Amyloid is linked to cognitive decline in patients with Parkinson disease without dementia

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ABSTRACT

Objective: To determine whether amyloid burden, as indexed by Pittsburgh compound B (PiB) retention, identifies patients with Parkinson disease with mild cognitive impairment (PD-MCI) compared to those with normal cognition (PD-nl). A related aim is to determine whether amyloid burden predicts cognitive decline in a cohort of subjects with PD without dementia.

Methods: In this prospective cohort study, we examined 46 subjects with PD without dementia, of whom 35 had normal cognition and 11 met criteria for PD-MCI at study baseline. All subjects underwent standardized neurologic and neuropsychological examinations and PiB PET at baseline, and clinical examinations were conducted annually for up to 5 years.

Results: At baseline, precuneus PiB retention did not distinguish PD-MCI from PD-nl. Subjects with PD-MCI declined more rapidly than PD-nl subjects on cognitive tests of memory, executive function, and activation retrieval. Of the 35 PD-nl subjects, 8 progressed to PD-MCI and 1 to dementia; of the 11 PD-MCI subjects, 5 converted to dementia. Both higher PiB retention and a diagnosis of PD-MCI predicted a greater hazard of conversion to a more severe diagnosis. Baseline PiB retention predicted worsening in executive function over time. The APOE ϵ 4 allele also related to worsening in executive function, as well as visuospatial function, activation retrieval, and performance on the Mini-Mental State Examination. In contrast to its relation to cognitive decline, PiB retention did not affect progression of motor impairment.

Conclusions: At baseline measurements, amyloid burden does not distinguish between cognitively impaired and unimpaired subjects with PD without dementia, but our data suggest that amyloid contributes to cognitive, but not motor, decline over time. *Neurology*® 2013;80:85-91

GLOSSARY

AD = Alzheimer disease; **CDR** = Clinical Dementia Rating; **CDR-SB** = Clinical Dementia Rating sum of boxes; **CI** = confidence interval; **DVR** = distribution volume ratio; **H&Y** = Hoehn & Yahr; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **NP** = neuropsychological; **PD** = Parkinson disease; **PD-MCI** = Parkinson disease with mild cognitive impairment; **PD-nl** = Parkinson disease with normal cognition; **PDD** = Parkinson disease dementia; **PiB** = Pittsburgh compound B; **UPDRS** = Unified Parkinson's Disease Rating Scale; **WAIS-R** = Wechsler Adult Intelligence Scale-Revised; **WMS-R** = Wechsler Memory Scale-Revised.

Cognitive impairments are common in Parkinson disease (PD) and increase in severity and frequency over time.¹⁻³ Whether cognitive impairments that fall short of a dementia diagnosis herald impending dementia is an unresolved question, but longitudinal studies in PD support this possibility.^{4,5} Dementia is common in PD, with a relative risk two- to sixfold higher than the general population,⁶ corresponding to lifetime risk estimates of 30%–80%.⁷ Multiple pathologic processes have been linked to dementia in PD: degeneration of basal forebrain cholinergic nuclei,⁸ frontal-subcortical circuit deafferentation due to degeneration of brainstem dopaminergic neurons,⁹ diffuse cortical Lewy bodies associated with α -synuclein,¹⁰ and Alzheimer-like lesions with A β -laden senile plaques.¹¹ Techniques to determine which of these is dominant have been limited until now. The advent of molecular neuroimaging with amyloid radioligand Pittsburgh compound B (PiB) affords an opportunity to examine in life the potential contribution of A β burden to the progression of cognitive impairments in patients with PD without dementia. We and others have previously shown

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Supplemental Data

From the Departments of Neurology (S.N.G., J.J.L., D.R., A.S., M.M., K.A.J., J.H.G.) and Radiology (K.A.J.), Massachusetts General Hospital, Boston; and Autonomous University of Barcelona–Medicine Doctoral Studies (M.M.), Barcelona, Spain.

