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Amyloid positron emission tomography with ^{18}F -flutemetamol and structural magnetic resonance imaging in the classification of mild cognitive impairment and Alzheimer's disease

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Abstract

Objective—To evaluate the contributions of amyloid-positive (Am+) and medial temporal atrophy-positive (MTA+) scans to the diagnostic classification of prodromal and probable Alzheimer's disease (AD).

Methods— ^{18}F -flutemetamol-labeled amyloid positron emission tomography (PET) and magnetic resonance imaging (MRI) were used to classify 10 young normal, 15 elderly normal, 20 amnesic mild cognitive impairment (aMCI), and 27 AD subjects. MTA+ status was determined using a cut point derived from a previous study, and Am+ status was determined using a conservative and liberal cut point.

Results—The rates of MRI scans with positive results among young normal, elderly normal, aMCI, and AD subjects were 0%, 20%, 75%, and 82%, respectively. Using conservative cut points, the rates of Am+ scans for these same groups of subjects were 0%, 7%, 50%, and 93%, respectively, with the aMCI group showing the largest discrepancy between Am+ and MTA+ scans. Among aMCI cases, 80% of Am+ subjects were also MTA+, and 70% of amyloid-negative (Am-) subjects were MTA+. The combination of amyloid PET and MTA data was additive, with an overall correct classification rate for aMCI of 86%, when a liberal cut point (standard uptake value ratio = 1.4) was used for amyloid positivity.

Interpretation— ^{18}F -flutemetamol PET and structural MRI provided additive information in the diagnostic classification of aMCI subjects, suggesting an amyloid-independent neurodegenerative component among aMCI subjects in this sample.

Keywords

PET; Amyloid imaging; MRI; Hippocampal atrophy; MCI

1. Introduction

Amyloid deposition in the neocortex of the brain may be the earliest detectable biomarker abnormality among subjects destined to develop Alzheimer's disease (AD) [1]. The prevalence of elevated brain amyloid levels increases from 6% in 50- to 59-year-old individuals to 50% in those >80 years [2]. Elevated brain amyloid load has been associated with impairment in memory performance [3,4] and greater risk for progression to mild cognitive impairment (MCI) and dementia among nondemented elderly subjects [1,5,6], but not among AD patients in whom amyloid levels appear to have plateaued [1,3,7].

Brain amyloid load is known to be associated with hippocampal (HP) volume loss and cognitive impairment among elderly healthy subjects and patients with MCI [1,7]. Atrophy of medial temporal structures and cortical thinning, observed in structural magnetic resonance imaging (MRI) studies, are regarded to be downstream events in individuals who are amyloid positive (Am+) [7]. These atrophic changes, which may be present for many years before the clinical symptoms appear or cognitive decline occurs [8,9], represent the neurodegenerative component of AD, and may be "the direct substrate of cognitive impairment and progression to AD [1]."

In this study, we evaluated the relationship between amyloid load, severity of medial temporal atrophy (MTA score and HP volumes), Clinical Dementia Rating (CDR) score (0, 0.5, or 1), and neuropsychological scores on amnesic and nonamnesic tests among elderly individuals who were cognitively normal, had MCI, or had AD. The goal of this crosssectional study was to improve our understanding of the interrelationships between amyloid deposition, MTA, and the severity and type of cognitive impairment in each subject group.

2. Methods

Subjects were recruited from seven memory clinics at academic centers in Europe as part of a phase 2 clinical trial (GE ALZ-201), including 10 young subjects with no cognitive impairment (YN), 15 elderly subjects with no cognitive impairment (EN), 20 subjects with amnesic MCI (aMCI), and 27 subjects with probable AD. The YN subjects were between the ages of 25 and 55 years, whereas all other subjects were >55 years. Control subjects were recruited either through an advertisement in local newspapers or were the spouses of patients with AD or MCI.

