Plasma Aβ and PET PiB binding are inversely related in mild cognitive impairment

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ABSTRACT

Objective: To evaluate the relations between PET Pittsburgh compound B (PiB-PET) binding (amyloid imaging) and plasma Aβ in patients with mild cognitive impairment (MCI) and similarly aged controls.

Methods: In 20 patients with MCI and 19 cognitively intact controls (case-control study), PiB binding potential (BP_{nd}) was assessed in 4 regions, and total brain excluding cerebellum, referenced to cerebellar binding. The mean of plasma Aβ levels measured in duplicate was analyzed.

Results: Plasma Aβ42/Aβ40 ratio was decreased in MCI compared to controls (mean 0.15 SD 0.04 vs mean 0.19 SD 0.07, $p = 0.03$) but Aβ40 ($p = 0.3$) and Aβ42 ($p = 0.06$) levels did not differ between the 2 groups. PiB BP_{nd} was increased in MCI compared to controls in the cingulate ($p = 0.02$), parietal ($p = 0.02$), and total brain ($p = 0.03$), but not in prefrontal cortex ($p = 0.08$) or parahippocampal gyrus ($p = 0.07$). Linear regression analyses adjusting for age, sex, and cognitive test scores showed that low Aβ42/Aβ40 ratio was associated with high cingulate, parietal, and total brain PiB binding ($0.01 < p \leq 0.05$). These associations between PiB binding and the Aβ42/Aβ40 ratio were strongest in PiB-positive subjects and within the MCI group.

Conclusions: Though cross-sectional, the findings support the "sink" hypothesis that increased brain Aβ is accompanied by lower peripheral levels of Aβ, particularly the Aβ42/Aβ40 ratio in patients with MCI. The association between PiB binding and the plasma Aβ42/Aβ40 ratio suggests possible use of plasma Aβ combined with PiB binding as a risk biomarker with potential clinical application. ***Neurology*® 2011;77:125–131**

GLOSSARY

AD = Alzheimer disease; **BP** = binding potential; **DVR** = distribution volume ratio; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **PiB** = Pittsburgh compound B; **SRT** = Selective Reminding Test.

The amyloid β peptides Aβ40 and Aβ42 are 2 major species in amyloid plaques in the brains of patients with Alzheimer disease (AD).[1] PET amyloid imaging with Pittsburgh compound B (PiB) shows that patients with AD have increased cortical PiB binding compared to controls, and patients with mild cognitive impairment (MCI) have levels between AD and controls.[2-5] In CSF, low Aβ levels in AD have been explained by the "sink hypothesis," which postulates that increasing brain sequestration of amyloid leads to lower Aβ in CSF and plasma.[6,7]

A few studies in small samples show that increased PiB binding is associated with low CSF Aβ levels[8,9] but there are equivocal reports.[10] In a sample of 189 healthy subjects without dementia, increased cortical PiB binding was associated with low CSF Aβ42 levels but not with plasma Aβ levels.[6] In a multisite study, increased PiB cortical binding was associated with low plasma Aβ42 and Aβ42/40 levels across a diagnostically heterogenous sample of AD, MCI, and control subjects but not within each diagnostic group.[11] These studies were confounded by highly variable plasma Aβ values, undetectable plasma Aβ values in several

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subjects in one study,[6] and the use of multiple assays for plasma Aβ within each study.[11] Plasma Aβ levels are approximately one-hundredth of CSF Aβ levels, leading to difficulties in accurate measurement.

We investigated the amyloid sink hypothesis by examining the associations between PiB cortical binding and plasma Aβ measures in a study of patients with amnestic MCI and healthy control subjects.

