commissure–posterior commissure line. The PET images (in color) are taken from the same levels as the MR images and reflect the PET activity summed from 30 to 60 minutes after injection of PIB. PET data were scaled to normalize for activity in the cerebellar cortex. (A, C) Increased binding of PIB in many brain regions in these two subjects, particularly the prefrontal cortex, the medial and lateral parietal cortex, and the lateral temporal cortex (PIB-positive), is shown. (B) Only low levels of nonspecific PIB binding in white matter structures in this subject and no evidence of binding in cortices (PIB-negative) are shown.

Table. Clinical, Psychometric, and Biomarker Data of Individual Study Participants

Subject No.	CDR	Dx	Age	ApoE	MMSE[a]	Logical Memory[b]	CSF (pg/ml)				Plasma (pg/ml)		PIB Mean Cx (mean cortical, Cx) as Binding Potential (unitless ratio)
							Tau	$Ptau_{181}$	$A\beta_{40}$	$A\beta_{42}$	$A\beta_{40}$	$A\beta_{42}$	
14	0	ndem	63	2,3	28	9.0	267	43	9,383	750	168	64	−0.092
15	0	ndem	77	3,3	29	7.5	231	37	9,006	593	199	69	−0.061
10	0	ndem	83	2,3	29	12.5	588	107	19,481	1,071	357	351	−0.033
7	0	ndem	49	3,3	30	4.0	175	39	9,076	726	182	83	−0.015
13	0	ndem	83	3,3	30	15.0	157	24	7,761	460	219	94	−0.004
9	0	ndem	48	3,4	30	12.0	326	63	7,888	767	176	78	−0.001
18	0	ndem	59	3,4	29	10.0	246	57	5,763	632	n.d.	n.d.	0.007
16	0	ndem	64	3,4	30	15.0	319	67	8,595	665	159	128	0.017
12	0	ndem	75	3,4	30	18.0	437	79	8,553	483	214	64	0.020
23	0	ndem	58	2,2	30	10.5	190	38	10,657	693	183	92	0.022
20	0	ndem	61	3,3	30	8.0	164	33	8,352	602	155	96	0.033
17	0	ndem	60	3,3	29	13.5	229	43	10,632	627	221	49	0.034
22	0	ndem	61	3,4	30	8.0	413	77	8,267	826	181	105	0.048
21	0	ndem	63	3,4	30	8.5	157	35	11,510	557	135	88	0.048
24	0	ndem	58	3,3	27	13.0	265	48	12,530	790	144	67	0.050
1	0.5	nDAT	77	3,4	25	5.0	265	59	5,583	588	163	117	−0.047
3	0.5	nDAT	77	3,3	28	7.5	380	69	9,670	572	207	163	0.010
19	***0***	***ndem***	***61***	***3,3***	***28***	***8.0***	***461***	***84***	***14,013***	***443***	***165***	***110***	***0.299***
4	***0***	***ndem***	***72***	***3,4***	***30***	***7.0***	***1,068***	***181***	***15,080***	***326***	***165***	***143***	***0.587***
8	***0***	***ndem***	***74***	***3,4***	***25***	***9.0***	***467***	***64***	***16,903***	***359***	***131***	***101***	***0.777***
11	***1***	***DAT***	***73***	***3,3***	***24***	***4.0***	***315***	***54***	***8,194***	***266***	***196***	***129***	***0.418***
2	***2***	***DAT***	***73***	***3,4***	***13***	***0.0***	***963***	***121***	***13,937***	***426***	***157***	***71***	***0.570***
6	***1***	***DAT***	***79***	***3,3***	***21***	***3.5***	***1,358***	***241***	***16,159***	***230***	***144***	***113***	***0.776***
5	***0.5***	***DAT***	***81***	***3,4***	***26***	***6.5***	***319***	***51***	***9,075***	***273***	***157***	***151***	***1.105***

Bold italics indicates subjects who were Pittsburgh Compound-B (PIB)–positive on visual inspection of positron emission tomography images.

[a]Range 0 to 30, higher value indicates better performance.

[b]Logical Memory component of the Wechsler Memory Scale (range, 0-23, higher value indicates better performance).

CSF = cerebrospinal fluid; CDR = Clinical Dementia Rating; Dx = clinical diagnosis; ApoE = apolipoprotein E genotype (allele, allele); MMSE = Mini-Mental State Examination; ptau = phospho-tau; Cx = cortex; ndem = not demented; n.d. = not done; nDAT = non-DAT; DAT = dementia of the Alzheimer type.

icant neuronal loss in vulnerable regions, such as the entorhinal cortex.[19] However, cognitively normal individuals with neuropathological AD (preclinical AD) do not demonstrate such neuronal loss,[20] and we observed reduced CSF $A\beta_{42}$ levels in three cognitively normal subjects. Thus, our data suggest that a specific plaque-associated alteration in $A\beta_{42}$ metabolism is involved in the PIB/CSF $A\beta_{42}$ association, because the nondemented subjects in our cohort are unlikely to have appreciable neuronal loss given our prior findings.[20]