Clinical-neurological and conventional neuropsychological assessment, routine blood analysis, and brain MRI scans were used to evaluate the subjects. Control subjects were required to be free of cognitive impairment on medical history, have a CDR score of 0, and have no more than one first-degree relative with a diagnosis of AD. A diagnosis of aMCI, which was based on Petersen et al criteria [10], was made by the clinician evaluating the

subject. With the exception of two subjects who had a CDR score of 0, the remainder had a CDR score of 0.5. The Mini-Mental State Examination (MMSE) score range for inclusion was 27 to 30 for aMCI. A diagnosis of AD was based on National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria for probable AD and *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition) criteria for dementia of the Alzheimer type. MMSE scores for AD subjects ranged from 15 to 27; the CDR score was 0.5 in eight and 1.0 in the remaining 19 AD subjects. The interval between the time of the clinical diagnosis of AD and study enrollment ranged between 1 month and 6 years.

Patient demographics and neuropsychological test results are listed in Table 1. Tests used to document the episodic memory deficit at screening varied between sites: the Alzheimer's Disease Assessment Scale List Learning Delayed Recall Test [11] at five sites, the Free and Cued Recall Test [12] at two sites, and the Rey Auditory Verbal Learning test [13] at one site. The proportion of EN, aMCI, and AD subjects tested at the three sites using these tests was roughly equivalent. It was possible to analyze these different episodic memory test scores together using z transformation of the scores.

The protocol was approved by the ethical committees of the participating centers, and written informed consent was obtained from each subject. The study was entirely sponsored by GE Healthcare (Amersham, United Kingdom). The trial design and execution were directed by the study sponsor. Full access to all the data in this study was provided to the corresponding author (R.D.) from the original publication, in which these data were reported [14]. Subsequently, under a research agreement between GE Healthcare and Mount Sinai Medical Center (Miami Beach, FL), all the data, including raw volumetrically acquired MRI scan data on all the subjects in this study, were made available to the corresponding author of this study.

2.1. MRI scans

MRI scans were volumetrically acquired using T1-weighted three-dimensional acquisition protocols with isotropic voxels of approximately 1 mm^3 . HP volumes were calculated using the Individual Brain Atlas using Statistical Parametric Mapping program with customized templates which were normalized to intracranial volume [15]. Bilateral HP and entorhinal cortex atrophy measures (range, 0–4) were evaluated using a visual rating system (VRS) [16] to derive a mean MTA score (Figure 1). The MTA rater was blind to the diagnosis of the subjects. A threshold or cut point of 1.5+ for the MTA score (MTA^T) was derived empirically from the logistic regression model [17] (Wald Statistic Chi-Square = 8.2 [$P < .004$]) using a database of MTA values for EN ($n = 274$) versus aMCI ($n = 87$) subjects who have been evaluated at our center [16,18]. We used the MTA^T score, rather than HP volumes, to classify subjects as MTA positive (MTA^+) or MTA negative (MTA^-), as MTA scores, possibly because they reflect atrophy in the entorhinal cortex as well as the HP, correlated more highly with cognitive scores and were equivalent to or better than HP volume scores in classifying diagnostic groups [19].

2.2. Positron emission tomography amyloid scans

Positron emission tomography (PET) scans were acquired using ^{18}F -flutemetamol injection (maximum activity, 185 MBq) and 85- to 115-minute acquisition window. ^{18}F -flutemetamol detects fibrillar amyloid aggregates, a pathological hallmark of AD, in brain parenchyma and vessel walls in vivo, and it may also have some affinity for diffuse plaques. Dynamic brain scanning was performed at three different scanning centers using a 16-slice Biograph PET/computed tomography scanner (Siemens, Erlangen, Germany), an ECAT EXACT HR+ scanner (Siemens), and a GE Advance scanner (Milwaukee, WI), respectively. The image acquisition window was 85 to 115 minutes after tracer injection. Images were reconstructed and smoothed to a resolution of 6 mm full width at half maximum. Atrophy correction of PET data was not performed because this would have involved estimating the signal contribution from the atrophied areas, thereby resulting in an increase in data variance. Standard uptake value ratios (SUVRs) were computed for a composite of anterior and posterior cingulate, prefrontal, lateral temporal, and parietal regions, normalized to the tracer uptake in the reference region, namely, the cerebellar cortex.