METHODS Patients of both sexes presented to a Memory Disorders Center between September 2007 and January 2010. Inclusion criteria were age 55–90 years, a Mini-Mental State Examination (MMSE) score of 22 or higher,[12] amnestic MCI defined as subjective memory complaints, and a score >1.5 SD below norms on one of the following tests of memory: Free and Cued Selective Reminding Test immediate and delayed recall, Wechsler Memory Scale–III Visual Reproduction I and II immediate and delayed recall, and Wechsler Memory Scale–Revised Logical Memory I and II immediate and delayed recall. Patients with amnestic MCI with and without deficits in other cognitive domains were included. A comprehensive neuropsychological test battery was administered. From this battery, the MMSE (global cognition) and the 12-item 6-trial Selective Reminding Test (SRT) total and delayed recall (episodic verbal memory) were chosen a priori for statistical analyses. Key exclusion criteria were clinical stroke or cortical stroke or large subcortical lacune or infarct (≥2 cm diameter in any MRI slice), cognitive deficits primarily due to medical conditions/medications, specific neurologic disorder (e.g., Parkinson disease, alcohol/substance abuse/dependence currently or in the past 6 months), current major depression, and history of psychosis. If inclusion and exclusion criteria were met, the final diagnosis of MCI was based on a consensus between 2 expert raters (D.P.D. and Y.S.).

Healthy control subjects, group-matched by age and sex, were recruited by local media advertising. Inclusion and exclusion criteria for controls were similar, except that cognitive criteria required MMSE score of 28 or higher and scores within 1 SD of norms on the 3 tests of memory used for MCI inclusion criteria.

Standard protocol approvals, registrations, and patient consents. The study was approved by the New York State Psychiatric Institute/Columbia University Institutional Review Board and all subjects signed informed consent.

Plasma Aβ42 and Aβ40. Ten-milliliter venous blood samples (tripotassium EDTA) were used to assess plasma Aβ levels. Plasma levels were measured blind to cognitive status using a combination of monoclonal antibody 6E10 (specific to an epitope present on 1–16 amino acid residues of Aβ) and rabbit antisera (R165 vs Aβ42 and R162 vs Aβ40) in a double antibody sandwich ELISA as described previously.[13,14] This method measures the free or soluble form of Aβ, not the oligomeric or bound forms. The detection limit for these assays was 9 pg/mL. Strong test-retest and intra-assay and inter-assay reliability have been reported.[14] The Aβ levels from each blood draw were measured in duplicate, using separate aliquots so that none of the samples were refrozen and rethawed for the repeat assay. The means of the 2 measurements were used in statistical analyses. Aβ levels were not available for clinical diagnosis.

^{11}C-PiB synthesis. The full radiosynthesis of [N-Methyl ^{11}C]-2-(4-methylaminophenyl)-6-hydroxybenzothiazole ([^{11}C]-6-OH-BTA-1) is described elsewhere.[15] The average yield was found to be 14.5% at end of synthesis with a specific activity >37 GBq/μmol.

PET and MRI procedures and PET image processing are described in appendix e-1 on the *Neurology*® Web site at www.neurology.org.[16-21]

^{11}C-PiB kinetic analysis. The cerebellum is nearly devoid of amyloid plaques in patients with AD[22] and cerebellar gray matter shows little ^{11}C-PiB binding in healthy controls and AD.[2] Therefore, a ROI that included the entire cerebellum was drawn on the MRI. A binary mask of this ROI was created. To correct the cerebellar ROI to include gray matter only, unprocessed MRI were segmented using SPM5 to derive the probabilistic gray matter map. The gray matter map and all individual PET frames were multiplied (masked) by the cerebellar binary mask. On a frame-by-frame basis, the sum of all voxels in each masked PET image was divided by the sum of all voxels in the masked gray matter map to derive the gray matter cerebellar time activity curve.

^{11}C-PiB (BP_{ND}) PET modeling. In the 39 subjects who completed the ^{11}C-PiB scan, binding potential (BP_{ND}) was calculated for each ROI using the Logan graphical method from 90-minute PET data, using the gray matter probability-corrected time activity curve of the cerebellum as reference.[23] For comparison to other reports, distribution volume ratio (DVR) = BP_{ND} + 1.

Statistical analyses. Descriptive statistics were used to compare the demographic and clinical variables in patients with MCI and cognitively intact control subjects. Preliminary analyses examined bivariate correlations between ^{11}C-PiB BP_{ND} (binding potential, cerebellar reference) in the cingulate, parietal, and parahippocampal regions, and the Aβ measures (Aβ40, Aβ42, Aβ42/Aβ40 ratio), with demographic and cognitive variables.