Regardless of the underlying mechanism(s), these findings suggest that in vivo amyloid imaging, together with CSF $A\beta_{42}$ measures, may have utility as antemortem AD biomarkers. Accuracy of clinical diagnosis of AD ranges from 93% in specialty centers[5] to less than 50% in primary care settings.[21] Although low CSF $A\beta_{42}$ levels consistently have been associated with AD, this measure does not meet the criteria necessary for its use as a diagnostic biomarker due to substantial overlap between individual AD and control values.[22] However, virtually none of the clinical diagnoses of AD in the published CSF studies were verified at autopsy, and it is possible, given our results, that CSF $A\beta_{42}$ is actually an accurate predictor of brain amyloid burden regardless of clinical diagnosis. The utility of the emerging technology of in vivo amyloid imaging as an AD biomarker remains to be determined. Although it must be emphasized that this cohort is limited in number, and caution must be taken before extrapolating to the general population, our results suggest that PIB binding, in combination with CSF $A\beta_{42}$ levels, may be helpful in improving clinical diagnostic accuracy. Although the separation of positive and negative cases was greater for PIB binding than for CSF $A\beta_{42}$, the latter is much less expensive and more widely applicable, and it may provide useful information standing alone or as a screen to identify good candidates for PIB PET studies or other imaging technologies useful in detecting amyloid. Our data show no relation between levels of plasma $A\beta_{42}$ and PIB binding, even in the cognitively normal subjects with positive PIB binding. This is analogous to findings in an animal model with amyloid deposition in which baseline levels of plasma Aβ do not correlate with brain amyloid load.[23] Some

