Assessing Mild Cognitive Impairment with Amyloid and Dopamine Terminal Molecular Imaging

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We evaluated PET-based classification of neurodegenerative pathology in mild cognitive impairment (MCI). **Methods:** Our study was a cross-sectional and prospective evaluation of a cohort of 27 MCI subjects drawn from a university-based cognitive disorders clinic. We compared expert clinical consensus classification of MCI at entry and possible dementia at follow-up with molecular imaging–based classification using ^{11}C-dihydotetrabenazine PET measurement of striatal dopamine terminal integrity and ^{11}C-Pittsburgh compound B (^{11}C-PiB) PET measurement of cerebral amyloid burden. **Results:** Eleven subjects were initially classified clinically as amnestic MCI, 7 as multidomain MCI, and 9 as nonamnestic MCI. At a mean follow-up of 3 y, 18 subjects converted to dementia. PET imaging evidence of significant cerebral amyloid deposition or nigrostriatal denervation was a strong predictor of conversion to dementia. There was only moderate concordance between expert clinical classifications and PET-based classifications of dementia subtypes. **Conclusion:** Combined PET molecular imaging of cerebral amyloid burden and striatal dopamine terminal integrity may be useful for identifying subjects at high risk for progression to dementia and in defining neurochemically differentiated subsets of MCI subjects.

Key Words: dementia; Alzheimer disease; Lewy body dementia; frontotemporal dementia

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Mild cognitive impairment (MCI) is recognized as a substantial risk factor for subsequent development of dementia (*1*). There is considerable interest in MCI subjects as suitable target populations for clinical trials aimed at delaying dementia onset. MCI, however, is a heterogeneous entity caused by all major neurodegenerative pathologies and vascular etiologies (*1–7*). Some MCI subjects do not have a progressive course, and others may improve over time (*8–12*). Clinical trials enrolling MCI subjects face the same challenge as trials involving subjects with early dementias: the strong likelihood of enrolling heterogeneous subject populations, plus the problem of enrolling subjects who will not go on to develop dementia. The development of PET ligands identifying characteristic pathologic features of different neurodegenerative dementias offers the possibility of a minimally invasive subclassification of MCI subjects based on well-characterized correlates of pathology (*13,14*). Because potential treatments to prevent or delay onset of dementia are likely to target specific pathologic processes, the identification of subject groups with specific underlying pathologic features is likely to improve the statistical power of clinical trials.

There are 3 primary causes of neurodegenerative dementias—Lewy body dementia (LBD), Alzheimer disease (AD), and frontotemporal dementias (FTDs). LBD is characterized by substantial loss of nigrostriatal dopaminergic terminals, together with cerebrocortical Lewy bodies and Lewy neurites. AD and a significant percentage of LBD subjects exhibit neuritic plaques composed of fibrillar amyloid precursor protein fragments (Aβ amyloid). FTDs generally lack these features and are characterized by deposition of a variety of protein species including τ-protein and TAR-DNA-binding protein-43.

Studies correlating amyloid imaging results with the postmortem assessments of amyloid burden indicate a good correlation between imaging and pathologic measures of amyloid burden (*15*). Prior postmortem studies evaluating nigrostriatal degeneration in pathologically defined AD and LBD samples indicated a high specificity for substantial loss of nigrostriatal dopaminergic terminals as a marker for LBD (*16,17*). These results, and others, indicate that molecular imaging with amyloid and nigrostriatal dopamine terminal ligands may identify characteristic pathologic features of neurodegenerative dementias.

We previously reported PET imaging–based classification of early, mild dementias with amyloid and dopamine terminal molecular imaging. We demonstrated only moderate (Cohen's $\kappa = 0.39$) concordance between molecular imaging–based

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classifications and expert consensus–based clinical classifications (*18*). To clarify the potential role of this imaging-based approach in the subclassification of MCI and to evaluate the prediction of progression to dementia, we report the results of combined PET imaging with the nigrostriatal dopamine terminal marker ^{11}C-dihydotetrabenazine and the Aβ amyloid marker ^{11}C-Pittsburgh compound B (^{11}C-PiB) in a cohort of MCI subjects.