Linear regression analyses were conducted on each of the 3 PiB measures, adjusting for age and sex, with each of the Aβ measures as predictors. These analyses were repeated after also including a global cognitive measure (MMSE) or episodic verbal memory measures (SRT total recall or delayed recall) as covariates. PiB binding was classified a priori as high binding if BP_{nd} was greater than 0.35 (equivalent to DVR greater than 1.35) and the associations between low and high PiB binding and the Aβ measures were evaluated. This cutoff was nearly 2 SD above the control mean value and is in the midrange of different cutoffs used in the literature.[5,24]

RESULTS There were 20 patients with MCI and 19 cognitively intact control subjects. Patients with MCI were recruited from 89 patients assessed for eligibility; 29 were eligible and 20 agreed to participate in the study. Control subjects were recruited from 102 subjects assessed for eligibility; 33 were eligible and 19 agreed to participate in the study. Demographic and clinical data are provided in table 1. Plasma Aβ40 and Aβ42 levels did not correlate significantly with each other so they were analyzed separately. In the total sample and separately in the MCI

Table 1 Demographic and clinical characteristics of the sample

Variable	Patients with mild cognitive impairment (n = 20)	Cognitively intact controls (n = 19)	t Test	p Value
Age, y	70.6 (8.4)	67.6 (7.4)	1.2	0.2
Sex, % female	60	74	$\chi^2 = 0.8$	0.36
Education, y	15.9 (2.9)	16.4 (2.5)	0.6	0.6
MMSE (range 0–30)	26.5 (2.7)	29.3 (0.8)	4.3	<0.001
SRT total recall (0–72)	36.6 (9.2)	51.0 (9.0)	4.9	<0.001
SRT delayed recall (0–12)	3.7 (2.3)	8.2 (2.9)	5.3	<0.001
Plasma Aβ40, pg/mL	125.9 (20.7)	119.6 (18.1)	1.01	0.32
Plasma Aβ42, pg/mL	17.9 (4.9)	22.1 (8.4)	1.93	0.06
Plasma Aβ42/Aβ40	0.15 (0.04)	0.19 (0.07)	2.25	0.03

Abbreviations: MMSE = Mini-Mental State Examination; SRT = Selective Reminding Test.

and control groups, none of the plasma Aβ measures were related to age, sex, MMSE, or SRT total recall or delayed recall. In patients with MCI compared to controls, the Aβ42/Aβ40 ratio was lower and plasma Aβ42 tended to be lower ($t = 1.93$, $p = 0.06$) with no difference in Aβ40 levels ($t = 1.0$, $p = 0.3$).

PiB binding in each of the 3 regions was unrelated to age or sex. Increased PiB binding in cingulate, parietal, and total brain was associated with lower MMSE and SRT total and delayed recall (rs = −0.32 to −0.42, ps < 0.01 to 0.05). Increased PiB binding in the prefrontal cortex was associated with lower SRT total ($r = -0.34$, $p = 0.03$) and delayed recall ($r = -0.33$, $p = 0.04$) but not MMSE. Increased PiB binding in the parahippocampal gyrus was associated with lower MMSE ($r = -0.37$, $p = 0.02$) but not lower SRT total or delayed recall. PiB BP_{nd} was increased in MCI compared to controls in the cingulate ($p = 0.02$), parietal ($p = 0.02$), and total brain ($p = 0.03$), but not in prefrontal cortex ($p = 0.08$) or parahippocampal gyrus ($p = 0.07$).