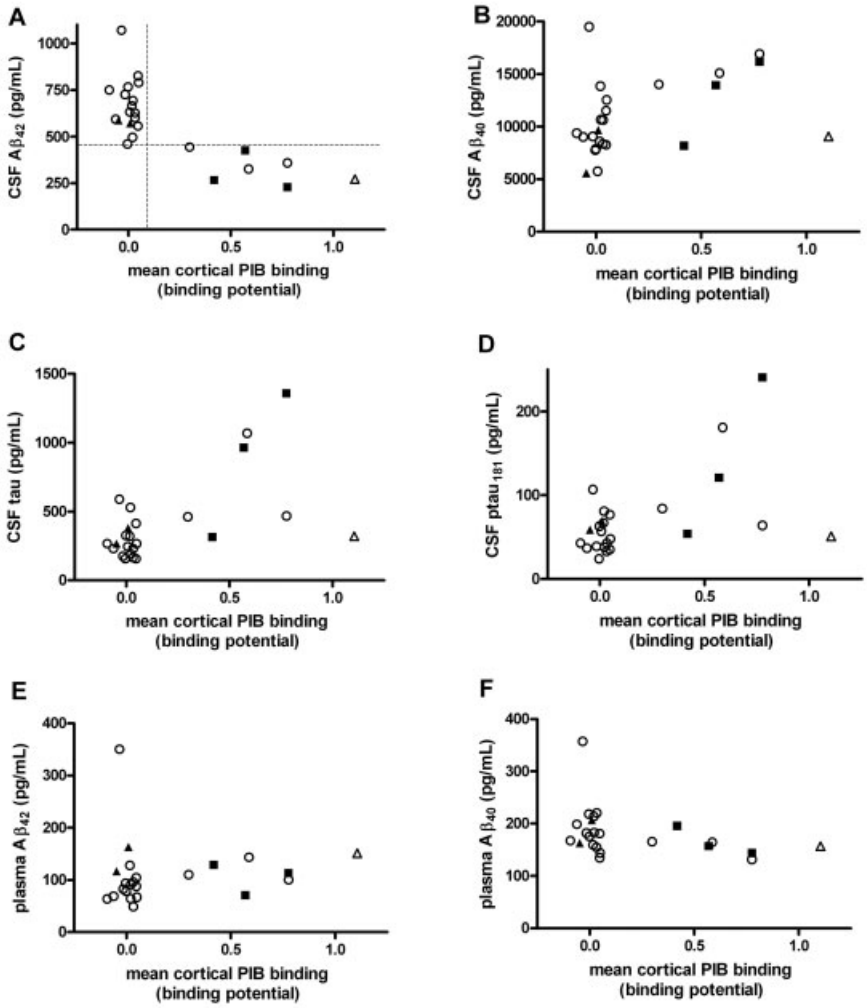

Fig 2. Scatterplots showing the various cerebrospinal fluid (CSF) and plasma measures in individual subjects as a function of in vivo amyloid load as assessed by Pittsburgh Compound-B (PIB) binding. (A) Subjects with positive mean cortical PIB binding (n = 7) exhibited the lowest CSF amyloid-β_{42} ($A\beta_{42}$) levels, and subjects with negative PIB binding (n = 17) displayed greater CSF $A\beta_{42}$ values, with no overlap between the two groups. (B–F) There appeared to be no relation between PIB binding and the other Alzheimer's disease–related markers in CSF ($A\beta_{40}$, tau, phospho-tau_{181}) or plasma ($A\beta_{40}$ and $A\beta_{42}$). Open circles *indicate Clinical Dementia Rating (CDR) score of zero (nondemented; n = 18);* open triangles *indicate CDR 0.5 (very mild dementia of the Alzheimer's type [DAT]; n = 1);* solid triangles *indicate CDR 0.5 (very mild dementia, non-DAT; n = 2);* solid squares *indicate CDR 1 or 2 (mild or moderate DAT; n = 3).*

studies suggest increases in plasma $A\beta_{42}$ are present in the years just before conversion from cognitively normal to DAT.[24,25] Our limited data may not be consistent with these findings; however, the number of CDR 0 cases that have positive PIB binding in this study is small, and we do not yet know whether these individuals will go on to experience development of DAT at a more rapid rate or within the next few years. Longitudinal follow-up of a greater number of individuals with CSF and PIB data will be required to fully address this issue.

Our findings have implications for the development of possible *antecedent* biomarkers of AD. Three subjects exhibiting positive PIB binding and low CSF $A\beta_{42}$ levels were cognitively normal (CDR 0), suggesting the presence of cortical amyloid and low CSF $A\beta_{42}$ levels in these subjects in the absence of cognitive impairment. These data are consistent with previous clinicopathological findings from our own group[26] and others[3] demonstrating the presence of neuropathological AD in some nondemented elderly individuals (ie, preclinical AD). In our sample, neuropathological AD is present in approximately 30% of cognitively normal subjects who die at 75 years or older.[26] Thus, because AD pathology likely begins years before the onset of cognitive impairment or other symptoms, we hypothesize that positive PIB binding and low CSF $A\beta_{42}$ values may also be useful as antecedent biomarkers iden-

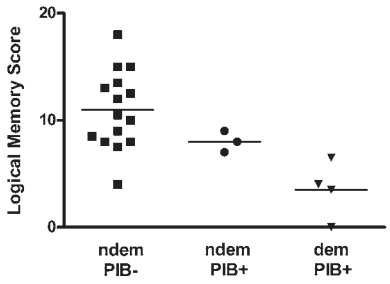

Fig 3. Scatterplot of scores on the Logical Memory component of the Wechsler Memory Scale from subjects who were nondemented and Pittsburgh Compound-B (PIB)–negative, nondemented and PIB-positive, or demented (dementia of the Alzheimer's type [DAT]) and PIB-positive. Scores for the nondemented subjects who were PIB-positive are within the lower range of performance of the nondemented, PIB-negative group, but superior to the scores for demented (DAT), PIB-positive subjects. Squares *indicate nondemented (Clinical Dementia Rating [CDR] 0), PIB-negative (n = 15);* circles *indicate nondemented (CDR 0), PIB-positive (n = 3);* triangles *indicate demented (DAT), PIB-positive (n = 4);* horizontal lines *indicate the mean values for each group. One-way analysis of variance followed by Tukey multiple-comparisons post hoc tests indicate a significant difference between the nondemented, PIB-negative group and the demented (DAT), PIB-positive group ($p < 0.01$), but no significant difference between the nondemented, PIB-positive group and the other two groups.*

tifying preclinical (presymptomatic) AD. The true test of this hypothesis will require longitudinal clinical assessment of subjects in our cohort to ascertain who experiences development of DAT in the future. Interestingly, the three nondemented, PIB-positive subjects with low CSF $A\beta_{42}$ levels performed comparably with the nondemented, PIB-negative subjects on the Logical Memory subtest, a measure of episodic memory from the Wechsler Memory Scale,[27] but all scored in the lower range of "normal." Although it is not possible to draw conclusions from this small sample, this performance is consistent with the idea that these subjects may exhibit subtle cognitive changes that herald the appearance of clinically manifest DAT. Reduced psychometric scores have also recently been observed in cognitively normal individuals with PS1 mutations.[28] Assessment of a greater number of individuals, however, will be necessary before any firm conclusions can be drawn regarding the usefulness of select psychometric tools in identifying preclinical AD. Finally, because one of these PIB-positive subjects with a CDR score of zero was relatively young (<65 years old), our results also support the idea that alterations in Aβ metabolism are important in the initial AD process, and hence could be an attractive therapeutic target for the preclinical and early clinical stages of disease.[29]

Disclosure

GE Healthcare (formerly Amersham Health, Chalfont St. Giles, UK) entered into a license agreement with the University of Pittsburgh regarding the amyloid imaging technology described in this article. W.E.K., and C.A.M., are co-inventors of PIB and, as such, have a financial interest in the license agreement.

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