MATERIALS AND METHODS

Subjects

Twenty-seven subjects with primary symptoms of cognitive impairment were recruited from the University of Michigan Cognitive Disorders Clinic. This was a convenience sample of subjects meeting criteria for MCI and satisfying the following inclusion and exclusion criteria (*18*). Included subjects were over the age of 40, had cognitive symptoms for longer than 9 mo, and were capable of completing neuropsychologic testing and research neuroimaging. Subjects with a modified Hachinski scale score greater than 4 or meeting NINDS-AIREN (National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences) criteria suggesting vascular dementia were excluded. Subjects were excluded also if a finding suggested the following possible nonneurodegenerative causes of cognitive decline: clinically significant abnormality on screening blood tests including vitamin B_{12} level and thyroid function tests, a Geriatric Depression Score greater than 6, a history of seizure disorder, a history of cranial radiation therapy, a history of mental retardation, a recent history of focal brain injury, focal neurologic deficits that developed simultaneously with cognitive complaints, or the presence of a systemic or medical illness that would confound the diagnosis of a degenerative dementia. The Institutional Review Board of the University of Michigan (IRBMED) approved this investigation, and all participants signed an IRBMED-approved written informed consent.

Clinical Classification

Clinical classification was performed as described previously (*18*). Clinical evaluations included history and neurologic examination, brain MR imaging, laboratory evaluation to exclude potential confounders, and a standardized neuropsychologic evaluation. The neuropsychologic evaluation administered to all subjects included the measures from the National Alzheimer Coordinating Center Unified Dataset, consisting of the Mini-Mental State Examination, Boston Naming Test, Digit Span Forwards and Backwards, Trail Making Test (parts A and B), Logical Memory and Logical Memory Delayed Recall, and Semantic Fluency (Animal Naming). Caregivers completed the Neuropsychiatric Inventory. Clinical, structural imaging, laboratory, and neuropsychologic data for each subject were abstracted into a standard form by 1 of the investigators. A panel of experienced clinicians masked to the PET neuroimaging reviewed these data and assigned a classification to each subject with reference to recommended clinical criteria for MCI and MCI subtypes (amnestic MCI [aMCI], multidomain MCI [mdMCI], and nonamnestic MCI [naMCI]) based on clinical and neuropsychologic criteria (*19*). If there was discrepancy between raters, consensus was reached by discussion.

Subjects' neurologic and neuropsychologic examinations were repeated in 2- to 4-y intervals from the initial consensus evaluation. Clinical classification was repeated using the same consensus procedure and the same raters, who were masked to the initial clinical consensus evaluations. Consensus assessment included evaluation of progression to dementia. Subjects with persistent MCI were classified as described above. Subjects converting to dementia were then classified as 1 of the 3 major forms of neurodegenerative dementia using standard criteria for AD, LBD, and FTD (*20–22*).

PET Imaging

Subjects underwent ^{11}C-PiB and ^{11}C-dihydotetrabenazine PET imaging on a Siemens ECAT HR$^+$ camera operated in 3-dimensional mode (septa retracted), and they were scanned within 2–3 wk of initial evaluation. The 2 radiotracer scans were usually performed on the same half day, with at least 2 h between scans to allow for physical decay of the first tracer before the second scan. ^{11}C-PiB was administered as an intravenous bolus of 45% of the total mass dosage over 30 s, followed by constant infusion of the remaining 55% of the dose over the 80-min study duration (*23*). ^{11}C-PiB PET images were acquired as a dynamic series of 17 scan frames over a total of 80 min as follows: 4 × 30 s, 3 × 1 min, 2 × 2.5 min, 2 × 5 min, and 6 × 10 min. Parametric ^{11}C-PiB distribution volume ratio (DVR) images were computed by averaging the last 4 scan frames (40–80 min) normalized to the mean value in the cerebellar hemisphere cortical gray matter. (+)-^{11}C-dihydotetrabenazine was administered intravenously as a bolus containing 55% of the total mass dose over 30 s, followed by continuous infusion of the remaining 45% of the dose over the 60-min study duration (*24*). A dynamic series of PET images was acquired over 60 min: 4 × 30 s, 3 × 1 min, 2 × 2.5 min, 2 × 5 min, and 4 × 10 min. Parametric ^{11}C-dihydotetrabenazine DVR images were computed by averaging the last 3 scan frames (30–60 min) and normalized to the mean value in the occipital cerebral cortex. This bolus-plus-infusion approach leads to steady-state or equilibrium conditions, and the tissue concentration ratio yields DVR directly.