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that PiB uptake is higher in parkinsonian patients with dementia than in patients with PD without dementia.^{12–14} We report a longitudinal study of patients with PD without dementia and show that PiB uptake is associated with multiple indices of cognitive decline, including conversion to dementia.

METHODS **Standard protocol approval and patient consents.** The Partners HealthCare System Institutional Review Board approved this study. Informed consent was obtained from all patients participating in the study.

Participants. We enrolled 47 patients with PD without dementia between 2006 and 2011 into a prospective cohort study. A total of 46 met research diagnostic criteria for idiopathic PD¹⁵; 1 was excluded because of drug-induced parkinsonism. There were 33 men and 13 women, with mean $\pm$ SD age 68.5 ± 6.2 years at study baseline, education 16.8 ± 2.6 years, Hoehn & Yahr (H&Y) scale 2.3 ± 0.7 , and Unified Parkinson's Disease Rating Scale (UPDRS) motor subscore 19.7 ± 8.4 (table 1). All were taking optimal doses of dopaminergic medications prescribed by their neurologist and were tested in the "on" condition. None were taking drugs with prominent anticholinergic effects, such as trihexyphenidyl, that might be expected to impair cognition. Of the 46, 35 scored in normal ranges on a set of cognitive tests (see below) at study baseline, and 32 of these had no cognitive complaint. Eleven met criteria for mild cognitive impairment,¹⁶ with a cognitive complaint, such as memory loss, that was corroborated by an informant, plus at least 1 cognitive test score that fell in the impaired range. We used published normal cognitive test values with 1 SD thresholds.^{17–24} Patients with Parkinson disease with mild cognitive impairment (PD-MCI) had a global Clinical Dementia Rating (CDR) score of at least 0.5; 8/11 were amnesic, multidomain; 3/11 were nonamnesic, multidomain. The memory box score was at least 0.5 in 10 of these subjects. The mean Mini-Mental State Examination (MMSE) score was 29.1 ± 1.0 for the Parkinson disease with normal cognition (PD-nl) group, and 26.3 ± 2.9 for the PD-MCI group. Some subjects developed PD dementia (PDD) over the course of the study, as defined by the 2007 Movement Disorders criteria.⁶

Clinical and neuropsychological examinations. Neurologic examination included the H&Y scale²⁵ and 4-part UPDRS.²⁶ *APOE* genotype²⁷ was measured in 43/46 participants. Psychiatric assessments included the Neuropsychiatric Inventory Questionnaire²⁸ and Geriatric Depression Scale.²⁹ Neuropsychological (NP) assessment included the MMSE,³⁰ American National Adult Reading Test,³¹ Wechsler Memory Scale-Revised (WMS-R), Logical Memory I and IIA,³² WMS-R Digit Span Forward and Backward,³³ Category Fluency,³⁴ Trailmaking A and B,³⁵ Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol,³⁶ Boston

Naming,³⁷ Controlled Oral Word Fluency,³⁸ Benton Visual Form Discrimination,³⁹ and Free and Cued Selective Reminding⁴⁰ (table 2). Timed tests were considered in the context of bradykinesia. The CDR sum of boxes (CDR-SB) score⁴¹ was calculated from information provided by the subject's knowledgeable informant who rated the subject's abilities in the spheres of memory, orientation, judgment, community activities, home and hobbies, and personal care.

Across all NP tests and visits, in 14 instances an NP score was missing due to severity of cognitive impairment. In these instances, we estimated the missing value with a multiple regression equation with the predictors of MMSE and CDR-SB, derived from the nonmissing NP data. Estimated values were constrained to the acceptable range for the NP. A perturbation of random normal error with variance estimated from the regression mean square error was added so that the new score variances were not artificially attenuated.