Relation of plasma β-amyloid peptides to PiB PET levels. In the total sample, in linear regression analyses adjusting for age and sex, all 3 measures of plasma Aβ were significantly related to PiB in parietal cortex, and Aβ40 and the Aβ42/Aβ40 ratio were significantly related to PiB in cingulate (table 2). Higher Aβ40 and lower Aβ42/Aβ40 ratio were significant for cingulate in these analyses ($p = 0.02$ and $p = 0.02$, respectively) and lower Aβ42/Aβ40 ratio was significant for parietal cortex in similar analyses ($p = 0.01$). Two healthy control subjects had high Aβ42/Aβ40 ratio (figure). After excluding these 2 subjects, in linear regression analyses adjusting for age and sex, the results did not change appreciably for cingulate (Aβ40 $p = 0.02$, Aβ42 $p = 0.06$, Aβ42/Aβ40 ratio $p = 0.002$) and parietal cortex (Aβ40 $p = 0.06$, Aβ42 $p = 0.02$, Aβ42/Aβ40 ratio $p = 0.001$). In similar linear regression analyses, the relations between plasma Aβ peptide measures and PiB binding in the prefrontal cortex or the parahippocampal gyrus did not reach significance. Higher plasma Aβ40 ($p = 0.04$) and lower Aβ42/Aβ40 ratio ($p = 0.02$), but not Aβ42, were related to total brain PiB binding (table 2). The directions of the associations between plasma Aβ40 and PiB binding (positive association) and between both Aβ42 and Aβ42/Aβ40 ratio with PiB binding (negative association) were consistent across the PiB measures examined (table 2).

Table 2 Relation of amyloid β peptide levels to PiB PET binding[a]

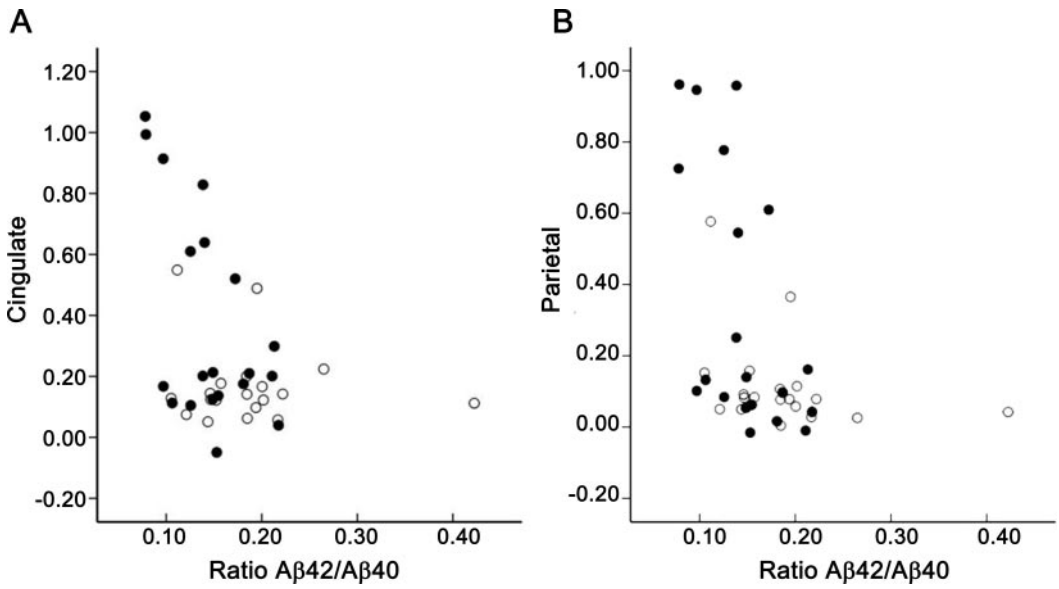
	Model	
Predictor	β	p
Cingulate		
Aβ40	0.006	0.02
Aβ42	−0.01	0.13
Ratio Aβ42/Aβ40	−1.68	0.02
Parietal		
Aβ40	0.005	0.04
Aβ42	−0.014	0.04
Ratio Aβ42/Aβ40	−2.12	0.007
Prefrontal cortex		
Aβ40	0.004	0.06
Aβ42	−0.006	0.31
Ratio Aβ42/Aβ40	−1.14	0.09
Parahippocampal gyrus		
Aβ40	0.001	0.28
Aβ42	−0.004	0.13
Ratio Aβ42/Aβ40	−0.516	0.07
Total brain		
Aβ40	0.003	0.04
Aβ42	−0.007	0.12
Ratio Aβ42/Aβ40	−1.08	0.02

Abbreviation: PiB = Pittsburgh compound B.
[a] Linear regression model on PiB-PET binding potential (cingulate or parietal cortex or hippocampus) adjusted for age and sex with plasma Aβ40 or Aβ42 or Aβ42/Aβ40 ratio as the predictor.