We analyzed our results based on two thresholds, or cut points, to classify subjects as Am+ or amyloid negative (Am-). A threshold SUVR (SUVR^T) of 1.56+ was calculated by locating the exact midpoint expressed in standard deviations between the mean SUVRs of the AD and the EN group.

$$\text{factor} = \frac{\text{SUVR}(\text{ADmean}) - \text{SUVR}(\text{ENmean})}{\text{SUVR}(\text{ADsd}) + \text{SUVR}(\text{ENsd})}$$

$$\text{SUVR}^T = \text{SUVR}(\text{ADmean}) - \text{factor} \times \text{SUVR}(\text{ADsd})$$

A second threshold SUVR (SUVR^{T2}) of 1.40+ was empirically derived from a logistic regression model ($B = 2.6$, standard error = 1.2, $df = 1$; Wald = 4.3; Exp $B = 13.3$ [$P < .05$]) of SUVR data from EN and aMCI subjects in this study.

2.3. Statistical methods

Test of means was conducted using one-way analyses of variance. Post hoc tests of means were conducted by the Tukey–Kramer procedure. Logistic regression [14] was used for deriving sensitivity, specificity, and correct classification of SUVR and MTA measures among AD, aMCI, and EN subjects. Correlation coefficients were used for examining the relationship between cognitive and imaging (SUVR and VRS-MTA) measures.

3. Results

As is evident in Table 1, there was a significant age difference between the four groups ($F(3,68) = 49.39$; $P < .001$), and post hoc tests revealed that the YN subjects were significantly younger than the EN, aMCI, and AD subjects; however, there was no age difference between any of the groups with older subjects. There were also statistically significant differences between groups with regard to MMSE scores ($F(3,68) = 67.99$; $P < .$

001), memory scores ($F(3,68) = 32.33$; $P < .001$), verbal fluency ($F(3,68) = 18.34$; $P < .001$), Trails A time ($F(3,67) = 11.71$; $P < .001$), and Trails B time ($F(3,68) = 4.94$; $P < .004$). The AD group had lower MMSE scores than the other three study groups. In addition, they had lower scores of all other neuropsychological measures compared with the YN and EN groups, but were equivalent to the aMCI groups with regard to neuropsychological test performance.

Diagnostic groups differed from each other with regard to SUVR composite scores ($F(3,68) = 28.93$; $P < .001$), VRS-MTA scores ($F(3,66) = 19.28$; $P < .001$), and HP volume scores ($F(3,68) = 5.75$; $P < .001$).

On post hoc analysis, no differences in the SUVR values between YN and EN groups were observed; however, aMCI subjects had higher SUVR scores than YN subjects, and AD subjects had higher SUVR scores than the three other groups (Table 2). There was no difference in VRS-MTA scores and HP volumes between YN and EN or between aMCI and AD subjects, but aMCI and AD subjects had higher MTA scores and lower HP volumes compared with the YN and EN subjects. Among all subjects, a correlation coefficient of 0.206 ($P = .043$) was observed between SUVR scores and HP volumes and 0.414 ($P < .001$) between SUVR scores and MTA ratings.

Among EN and aMCI subjects, significant correlations between SUVR scores and Trails A ($r = 0.53$; $P < .001$) and Trails B times ($r = 0.42$; $P < .01$) were observed, whereas correlations with episodic memory and animal fluency were nonsignificant (Table 3). No significant correlations between cognitive scores and SUVR scores were found among AD subjects. In contrast, there were significant correlations between MTA scores and episodic memory scores ($r = 0.54$; $P < .001$) and animal fluency scores ($r = 0.39$; $P < .02$), whereas correlations with Trails A and B times were nonsignificant. No significant correlations were observed between cognitive scores and MTA among AD subjects.

Using the SUVR^T cut point (1.56+) and the MTA^T cut point (1.5+), none of the YN subjects were either Am+ or MTA+; however, 7% of EN subjects were Am+, and 20% were MTA+ (Table 4). The correct classification rate for aMCI subjects with SUVR^T cut point was 69% ($P < .05$), with 50% sensitivity and 93% specificity, compared with EN. The correct classification rate using the MTA^T cut point was 77% ($P < .004$), with 75% sensitivity and 80% specificity. The combination of the SUVR^T and the MTA^T cut points resulted in only MTA being retained in the model, with the overall correct classification rate remaining at 77%. Among aMCI subjects who were Am+, 80% were also MTA+, and among those who were Am−, 70% were MTA+. Among the AD group, 96% of the subjects were either Am+ or MTA+, with 93% being Am+ and 82% being MTA+; only one AD subject was Am+ but MTA−, indicating a high degree of overlap among those who were Am+ and MTA+.