To reduce the number of variables, factor analyses based on performance grouped the NP tests into 4 distinct domains: episodic memory (Logical Memory IA and IIA); activation retrieval (verbal fluency, Category Fluency, Boston Naming, and Free and Cued Selective Reminding); executive function (Trails B and WAIS-R Digit Symbol); and visuospatial abilities (Benton Visual Form Discrimination). The executive function factor captures elements of attention and working memory. Cognitive composite scores were produced for each domain, where each composite was a mean of nonmissing *z* scores (relative to data from cognitively normal subjects with PD) for the set of NP tests. For each computed composite, no more than half of NP component variables were allowed to be missing for the factor score to be nonmissing.

PiB PET and image analyses. *N*-methyl-[¹¹C]2-(4'-methylaminophenyl)-6-hydroxybenzothiazole (PiB) was prepared at Massachusetts General Hospital as previously described.¹⁷ Subjects were positioned in a Siemens HR+ scanner (3D mode; 63 image planes; 15.2-cm axial field of view; 5.6-mm transaxial resolution; 2.4-mm slice interval; 69 frames: 12×15 seconds, 57×60 seconds; Knoxville, TN). After a transmission scan, 8–15 mCi of ¹¹C PiB was injected as a bolus, followed immediately by a 60-minute dynamic acquisition. PET data were reconstructed and corrected for attenuation. Each frame was evaluated to verify adequate count statistics and absence of head movement.

Each subject's precuneus, frontal cortex aggregate region of interest, and striatum were identified with the Automated Anatomical Labeling template following SPM spatial transformation, as described previously.¹² PiB retention was calculated using the Logan graphical analysis method,^{18,19} with cerebellar cortex as reference tissue input function; specific PiB retention was expressed as the distribution volume ratio (DVR), as in previous studies.^{20,21} The precuneus is an early, common site of amyloid deposition and frequently carries the highest cortical amyloid burden measured with PiB PET. PiB retention in the precuneus correlated highly with mean cortical PiB retention ($r = 0.94$). The frontal aggregate's

Table 1 Clinical characteristics of the PD cohort at study baseline

Diagnosis	No.	M/F	Age, y	Education, y	H&Y	UPDRS	CDR-SB ^a	MMSE ^a
All PD	46	33/13	68.5 $\pm$ 6.2	16.8 $\pm$ 2.6	2.3 $\pm$ 0.7	19.7 $\pm$ 8.4	0.5 $\pm$ 0.9	28.4 $\pm$ 2.0
PD-nl	35	24/11	68.9 $\pm$ 6.0	16.8 $\pm$ 2.7	2.2 $\pm$ 0.6	19.4 $\pm$ 7.2	0.1 $\pm$ 0.3	29.1 $\pm$ 1.0
PD-MCI	11	9/2	67.2 $\pm$ 6.8	16.7 $\pm$ 2.5	2.5 $\pm$ 0.7	20.5 $\pm$ 11.7	1.7 $\pm$ 1.2	26.3 $\pm$ 2.9

Abbreviations: CDR-SB = Clinical Dementia Rating sum of boxes; H&Y = Hoehn and Yahr stage; MMSE = Mini-Mental State Examination; PD = Parkinson disease; PD-MCI = Parkinson disease with mild cognitive impairment; PD-nl = Parkinson disease with normal cognition; UPDRS = Unified Parkinson's Disease Rating Scale.

^aPD-nl and PD-MCI significantly different ($p \leq 0.05$) by *t* test.