The linear regression analyses for cingulate and parietal cortex, and total brain PiB binding, were repeated with age, sex, each of the Aβ measures, and MMSE or SRT immediate or delayed recall as covariates. In these analyses, the association of lower Aβ42 and Aβ42/Aβ40 ratio with higher cingulate and parietal and total brain PiB binding remained at similar significance levels with the Aβ42/Aβ40 ratio being significant ($0.01 < p \leq 0.05$) in all of these analyses.

The figure shows the relation of the Aβ42/Aβ40 ratio to PiB by MCI status in the cingulate and parietal cortex. Approximately half of the participants

Figure Associations between Pittsburgh compound B (PiB) binding potential and plasma Aβ42/Aβ40 ratio in mild cognitive impairment (MCI) and controls



PiB binding potential (BP_{nd}) for the cingulate (A) and parietal (B) regions of interest and the plasma mean Aβ42/Aβ40 ratio in patients with MCI (closed circles) and cognitively intact control subjects (open circles).

with MCI showed elevated PiB binding and most controls did not show elevated PiB binding. The difference in PiB binding between subjects with MCI and controls was greatest in the parietal region in linear regression analyses adjusted for age and sex (MCI mean = 0.33, control mean = 0.12, p = 0.032). In exploratory analyses within PiB positive subjects (n = 9), the correlations between PiB binding measures and plasma Aβ levels were strong in PiB-positive subjects but not in PiB-negative subjects (table 3).

Within the MCI group, high cingulate, high parietal, and total PiB binding were associated with a lower Aβ42/Aβ40 ratio (ps = 0.02 to 0.03). Seven patients with MCI and 2 control subjects showed high binding in the cingulate and parietal regions. Of the 7 patients with MCI who had high PiB binding (>0.35), 6 had low Aβ42/40 levels (<0.16). One of the 2 controls with high PiB binding had low Aβ4240 ratio. Five patients with MCI had normal PiB and normal Aβ levels.

DISCUSSION The plasma Aβ42/Aβ40 ratio, and to a lesser extent plasma Aβ42, were decreased in patients with MCI compared to cognitively intact control subjects, consistent with the literature.[3-5,19] Increased PiB binding in the cingulate and parietal cortex, as well as increased total brain PiB binding, have been shown to occur in MCI compared to controls.[3,4] The increase in prefrontal cortex binding was not as strong as in the initial PiB report[2] but is consistent with subsequent reports which showed that the precuneus or parietal cortex rather than prefrontal cortex manifests the greatest differences between AD and controls.[3,4] The relative sparing of the parahippocampal gyrus is consistent with the literature

Table 3 Pearson correlations between regional PiB binding and plasma Aβ measures in PiB-positive and PiB-negative subjects

PiB binding potential (BP_{nd})	PiB-positive (BP_{nd} >0.35) subjects (n = 9)			PiB-negative (BP_{nd} ≤0.35) subjects (n = 30)		
	Aβ40	Aβ42	Aβ42/Aβ40	Aβ40	Aβ42	Aβ42/Aβ40
Cingulate	r = 0.81	r = −0.69	r = −0.82	r = 0.37	r = 0.26	r = 0.09
	p = 0.008	p = 0.04	p = 0.007	p = 0.04	p = 0.16	p = 0.63
Parietal	r = 0.49	r = −0.62	r = −0.67	r = 0.34	r = −0.15	r = −0.33
	p = 0.18	p = 0.08	p = 0.05	p = 0.06	p = 0.42	p = 0.08
Total	r = 0.38	r = −0.36	r = −0.43	r = 0.43	r = 0.15	r = −0.07
	p = 0.31	p = 0.35	p = 0.25	p = 0.02	p = 0.42	p = 0.72

Abbreviations: BP = binding potential; PiB = Pittsburgh compound B.

showing low binding in the medial temporal lobe with amyloid brain imaging.[2-4,19]

Increased PiB binding in the cingulate and parietal cortex, and total brain, was associated with decreased plasma Aβ42 and the Aβ42/Aβ40 ratio, and these associations remained significant even after controlling for age, sex, and cognitive test scores. The resilience of this finding in this sample supports the hypothesis that increased amyloid deposition in the brain is accompanied by lower peripheral Aβ levels in plasma. This association between PiB binding and plasma Aβ was strong in PiB-positive subjects and weak to absent in PiB-negative subjects, further supporting the sink hypothesis that increased sequestration of amyloid in the brain is associated with decrease in peripheral Aβ levels.