Using the SUVR^{T2} cut point (1.40+), as opposed to the SUVR^T cut point, two additional EN subjects were classified as Am+ (both were MTA−), thereby increasing the amyloid positivity rate from 7% to 20%. Among aMCI subjects, two additional subjects were classified as Am+ (one was MTA+), thereby increasing the sensitivity from 50% to 60%. However, using the SUVR^{T2} cut point resulted in no change in the percentage of Am+ YN

(0%) or AD subjects (93%). The overall correct classification rate of aMCI subjects increased nonsignificantly from 69% to 71%, with 60% sensitivity and 80% specificity, compared with EN subjects. The combination of the SUVR^{T2} and MTA^T cut points to classify subjects as Am+ and MTA+ in the logistic regression model yielded a sensitivity of 85% and a specificity of 87%, with a significantly improved ($\chi^2 [df=2] = 19.2; P < .001$) overall classification rate of 86%, as compared with a correct classification rate of 77% when the SUVR^T cut point was used. For HP volume alone, correct classification rate was 82% (80% sensitivity and 85% specificity), and SUVR scores were not retained in the model because predictive accuracy was not improved.

4. Discussion

In this report, we expanded on the findings of a previously published phase II study [11] that was designed to examine the efficacy of blinded visual assessment of images of ¹⁸F-flutemetamol uptake for distinguishing clinically probable AD subjects (n = 27) from EN subjects (n = 15). In addition to the relatively conservative SUVR cut point of 1.56 (SUVR^T), which was calculated for the original study, we used an SUVR cut point of 1.4 (SUVR^{T2}) for determining Am+ status, based on the optimal SUVR cut point for distinguishing aMCI from EN subjects. As a result, the frequency of Am+ subjects in the aMCI group increased from 50% to the more commonly reported 60% level [3].

Using MRI scan data, which were obtained, but not analyzed, in the original study, we measured HP volumes and visually rated MTA for all subjects, but chose MTA scores for most analyses because of better separation in scores between cognitively normal and impaired subjects and higher correlations with cognitive scores [16]. We classified subjects in each diagnostic group as MTA+ or MTA– to provide structural MRI-based biomarker data, analogous to Am+ or Am– data, representing the severity of neurodegenerative pathology in the medial temporal regions of these subjects [20,21]. Among EN subjects, the importance of identifying MTA+ status is the knowledge that those in this group who later progress to MCI or AD are more likely to have smaller HP volumes (and therefore greater MTA scores) than those who do not progress [8,9,22,23].

In this study, subjects with aMCI and AD were fairly typical on the basis of their cognitive characteristics (Tables 1 and 2). The aMCI group could be distinguished from the EN group on the basis of episodic memory and animal fluency scores (but not MMSE, Trails A, or Trails B scores), whereas the AD group could be distinguished from the EN group on the basis of all the neuropsychological test scores and from the aMCI group on the basis of MMSE, animal fluency, and Trails A scores, consistent with the findings in other studies comparing EN, aMCI, and mild AD subjects [24]. We found that among EN and aMCI subjects in this study, amyloid load was correlated with executive function and that MTA was primarily correlated with episodic memory performance and category fluency. Although the strong association between MTA and episodic memory performance is well known [13,15,16,24], the associations between amyloid load and cognition in normal aging and aMCI have been inconsistent [3,7,25–27]. It is not clear whether the association between amyloid load and episodic memory performance, reported in some studies [25–27], is mediated by coexisting HP atrophy. Our finding that episodic memory performance was

mainly associated with MTA severity and that executive function tests were mainly associated with amyloid load may reflect the locations in the brain where the earliest and most severe neurodegeneration [8,9] (i.e., medial temporal regions) and amyloid deposition [1–4] (i.e., the neocortex) occur, rather than specific biological effects of amyloid deposition or neurodegeneration.