Table 2 Baseline cognitive test scores for PD-nl and PD-MCI

	PD-nl	PD-MCI
Clinical Dementia Rating scale	0.1 ± 0.2	0.5 ± 0.0 ^a
Logical Memory IA	13.1 ± 4.1	10.5 ± 3.2
Logical Memory IIA	12.1 ± 3.9	9.5 ± 4.2
Digits forward	7.1 ± 1.0	6.5 ± 1.1
Digits backward	4.9 ± 1.2	4.5 ± 0.8
Trails A	38.9 ± 18.7	53.4 ± 21.6 ^a
Trails B	108.6 ± 68.2	187.2 ± 92.2 ^a
Category Fluency	33.9 ± 8.6	26.5 ± 9.5 ^a
Letter fluency	44.6 ± 13.8	34.0 ± 15.4 ^a
Digit Symbol	42.3 ± 9.7	33.5 ± 10.4 ^a
Boston Naming Test	28.4 ± 1.2	25.6 ± 3.6 ^a
Blessed Dementia Scale	2.0 ± 2.0	2.9 ± 1.9
Free Selective Reminding Test	30.4 ± 5.1	24.6 ± 4.0 ^a
Free and Cued Selective Reminding Test	47.5 ± 1.0	46.6 ± 1.4
Benton Visual Form Discrimination	29.1 ± 3.7	28.2 ± 3.5
AMNART verbal IQ	122.5 ± 7.8	110.9 ± 15.4 ^a
Neuropsychiatric Inventory Questionnaire	1.8 ± 2.2	3.6 ± 2.7 ^a
Geriatric Depression Scale	2.3 ± 2.1	4.5 ± 2.1 ^a
Motor symptom duration, y	7.4 ± 4.8	7.5 ± 6.0
Cognitive symptom duration, y	1.1 ± 1.8	3.5 ± 2.5
Fluctuations score	0.2 ± 0.5	1.0 ± 0.8 ^a

Abbreviations: AMNART = American National Adult Reading Test; PD-MCI = Parkinson disease with mild cognitive impairment; PD-nl = Parkinson disease with normal cognition.

^aPD-nl and PD-MCI significantly different ($p \leq 0.05$) by *t* test.

component regions are listed in appendix e-1 on the *Neurology*[®] Web site at www.neurology.org.

Protocol design. At study entry, subjects underwent comprehensive clinical and NP examinations and completed PiB PET imaging. Subjects returned for annual clinical and NP examinations for a mean of 2.5 ± 1.4 years (range 1–5 years). There were 156 total visits over this time: 41 subjects completed visit 2, 32 completed visit 3, 25 completed visit 4, and 12 completed visit 5.

Data analysis. We focused on 2 longitudinal measures: change in continuous numeric indicators of cognition (MMSE and the cognitive composites) and transition to more severe diagnoses. Change in continuous indicators was assessed with mixed random/fixed coefficient longitudinal regression models. Intercept and linear slope of change relative to years in the study were random subject terms, initially allowed to be correlated, occasionally forcing independence of random terms or the random slope to be fixed, in order to attain algorithm convergence. We conducted backward elimination of fixed terms, which included baseline diagnosis and its interaction with time, PiB DVR and its interaction with time, gender, years of education, baseline age, and baseline duration of motor symptoms. Residual distributions were checked to assess model fit and conformance with normality assumptions. Because of missing values, *APOE* $\epsilon 4$ status was assessed in a separate analysis. The relation of PiB DVR to time to transition to a more severe diagnosis was assessed with Cox proportional hazards regression models containing predictors of PiB DVR, baseline diagnosis and its interaction with PiB, baseline age/

duration, years of education, and gender. Earliest transition from PD-nl to PD-MCI (or PDD) and from PD-MCI to PDD were both included in the same analysis to increase sample size. All subjects either remained stable in their diagnosis across time (considered “censored” observations in the model) or transitioned to a more severe diagnosis. In 1 case, a subject with baseline PD-MCI reverted to PD-nl for the subsequent 3 years. That subject was considered stable PD-nl for the analysis, which is why the distribution of baseline diagnoses reported in the Cox regression below differs slightly from what is reported elsewhere. The assumption of proportional hazards was checked and verified. SAS (version 9.3) and JMP Pro (version 9.0.2) software were used for analyses and graphs.