There was an increase in plasma Aβ40 levels associated with PiB binding that varied depending on which ROI was examined (table 2). In a meta-analysis of 4 studies that examined plasma Aβ measures but without amyloid imaging, an increase in plasma Aβ40 levels, but not Aβ42 or the Aβ42/Aβ40 ratio, was weakly associated with MCI conversion to AD.[25] In AD, there is decreased clearance of both Aβ40 and Aβ42 without any difference in production rates.[26] Aβ42 plays a critical role in the pathogenesis of AD because Aβ42 aggregates much faster and is more toxic than Aβ40.[27] A minor increase in the Aβ42/Aβ40 ratio stabilizes toxic oligomeric species with intermediate conformations, and the relative ratio of Aβ peptides is more important than the absolute amounts of peptides for the induction of neurotoxic conformations.[28] Overall, Aβ42 and the Aβ42/Aβ40 ratio appear to be related to the pathogenesis of AD while Aβ40 may be related more to amyloid deposition in vessel walls and cerebral amyloid angiopathy.[29] We found that an increase in plasma Aβ40 levels was associated with cingulate, parietal, and total brain PiB binding, but the Aβ42/Aβ40 ratio was the plasma measure that showed the most consistent and robust associations with PiB binding across the ROIs examined.

Within the MCI group, 6 of 7 patients with high PiB binding had low plasma Aβ levels. This association was present in only one control subject, and this subject may show evidence of cognitive decline and AD when followed over time. A larger study that examined healthy elderly subjects, and did not explicitly include patients with MCI, did not observe the association between plasma Aβ levels and PiB binding.[6] Further, in that study the authors acknowledged that there was variability in assay procedures with plasma Aβ levels below the limit of detection in several samples,[6] which did not occur in our study. An earlier report in a small series from the same research group found no association between PiB binding and plasma Aβ in 18 healthy controls and 6 patients with dementia of whom 4 had AD.[30] The AIBL study of aging found associations between PiB and plasma Aβ across their entire sample that were similar to the findings in our study, but the associations within each diagnostic group were not significant.[11] The authors emphasized the poor reliability that arose from using multiple, discrepant assays of plasma Aβ.[11] The highly variable levels of plasma Aβ42 and Aβ40 in different studies,[13,31-34] and the reported lack of significant associations between levels of Aβ in plasma and CSF,[14,35] may, in part, be explained by the variability and poor reliability of assays for plasma Aβ levels, i.e., there may indeed have been an association that was obscured by the excessive variability in the results from the plasma assay. In our study, we used a single assay with established low intraclass coefficients and high test-retest reliability,[7] thereby strengthening the reliability of the plasma Aβ findings.

Increased amyloid deposition in the brain may occur several years to decades before clinically manifest symptoms.[36] Reduction in CSF Aβ42, likely reflecting Aβ aggregation in the brain, is associated with brain atrophy on structural MRI in the preclinical phase of AD, suggesting that Aβ aggregation leads to toxicity before clinically detectable disease.[37] A similar reduction in plasma Aβ may occur, as our group showed in a longitudinal study of a multiethnic community sample in which initially elevated plasma Aβ42 in healthy elderly was followed over time by significant reduction in plasma Aβ42 and Aβ42/40 levels in association with the clinically diagnosable onset of AD.[7,38] Increases in CSF tau (and ptau181) may be later events associated with further structural brain damage closer to the clinical onset of AD.[37]