PET Neuroimaging Classifications

PET image classifications were made by an expert familiar with the biodistributions of the tracers in normal and relevant pathologic conditions. Following the procedure used in our prior study and the phase III study of ^{123}I-FP-CIT SPECT for diagnosis of LBD, the assessments were designed to reproduce conditions that would likely be obtained if routine clinical use of these measures was implemented (*18,25*). Parametric ^{11}C-PiB and ^{11}C-dihydotetrabenazine DVR image sets for each subject were stripped of identifiers and then classified without knowledge of clinical data. DVR images from all subjects were displayed with a DVR scale maximum of 3.0. Image-based classifications were assigned on the basis of combined ^{11}C-PiB and ^{11}C-dihydotetrabenazine results in each subject, providing both ligand-binding pattern and ligand-binding magnitude information. Subjects were classified as abnormal if visual assessment of ^{11}C-dihydotetrabenazine DVR images indicated marked reduction of striatal ^{11}C-dihydotetrabenazine binding in either hemisphere with visual assessment of the DVR images. Cerebral ^{11}C-PiB retention was classified as abnormal when the frontal lobe cerebral cortical DVR exceeded subjacent frontal white matter DVR with visual inspection of the DVR images. The visual assessment of cortical ^{11}C-PiB retention is known to exhibit accuracy comparable to quantitative analyses of ^{11}C-PiB binding (*26,27*). In our prior study, qualitative visual classification was as effective as classification based on regional parametric analysis (*18*). Subjects with markedly reduced striatal ^{11}C-dihydotetrabenazine binding were classified as LBD. In our present series, some LBD subjects

had ^{11}C-PiB deposition, whereas others were ^{11}C-PiB–negative. Individuals with normal ^{11}C-dihydotetrabenazine binding and abnormally increased ^{11}C-PiB deposition were classified as AD. Individuals with normal ^{11}C-PiB and ^{11}C-dihydotetrabenazine scan results were classified as FTD. Representative images of AD, LBD, and FTD classifications were published previously as Figure 1 in our prior study (*18*).

Statistical Analyses

Data analysis was performed with Stata (version 12; Stata Corp.). Demographics and other characteristics of the subjects were summarized as frequencies and percentages for categoric variables and as mean and SD for continuous variables. Differences between groups on demographic and neuropsychologic variables were assessed using χ^2 tests for categoric variables, *t* tests or 1-way ANOVA for normally distributed variables, and Mann–Whitney-Wilcoxon or Kruskal–Wallis rank-sum tests for nonnormally distributed variables. κ-statistics were calculated to assess interassessment agreement.

RESULTS

We evaluated 27 subjects whom we were able to follow over a mean interval of approximately 3 y (Table 1). At study entry, 11 subjects were clinically classified as aMCI, 7 as mdMCI, and 9 as naMCI. The MCI classification subgroups were similar in terms of demographics, clinical features, and neuropsychologic features (Table 1). Two thirds of subjects converted to dementia (18/27) on follow-up consensus clinical assessments. For each MCI classification subgroup, approximately two-thirds converted to dementia (Table 2). With imaging-based classification, most subjects were classified as AD-like pathology (18/27), with minorities classified as LDB-like pathology (2/27) or FTD-like pathology (7/27) (Table 2). Most of the subjects with an imaging abnormality (positive ^{11}C-PiB PET or ^{11}C-dihydotetrabenazine PET result) converted to dementia (16/20), whereas a minority of those without imaging abnormalities converted to dementia (2/7; Table 2; odds ratio, 10.0 [95% confidence interval, 1.4–71.9]).