RESULTS Baseline differences in clinical and amyloid biomarkers between PD-nl and PD-MCI. At baseline, the PD-MCI group performed more poorly than the PD-nl group on most cognitive tests (table 2), as well as on the cognitive factors of episodic memory ($p = 0.0569$), executive function ($p = 0.0015$), and activation retrieval ($p < 0.0001$), but not visuospatial function ($p = 0.5066$). In contrast, the 2 groups’ mean H&Y scores (PD-nl 2.2 ± 0.6 , PD-MCI 2.5 ± 0.7) and UPDRS scores (PD-nl 19.4 ± 7.2 , PD-MCI 20.5 ± 11.7) did not differ. The mean PiB DVR in the precuneus region for the entire cohort was 1.14 ± 0.19 . Mean cortical PiB retention was 1.15 ± 0.14 . Although PD-MCI subjects were cognitively impaired, baseline PiB retention did not distinguish PD-nl (1.14 ± 0.22) from PD-MCI (1.13 ± 0.06) (figure 1). Neither precuneus nor frontal PiB retention pooled across the groups related to baseline performance on any of the cognitive factors (adjusting for age). The *APOE* $\epsilon 4$ allele was not strongly linked to PiB uptake. Its occurrence did not differ between PD-nl and PD-MCI. Amyloid burden in the striatum was similar in PD-nl, PD-MCI, and PDD subjects.

Longitudinal cognitive course of PD-nl and PD-MCI. Over time, cognitive symptoms progressed for the entire cohort. Of the 35 subjects with PD-nl, 26 remained stable, 8 progressed to PD-MCI, and 1 progressed to dementia. Of the 11 subjects with PD-MCI, 1 reverted to PD-nl, 5 remained stable, and 5 progressed to dementia. Thus, 14 of 46 patients with PD without dementia showed progression in cognitive impairments. The Cox regression analyses showed that subjects with PD-MCI at baseline converted to a more severe diagnosis sooner than baseline PD-nl subjects (hazard ratio = 3.45, 95% confidence interval [CI] = 1.016, 10.843; $p = 0.035$). Subjects with PD-MCI also worsened more quickly than subjects with PD-nl on the CDR-SB (random effects longitudinal model, interaction of baseline diagnosis and years in the study; $p < 0.0001$) and on the cognitive factors of executive function ($p = 0.032$), episodic memory ($p < 0.012$), and activation retrieval ($p = 0.020$).

Figure 1 PiB retention did not differentiate PD-nl and PD-MCI subjects

The black line extending across the whole figure represents the grand mean. The green line extending beyond the box for each group represents its mean. The red line for each group within the box represents the group median, box edges show the interquartile range, and box whiskers extend to as much as 1.5 interquartiles above and below the edges. Box width is proportional to group sample size. Subjects who subsequently progressed to a worse diagnosis are depicted as blue triangles, while those who remained stable are shown as red circles. PD-MCI = Parkinson disease with mild cognitive impairment; PD-nl = Parkinson disease with normal cognition; PiB = Pittsburgh compound B.

Impact of amyloid biomarkers on longitudinal course in PD. The pooled group of subjects who transitioned to a more severe cognitive diagnosis ($n = 14$) had higher