Using the more conservative SUVR^T cut point for Am+ status, none of our YN subjects, fewer than 10% of the EN subjects, 50% of the aMCI subjects, and 93% of the AD patients were found to be Am+. When SUVR^T data were combined with MTA data, the severity of MTA was most predictive of diagnosis, and the amyloid data were not additive for predicting the diagnosis. However, use of the more liberal SUVR^{T2} cut point resulted in a higher percentage of EN and aMCI subjects being classified as Am+, with the data being additive with MTA+ status for the classification of aMCI. Similar to the results of some other studies [4,25], using the SUVR^{T2} cut point, our data showed that amyloid load and the severity of brain atrophy (in this case, the MTA score) appear to have additive effects in predicting the severity of cognitive impairment among cognitively normal and MCI subjects. Also, the SUVR^{T2} cut point appeared to provide a more representative assessment of amyloid load among EN subjects [3], 20% of whom were classified as Am+, as opposed to 7% when using the SUVR^T cut point.

We found amyloid load and HP volume were weakly and inversely correlated among the entire subject group, but not in any individual diagnostic group. It has been hypothesized [1] that in the evolution of AD pathology, amyloid deposition is the earliest event, leading to downstream events, including neurodegeneration and cognitive impairment [1]. For example, in the Alzheimer's Disease Neuroimaging Initiative study, it was found that amyloid load increased initially, but tended to plateau much before the progressive loss of brain volume, in what was presumed to be the preclinical and very early clinical stages of AD [1]. However, the findings using the SUVR^T cut point in this study demonstrated that MTA+ status was more frequent than Am+ status. Even when using the more liberal SUVR^{T2} cut point, Am+ status among MTA+ subjects remained more frequent than Am+ status in aMCI subjects. Possible explanations for our findings include the following: (1) subthreshold levels of extracellular fibrillar amyloid deposition in the brain may trigger neurodegeneration; (2) amyloid deposition in the brain may not be a primary event, but secondary to a neurodegenerative process, possibly with initial deposition in an intracellular compartment; (3) a substantial subgroup of our aMCI subjects may not have early AD but some other neurodegenerative disease, such as HP sclerosis [28].

It is becoming evident that the relationship between amyloid deposition and neurodegeneration in AD may be more complex than was initially conceived. This complexity was alluded to in the study by Jack et al [25], but is more apparent from the analyses performed specifically within the EN and aMCI subject groups in the current study. In fact, Driscoll et al [29], who evaluated serial MRI scans among nondemented individuals during a 10-year period, were unable to show a relationship between rates of decline in brain volume and amyloid load at the end of the 10-year period. It has been suggested that the brain amyloid concentration that is biologically significant for any given individual may vary greatly, possibly because of variable susceptibility to the toxic effects of amyloid β or

because other pathologies, such as vascular disease, may modify susceptibility to amyloid β [7]. The stage of disease appears to be a determinant of the relationships between amyloid load and brain atrophy, with apparently strong relationships occurring in the subjective memory stage, but waning progressively in the MCI stage and the AD stage of disease [30]. Laboratory evidence also exists to support amyloid-independent mechanisms leading to neurodegeneration in AD, thus invoking the possibility that MTA in AD may occur as an early event in the absence of amyloid deposition in the brain [31].

A limitation in this study is the small sample size within the diagnostic groups, especially in the EN group, thereby reducing confidence in the generalizability of the results. Larger data sets from longitudinal studies are needed to validate and extend the findings to determine whether and how quickly amyloid burden leads to clinically significant cognitive deterioration. Nevertheless, even on the basis of results from this restricted data set, we believe it is important to routinely incorporate structural imaging with MRI in the analysis. Among aMCI subjects, amyloid load and neurodegeneration appear to occur independently of each other and appear additive for distinguishing aMCI from EN subjects. Stratification of subjects into those who are exclusively Am⁺ or MTA⁺, or have the combination of MTA and amyloid positivity may provide important clues regarding the etiology of cognitive impairment among such subjects as well as influence treatment decisions in the future.