Although the numbers of subjects are relatively small, MCI classification subgroup status did not obviously correlate with image-based classification (Table 3). Among subjects, for example, categorized as aMCI, most (9/11) received image-based classifications of AD but a minority (2/11) was categorized as FTD. Similarly, subjects classified as AD by image-based criteria were clinically classified as aMCI (9/18), mdMCI (6/18), and naMCI (3/18).

Using data from the 18 subjects who converted to dementia, we updated our prior analysis comparing PET imaging–based classification and expert clinical consensus classification of mildly demented subjects (Mini-Mental State Examination $>$ 17) (*18*). Adding this group of MCI subjects

TABLE 1
Demographic, Clinical, and Neuropsychologic Features of MCI Subjects

Parameter	aMCI	mdMCI	naMCI	*P*
Demographic				
Age (y)	74.5 (8.1)	70.3 (9.7)	73 (9.8)	0.41
Percentage female	9 (81.8%)	3 (42.9%)	3 (33.3%)	0.07
White	10 (90.9%)	6 (85.7%)	9 (100%)	0.536
Education (y)	15.0 (3.2)	16.4 (3.5)	16.2 (2.8)	0.608
Clinical feature				
Clinical Dementia Rating				0.434
0	0 (0%)	0 (0%)	1 (11.1%)	
0.5	8 (72.7%)	4 (57.1%)	7 (77.8%)	
1	3 (27.3%)	3 (42.9%)	1 (11.1%)	
Mini-Mental State Examination	25.5 (2.8)	25.9 (1.1)	27.2 (2.4)	0.292
Neuropsychiatric Inventory total score	2.9 (2.5)	2.3 (1.5)	2.4 (2.7)	0.858
Neuropsychiatric Inventory severity	4.6 (4.4)	3.4 (2.6)	3.7 (4.9)	0.755
Memory complaint	11 (100%)	7 (100%)	7 (77.8%)	0.115
Behavior complaint	0 (0%)	0 (0%)	2 (22.2%)	0.115
Parkinsonism	0 (0%)	0 (0%)	2 (22.2%)	0.115
Hallucinations	0 (0%)	0 (0%)	0 (0%)	
Neuropsychologic indices				
Logical memory	8.5 (5)	5.9 (2.4)	11.7 (5.1)	0.067
Digit Span Forward	7.7 (1.6)	7.6 (2)	7 (2.6)	0.74
Digit Span Backward	6.2 (2.1)	4.1 (0.9)	5.1 (1.7)	0.06
Animals	15.6 (4.3)	13.7 (5)	14.7 (4.4)	0.647
Trail Making Test				
Part A	36.7 (13.5)	44.9 (20.6)	150.7 (317.7)	0.429
Part B	192.5 (269.3)	183.4 (106.4)	373.7 (362.4)	0.147
Wechsler Adult Intelligence Scale	40 (11.1)	32 (11.7)	33.2 (7.8)	0.425
Delayed Recall	5 (4.9)	4 (2.3)	10.9 (5)	0.018
Boston Naming Test	26.4 (2.7)	22.3 (8.4)	26.2 (3.5)	0.625
Duration of follow-up (mo)	32.5 (14.3)	37.3 (14.9)	40.0 (12.0)	0.399

Data in parentheses are percentages (when followed by %) or are SDs.