baseline PiB retention than the group who remained diagnostically stable ($n = 32$; $p = 0.048$, Mann-Whitney test). We performed a nonparametric survival analysis of 2 groups formed with a median split on PiB retention. The group with higher PiB retention transitioned to a more severe diagnosis significantly sooner than the group with lower PiB retention ($p = 0.035$; figure 2). This was not due to a systematic difference in baseline cognitive function, as the high PiB DVR group performed better at baseline than the low PiB DVR group on the visuospatial abilities factor ($p = 0.023$), worse on the activation retrieval factor ($p = 0.005$), and similarly ($p > 0.05$) on the remaining 2 factors. As a continuous numeric predictor, higher amyloid burden also increased the likelihood of transition to a more severe diagnosis in the Cox regression ($p = 0.068$; hazard ratio = 8.78 per unit PiB, 95% CI = 0.634, 80.792), additive to and independent of the baseline PD-nl vs PD-MCI diagnosis effect. In addition, higher PiB retention significantly ($p = 0.035$) related to worsening in executive function for the sample as a whole: across subjects, a 1 unit higher score on PiB was associated with an estimated decline in the linear slope of trajectory of about 0.4 SDs of the executive function factor per year. Higher PiB retention was also marginally related to faster decline in visuospatial function ($p = 0.060$). The presence of an *APOE* $\epsilon 4$ allele was independently associated with decline in MMSE ($p = 0.005$), executive function ($p = 0.003$), activation retrieval ($p = 0.004$), and visuospatial abilities ($p = 0.013$). Progression of motor impairment, as assessed with H&Y and UPDRS motor subscale scores, did

Figure 2 Kaplan-Meier survival curves

Subjects with Pittsburgh compound B (PiB) retention above the median for the sample converted to a more severe diagnosis sooner than those with values below the median. Parkinson disease with normal cognition and Parkinson disease with mild cognitive impairment groups were pooled together for this analysis. Shading around survival curves indicates 95% confidence bands. "Censored" indicates the last visit for subjects who had not transitioned to a more severe diagnosis.

not relate to precuneus or striatum PiB retention, or to the *APOE* $\epsilon 4$ allele.

Of the 3 subjects with highest amyloid burden (figure 1), 2 transitioned from PD-nl to PD-MCI over the course of the study. Of these 2, 1 remains PD-MCI; the other discontinued the study due to a traumatic subdural hemorrhage. The third subject remains PD-nl.

DISCUSSION Diffuse cortical Lewy bodies and α -synuclein,¹⁰ loss of basal forebrain cholinergic neurons⁸ and medial nigral dopaminergic neurons,⁹ and Alzheimer disease (AD) pathology¹¹ have all been implicated in the development of cognitive impairments and dementia in PD. The results of this study support the contribution of cortical amyloid A β deposits. The hypothesis that amyloid contributes to dementia initially came from the Alzheimer field, where excessive A β is viewed as an early, perhaps inciting, event in a cascade of pathologic changes leading to synaptic loss, neuronal degeneration, and clinical dementia.^{22,23} The exact A β moiety involved remains controversial, with research focused on the relative importance of monomers, oligomers, or fibrils in senile plaques. The 42 amino acid peptide (A β 1-42) aggregates readily, is the principal component in the senile plaque, and seems to be the more toxic species.²⁴ Mechanisms whereby A β causes neurodegeneration remain under active investigation. Nonetheless, excessive amyloid accompanies dementia in AD and in other conditions, including dementia with Lewy bodies, where we confirmed in a human postmortem case that PiB binds to A β deposits in senile plaques.²⁵ Numerous subsequent investigators have confirmed this finding,²⁶ leaving no doubt that PiB selectively and specifically binds to A β -pleated sheets and gives an accurate representation of cerebral A β burden.

In this study, PD-nl and PD-MCI had similar, generally modest PiB retention, with most subjects well below the high values characteristic of AD. Because sample size was limited, additional studies will be required to confirm these findings. There is substantial PiB uptake in $\sim 30\%$ of healthy control subjects,²⁷ which squares with our current experience with patients with PD without dementia.¹² The significance of elevated PiB retention in cognitively normal individuals is uncertain, and it is an open research question whether their amyloidosis represents a disease process that will progress to dementia on some timescale or whether it represents a risk factor. Alternatively, these PiB-positive individuals may have yet-to-be-discovered mechanisms that blunt A β toxicity and spare neurons from degeneration. Data on this point are incomplete, although high PiB retention is common in mild cognitive impairment (MCI)²⁸ and is a powerful predictor of subsequent conversion to AD.²⁹ Our findings suggest that A β may play a similar role in PD: at baseline imaging A β may seem bland but deleterious effects emerge as patients decline cognitively

over time to MCI and then dementia. Together, α -synuclein and A β -42 increase each other's toxicity.³⁰ Amyloid may therefore contribute to cognitive impairment in PD both directly and indirectly, by enhancing α -synuclein toxicity. Thus, lower levels of amyloid may be necessary to cause dementia in the synucleinopathies than in AD.