Our finding of increased PiB uptake being associated with lower plasma Aβ levels in MCI supports this proposed timeline of disease progression in the brain, and suggests that plasma Aβ may be similar to CSF Aβ in showing associations with PiB binding. One limitation is that we did not assess CSF Aβ systematically in this sample. Drawing blood is more feasible and acceptable to patients than withdrawal of CSF, but CSF Aβ, tau, and phospho-tau levels clearly have strong predictive utility for conversion to AD. Combining PiB PET with plasma Aβ may have potential clinical application if this combination is found to be more useful than PiB binding or plasma Aβ alone in improving diagnostic accuracy or predicting outcome, and CSF markers if available may further enhance diagnostic accuracy and prediction. Prediction of outcome requires longitudinal data. Continued follow-up, which has begun in our sam-

ple, will also help to clarify if patients with MCI who have increased PiB binding and decreased Aβ42 levels have a high conversion rate to the clinical diagnosis of AD, and if patients with MCI who do not have increased PiB binding and low plasma Aβ levels do not convert to AD.

AUTHOR CONTRIBUTIONS

Dr. Devanand conceptualized the study, obtained grant funding, conducted the study, assisted in analyzing the data, and wrote and edited the manuscript. Dr. Schupf was primarily responsible for conducting the statistical analysis and assisted in the writing and editing of the manuscript. Dr. Stern assisted in the conduct of the study and reviewed and edited the manuscript. Dr. Parsey was responsible for image analysis and reviewed and edited the manuscript. Dr. Pelton assisted in the conduct of the study and reviewed and edited the manuscript. Dr. Mehta was responsible for conducting the plasma assays and reviewed and edited the manuscript. Dr. Mayeux conceptualized the study and reviewed and edited the manuscript.

DISCLOSURE

Dr. Devanand has served on scientific advisory boards for Bristol-Myers Squibb and sanofi-aventis and receives research support from Eli Lilly and Company, Novartis, and the NIH/NIA. Dr. Schupf has served as a consultant to Elan Corporation and receives research support from the NIH and the Alzheimer's Association. Dr. Stern has served as a consultant for Allergan Inc., Cephalon, Inc., Elan Corporation, Eisai Inc., Pfizer Inc, Ortho-McNeil Neurologics®, Merck Serono, GlaxoSmithKline, Eli Lily and Company, Janssen, and the NIH (NIA, NINDS). Dr. Parsey has received research support from GE Healthcare, Novartis, Sepracor Inc., GlaxoSmithKline, the NIH, and the Dana Foundation. Dr. Pelton has received speaker honoraria from Bristol-Myers Squibb Company and Pfizer Inc; serves as a consultant for sanofi-aventis; and receives research support from Forest Laboratories, Inc. and the NIH/NIA. Dr. Mehta receives research support from the NIH/NIA. Dr. Mayeux serves on scientific advisory boards for PsychoGenics Inc. and Quintiles and receives research support from the NIH.

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HIGH-DOSE INTRAVENOUS IMMUNOGLOBULIN THERAPY IN MULTIFOCAL NEUROPATHY

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We treated five consecutive patients with multifocal motor neuropathy (MMN) with high-dose intravenous immunoglobulin (IVIg). Four patients had increased levels of anti-asialo-GM_1 IgM and two of anti-GM_1 IgM as well; one patient had no reactivity. We treated them twice with 0.4 g/kg IVIg for 5 consecutive days at a 2-month interval, followed by maintenance infusions up to 6 to 12 months. All patients with high anti-asialo-GM_1 had a consistent clinical improvement starting 3 to 10 days after the first IVIg course; in one patient, recovery was complete and persistent for 12 months without additional treatment, while in three patients, improvement only lasted 20 to 30 days. There was a similar improvement in these patients after the second course of IVIg which was maintained by periodic 2-day IVIg infusions. Clinical improvement in these patients was associated with a reduction of conduction block in most, but not all, motor nerves, while antibody titers were not consistently modified by treatment. There was no clinical or electrophysiologic improvement in the patient without antiglycolipid activity after 6 months of IVIg. IVIg may be a safe and effective therapy for MMN.

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Comment from Andrew G. Engel, MD, FAAN, Associate Editor: *Reported clinical and EMG improvement in 4 of 5 patients treated with IVIg that could be maintained by the additional use of low-dose oral cyclophosphamide. The paper underlined the importance of distinguishing multifocal neuropathy form ALS.*