TABLE 2
Results of Subject Follow-up Based on Either Initial Clinical or Initial Image-Based Classifications

Classification	Total	Did not convert to dementia	Did convert to dementia
Baseline clinical			
aMCI	11	4	7 (7 AD)
mdMCI	7	2	5 (4 AD and 1 FTD)
naMCI	9	3	6 (4 LBD, 1 AD, and 1 FTD)
Baseline image-based			
AD	18	4	14 (11 AD, 2 LBD, and 1 FTD)
LBD	2	0	2 (1 LBD and 1 FTD)
FTD*	7	5	2 (1 AD and 1 LBD)

*FTD defined as absence of both increased ^{11}C-PiB and decreased ^{11}C-dihydotetrabenazine binding; could be normal.

converting to dementia to our prior cohort of 75 mildly demented subjects provides a total of 93 subjects for comparison (Table 4). Updated analysis results are similar to prior results. The overall Cohen's κ was 0.41 (95% confidence interval, 0.26–0.55), and the performance characteristics of expert clinical consensus image–based classification were similar to our previously reported results (Table 5). As with our prior analysis, the greatest source of discrepancy between image-based and clinical classifications was in subjects classified clinically as FTD but whose ^{11}C-PiB PET imaging revealed significant cerebral Aβ amyloid deposition (Table 6).

DISCUSSION

A general problem with disease-modifying clinical trials in demented subjects is that pathology may be so advanced as to substantially reduce or preclude detectable therapeutic effects. MCI subject populations are likely less susceptible to this problem. A further virtue of targeting MCI subjects is that a trial endpoint of conversion to dementia may allow employment of survival analysis methods, increasing trial statistical power, an approach precluded in trial designs with demented subjects. With high risk for conversion to dementia and probable lower intensity of pathology, MCI is an attractive target population for disease-modifying trials. MCI populations, however, include both subjects with underlying progressive illnesses and subjects who will not progress or will actually improve. MCI secondary to dementing disorders, such as early dementia, is a heterogeneous population with several underlying pathologies. Identification of MCI subjects most likely to progress to dementia would increase the statistical power of trials to identify clinically relevant effects. Accurate, pathologically based classification of MCI subjects would facilitate enrollment of more homogeneous subject populations and also increase statistical power in disease-modifying trials.

Amyloid imaging and nigrostriatal dopamine terminal imaging are well validated by postmortem studies as biomarkers for cerebral Aβ amyloid deposition and LBD (*16,17,28,29*). In our dataset, abnormal ^{11}C-dihydotetrabenazine or ^{11}C-PiB PET results strongly predicted progression to dementia, which is consistent with considerable data from prior amyloid imaging studies of MCI subjects (*30–32*). Amyloid imaging does not, however, differentiate AD from LDB because many LDB subjects exhibit high amyloid burden (*33–35*). In addition, LBD subjects without high amyloid burdens will not be identified by amyloid imaging. Our combined molecular imaging approach likely identifies MCI subjects at high risk for progression and may allow relatively specific identification of MCI subjects likely to progress to AD and LBD (*18,36,37*).

An alternative approach to increasing the likelihood of identifying MCI subjects at high risk for progression to dementia is to use clinically defined MCI subclassifications as markers for increased chance for progression to dementia. aMCI, for example, is proposed as a particularly strong risk factor for AD (*38*). This approach, however, will still likely result in heterogeneous subject populations. Although our number of MCI subjects is modest, the lack of qualitative association of any MCI subtype with image-based classification is consistent with the heterogeneity of MCI and MCI subtypes. Of the 11 subjects in our study classified clinically as aMCI, 9 were classified by imaging criteria as AD (high ^{11}C-PiB binding and normal ^{11}C-dihydotetrabenazine binding) with 2 (18%) classified as FTD (normal ^{11}C-PiB and ^{11}C-dihydotetrabenazine binding). This result is similar to findings in a phase II trial of bapinuzemab in AD, in which 15% of subjects enrolled with clinically defined mild AD were found subsequently to have normal ^{11}C-PiB PET results

TABLE 3
MCI Classifications

Classification	AD*	LBD	FTD	Total
aMCI†	9	0	2	11
mdMCI	6	0	1	7
naMCI	3	2	4	9
Total	18	2	7	27

*Image-based classification of MCI subjects (AD, LBD, FTD).
†Initial expert clinical consensus classification of MCI (aMCI, mdMCI, naMCI).