Additional support for amyloid's association with cognitive decline in PD comes from CSF measurements of A β . Mean CSF A β 1-42 in PD has been reported to be lower than in healthy controls and higher than in AD,³¹ with A β 1-42 levels decreasing systematically from cognitively normal PD to PD-MCI to PDD, down to AD levels.³² In addition, a recent longitudinal study found that low CSF A β 1-42 predicted progression to dementia in PD.³³ The CSF formula of low A β 1-42 and high tau is characteristic of AD and denotes subjects with MCI who are likely to progress to AD.³⁴ Although the basis for decreased CSF A β is unclear, high PiB uptake is strongly associated with low CSF A β 1-42.³⁵ We did not measure CSF A β in our study, but anticipate that future studies will confirm this relationship in PD as well as in AD.

A β -related declines occurred in some cognitive domains and predicted conversion of diagnosis. Amyloid burden specifically related to progressive impairment of executive function and weakly to visuospatial function. These results are tantalizing, as frontal lobe functions and visuospatial skills are prominently affected in PD.⁶ *APOE* genotype also related to declining performance in most cognitive domains. *APOE* $\epsilon 4$ has been implicated in cognitive impairment in PD (reference 36, but see reference 37) and may have influenced amyloid burden in our cohort.³⁸ Although we did not find a significant correlation between amyloid burden and *APOE* genotype, this may have been due to sample size. Because advanced age is also known to influence A β accumulation in the brain,³⁹ we matched our groups for age and adjusted for age in our analyses. Consistent with prior results identifying MCI in PD as a risk factor for dementia,^{4,5} we also found that subjects with PD-MCI declined more rapidly on cognitive testing than subjects with PD-nl and converted to dementia more rapidly than subjects with PD-nl converted to PD-MCI or PDD.

Strengths of this study include its prospective design enrolling a well-characterized cohort of patients with PD who underwent annual comprehensive neurologic and NP examinations over 2.5 years. Additional strengths are careful PiB scans and sophisticated image analyses conducted by experienced personnel. Although the relatively small number of enrolled subjects could be seen as a weakness, the number was selected based on a power analysis at study onset and proved sufficient to demonstrate the deleterious long-term effects of cortical A β deposits on cognition in PD. Finding the association

between amyloid burden and cognitive impairment in PD has clear therapeutic implications. Various drug strategies are evolving to decrease A β production, to prevent its aggregation, or to accelerate its clearance from the brain; clinical trials in AD are already underway based on these approaches. As a proof of principle, antibodies directed against A β 1-42 have been shown to decrease senile plaque number and tau phosphorylation in human autopsy cases.⁴⁰ Should this immune treatment or any of the other anti-amyloid approaches under consideration prove effective in AD, similar treatments will become immediately relevant for treating PD with the expectation of preventing dementia, or at least slowing progression of cognitive impairments.

AUTHOR CONTRIBUTIONS

Dr. Gomperts: study concept and design, acquisition of data, data analysis and interpretation, writing the manuscript. Dr. Locascio: data analysis and interpretation, critical revision of the manuscript for important intellectual content. Dr. Rentz: data analysis and interpretation, critical revision of the manuscript for important intellectual content. Ms. Santarlasci: acquisition of data and data analysis. Dr. Marquie: critical revision of the manuscript for important intellectual content. Dr. Johnson: interpretation of data analyses, critical revision of the manuscript for important intellectual content. Dr. Growdon: study concept and design, acquisition of data, interpretation of data analyses, writing the manuscript, study supervision.

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