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Fig. 1.

Visual rating of medial temporal atrophy. Images depicting four degrees of atrophy in hippocampus and entorhinal cortex according to Visual Rating Scale, where 0 = no atrophy, 1 = minimal atrophy, 2 = mild atrophy, 3 = moderate atrophy, and 4 = severe atrophy (score shown corresponds to both structures) [16].

Table 1

Demographic and neuropsychological variables

Measure	Young normal (n = 10)	Elderly normal (n = 15)	Amnesic mild cognitive impairment (n = 20)	Probable Alzheimer's disease (n = 27)
Age (years)	38 [*] ± 11	69 [†] ± 8	73 [‡] ± 7	69 [‡] ± 7
Education (years)	15.8 ± 2.7	12.9 ± 3.0	14.8 ± 3.0	14.4 ± 4.1
Gender (male/female)	4/6	9/6	11/9	12/15
Mini-mental state examination	29.4 [*] ± 1.0	28.8 [*] ± 1.0	28.0 [*] ± 0.9	23.3 [‡] ± 2.2
Episodic memory (% correct responses)	0.79 [*] ± 0.15	0.80 [*] ± 0.12	0.46 [‡] ± 0.11	0.40 [‡] ± 0.19
Animal fluency	24 [*] ± 5	24 [*] ± 6	17 [‡] ± 5	13 [‡] ± 5
Trails A (seconds)	24 [*] ± 5	35 ^{*,†} ± 13	48 ^{‡,‡} ± 18	69 ^{‡,§} ± 34
Trails B (seconds)	77 [*] ± 24	72 [*] ± 28	134 ^{*,‡} ± 77	195 [‡] ± 169

^{*}, [†], [‡], [§] Means with different superscripts are significantly different by post hoc Tukey–Kramer test ($P < .05$); Shared superscripts indicate that means are not different.

Table 2

Positron emission tomography amyloid load (standard uptake value ratio), hippocampal volume, and medial temporal atrophy rating

Measure	Young normal	Elderly normal	Amnesic mild cognitive impairment	Probable Alzheimer's disease
Standard uptake value ratio composite	1.2 [*] ± 0.1	1.4 ^{*,†} ± 0.2	1.7 [‡] ± 0.5	2.2 [‡] ± 0.4
VRS-MTA score	0.4 [*] ± 0.4	1.0 [*] ± 0.6	2.1 [‡] ± 0.9	2.1 [‡] ± 0.8
Hippocampal volume (%)	0.66 [*] ± 0.09	0.65 [*] ± 0.04	0.56 [‡] ± 0.09	0.55 [‡] ± 0.12

^{*}, [†], [‡] Means with different superscripts are significantly different by post hoc Tukey–Kramer test ($P < .05$).

Table 3

Correlations of neuropsychological scores to amyloid load (standard uptake value ratio scores) and medial temporal atrophy scores among elderly normal and amnesic mild cognitive impairment subjects

Cognitive test	Correlation (<i>r</i>) with standard uptake value ratio scores		Probability of <i>r</i>	Correlation with medial temporal atrophy scores		Probability of <i>r</i>
Episodic memory	-0.23	0.18		-0.54	0.001	
Trails A	0.53	0.001		0.23	0.19	
Trails B	0.42	0.01		0.16	0.35	
Cat fluency	-0.28	0.09		-0.39	0.02	

NOTE. 35 total subjects (15 elderly normal subjects and 20 amnesic mild cognitive impairment subjects). Correlation between episodic memory measure and hippocampal volume: $r = 0.46$ ($P = .007$).

Table 4

Amyloid and medial temporal atrophy–positive status among subject groups

Measure	Young Normal	Elderly Normal	Amnestic mild cognitive impairment	Probable Alzheimer's disease
Magnetic resonance imaging positive	0%	20%	75%	82%
Amyloid positive	0%	7%	50%	93%
Amyloid positive or magnetic resonance imaging positive	0%	20%	85%	96%

NOTE. Using a standard uptake value ratio cutoff of 1.56 and a medial temporal atrophy cutoff of 1.5.