TABLE 4
Demographic, Clinical, and Neuropsychologic Features of MCI and Demented Subjects

Parameter	AD (n = 48)	LBD (n = 18)	FTD (n = 27)	P
Demographic				
Age (y)	71.4 (8.8)	71.6 (7.4)	66.1 (8.5)	0.031
Percentage female	22 (45.8%)	6 (33.3%)	12 (44.4%)	0.648
White	45 (93.8%)	16 (88.9%)	27 (100%)	0.250
Education (y)	15 (3.1)	14.8 (2.9)	15.5 (3.4)	0.777
Clinical feature				
Clinical Dementia Rating				0.497
0	0 (0%)	0 (0%)	1 (3.7%)	
0.5	18 (37.5%)	9 (50%)	10 (37%)	
1	30 (62.5%)	9 (50%)	16 (59.3%)	
Mini-Mental State Examination	23.4 (3.1)	23.1 (4.4)	22.3 (3.9)	0.466
Neuropsychiatric Inventory total score	2.8 (2.3)	2.6 (2.5)	2.7 (2.2)	0.867
Neuropsychiatric Inventory severity	4.1 (4)	4.2 (5)	4.4 (4.3)	0.840
Memory complaint	43 (89.6%)	16 (88.9%)	21 (77.8%)	0.340
Behavior complaint	5 (10.4%)	4 (22.2%)	9 (33.3%)	0.052
Parkinsonism	3 (6.2%)	13 (72.2%)	1 (3.7%)	0.000
Hallucinations	0 (0%)	8 (44.4%)	1 (3.7%)	0.000
Neuropsychologic indices				
Logical memory	5.8 (3.9)	8.9 (4.6)	7 (5)	0.046
Digit Span Forward	7.4 (1.8)	6.8 (2.9)	5.7 (2.5)	0.023
Digit Span Backward	4.7 (1.6)	4.5 (2)	3.7 (1.7)	0.107
Animals	12.5 (4.7)	11.3 (4.5)	11.7 (4.7)	0.486
Trail Making Test				
Part A	56.4 (33.7)	84.6 (42.6)	172.1 (298.9)	0.016
Part B	431.5 (374.6)	428.6 (316.2)	576.6 (387.8)	0.223
Wechsler Adult Intelligence Scale	31.5 (17.5)	24.3 (19.3)	30.4 (25.7)	0.038
Delayed Recall	3.6 (3.5)	8 (4.7)	9.6 (17.7)	0.001
Boston Naming Test	23.2 (5)	24.1 (4.6)	23.2 (5.8)	0.822

Data in parentheses are percentages (when followed by %) or are SDs.

(*39*). Similarly, all forms of clinically defined MCI were represented among our subjects classified as AD by image-based criteria (Table 3).

One drawback of this approach is that both the clinical and the molecular imaging–based classification schemes presume exclusive categories. Combinations of pathology, notably comorbid vascular and neurodegenerative pathologies, are common in large autopsy series of demented subjects. Although conventional, this classification approach inevitably obscures some of the complexities of overlapping pathologies contributing to the clinical features of dementing illnesses. Some FTD cases, for example, notably those associated with τ mutations, exhibit significant parkinsonism and loss of nigrostriatal neurons. In addition, our molecular imaging–based FTD classification is a negative approach, based on absence of ^{11}C-dihydotetrabenazine PET or ^{11}C-PiB PET abnormalities. In the case of demented individuals, for example, this approach could lead to individuals with vascular dementia being classified as FTDs. We attempted to mitigate this problem by excluding subjects with higher Hachinski scores, but misclassification of vascular cognitive impairment as FTD remains a possibility with this approach. Similarly, this negative approach to FTD classification would also lead to subjects without dementia-related pathologies being classified as FTD. This fact highlights the importance of developing new ligands specific for FTD-related pathologies, such as τ-protein or TAR-DNA-binding protein-43 deposition, that would serve as positive biomarkers.

Another limitation of our study is the relatively small sample size. Only 2 subjects converting from MCI to

TABLE 5
Performance of Clinical Diagnosis* Versus Image-Based Classification in 93 Subjects

Classification	Image-based	Sensitivity	Specificity	Positive predictive value	Negative predictive value	κ
Clinical	AD	0.67	0.78	0.85	0.55	0.41
	FTD	0.6	0.77	0.33	0.91	0.28
	LBD	0.65	0.91	0.61	0.92	0.54

*Expert clinical consensus diagnosis. Analysis assumes that image-based classification is gold standard.

TABLE 6
Comparison of Image-Based and Clinical Consensus Classifications

Classification	Image-based			Total
	AD	LBD	FTD	
Clinical				
AD	41*	4	3	48
LBD	4	11*	3	18
FTD	16	2	9*	27
Total	61	17	15	93

*Subjects with concordant clinical classifications. Largest discrepant group is subjects classified as FTD but meeting image-based criteria for AD—that is, elevated ^{11}C-PiB binding.

dementia exhibited abnormal striatal ^{11}C-dihydotetrabenazine binding with initial PET imaging. Most of the MCI-to-dementia convertors exhibited abnormal ^{11}C-PiB PET imaging. Demonstrating that this double-PET-scan approach is superior to single imaging with ^{11}C-PiB PET or another imaging modality will require a larger prospective study. One potentially interesting result was that 3 of the 4 subjects classified as converting to LBD with the final consensus clinical evaluation were not classified as LBD on initial imaging. The most likely explanation for discrepant imaging and clinical classifications is imprecision of clinical classification, but another intriguing possibility exists. We previously reported apparently rapid loss of striatal ^{11}C-dihydotetrabenazine binding in a subject with rapid-eye-movement sleep behavior disorder who converted to LBD (*40*). This prior case experience raises the possibility of apparently rapid declines in striatal dopaminergic innervation in LBD during phases when subjects convert from MCI or other potential precursor states to overt dementia. This finding raises the interesting possibility that dopamine terminal PET or SPECT imaging, although generally thought to be useful in establishing a diagnosis of LBD in individuals in established dementia, may be insensitive in precursor states like MCI. Larger prospective studies are required to address this question.

We previously applied this combined-tracer PET imaging approach to subjects with early, mild dementia. Concordance with expert clinical diagnosis was only moderate, consistent with the results of long-term pathologic follow-up of dementias (*41*). We extended our prior analysis of concordance between molecular imaging–based and clinical classifications of early dementia by adding the results of final expert clinical consensus and image-based classifications of the 18 MCI subjects who converted to dementia to our prior dataset. With this expanded dataset (93 subjects), we continue to see only moderate concordance ($\kappa = 0.41$) between expert clinical consensus and molecular imaging–based classifications. We suspect that discrepancies between imaging and clinical classifications reflect imprecision of clinical classifications, but pathologic correlation is necessary to assess this hypothesis definitively.

This combined-tracer approach may be useful for selecting MCI subjects for inclusion in disease-modifying therapy trials both by selecting populations at high risk for conversion to dementia and by selecting a more homogeneous subject population on the basis of underlying pathologic–neurochemical abnormalities. Alternatively, this approach may be useful in defining more accessible biomarkers in MCI subjects. Other measures, such as ^{18}F-FDG PET and structural MR imaging, have been explored as biomarkers to predict progression from MCI to dementia and for a more accurate classification of MCI or dementias. Significant results are reported with these imaging modalities. Determining the optimal approach for assessing prognosis and classification will require larger prospective studies with pathologic correlation as the ultimate gold standard.

CONCLUSION

Combined PET molecular imaging of cerebral amyloid burden and striatal dopamine terminal integrity may be useful in identifying subjects at high risk for progression to dementia and in defining neurochemically differentiated subsets of MCI subjects.

DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734. Roger L. Albin accessed all relevant data for this study and takes responsibility for integrity of data and analysis. The sponsors played no role in data acquisition, analysis, interpretation or manuscript preparation. This study was supported in part by the following: PHS P01 NS15655 and P30 AG08671 and a gift from an anonymous donor.

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