European Journal of Nuclear Medicine and Molecular Imaging (2019) 46:2090–2098
https://doi.org/10.1007/s00259-019-04409-1

ORIGINAL ARTICLE

Longitudinal cognitive decline in mild cognitive impairment subjects with early amyloid-β neocortical deposition

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Received: 15 March 2019 / Accepted: 18 June 2019 / Published online: 1 July 2019

Abstract

Purpose The rate of clinical progression of cognitive impairment in subjects with early amyloid deposition is unknown. The primary aim of the study was to follow the rate of cognitive decline over 1 year in patients with amnestic mild cognitive impairment (aMCI) by determining amyloid retention levels in terms of standardized uptake value ratios (SUVr) that ranged from 0.85 to 1.57. The secondary objective was to compare the rate of cognitive decline between subjects with and without early amyloid positivity.

Methods Of 66 aMCI subjects evaluated with [^{18}F]florbetaben PET imaging and neuropsychological tests at baseline, 41 completed the 1-year follow-up. Amyloid status was determined with SUVr cut-off values generated from baseline images by visual assessment by three independent certified readers. Repeated-measures ANOVA with amyloid load and neuropsychological scores as the main effects was use to test group, time and group-by-time interactions. The Tukey post-hoc test was used to analyse all significant interactions.

Results Of the 41 aMCI subjects, 38 completed the assessment according to the study protocol. Amyloid-positive (Aβ+) subjects ($N = 18$, age 75.6 ± 5.8 years, six men, 12 women) showed greater clinical deterioration according to the Mattis Dementia Rating Scale (MDRS) score ($p = 0.006$). Amyloid-negative (Aβ−) subjects ($N = 20$, age 72.4 ± 5.8 years, 11 men, 6 women) showed no significant changes in MDRS score over 1 year. MDRS score significantly decreased (MDRS+) in 37% of the aMCI subjects, and remained stable (MDRS−) in the remaining 63%. Among subjects with cognitive deterioration, 86% were Aβ+ and 14% were Aβ−, while 25% of the MDRS− subjects were Aβ+ and 75% were Aβ− ($\chi^2 = 13$, $P = 0.0003$). SUVr above 1.21 identified individuals who would show significant progression over 1 year, with a sensitivity of 67% and a specificity of 90%, as compared to Aβ− subjects. The positive predictive value, negative predictive value, and likelihood ratio were 86% (95% CI 70–94%), 75% (95% CI 58–87%), 7 (95% CI 5–10).

Conclusion This study demonstrated that early amyloid deposition predicts cognitive decline in subjects with aMCI, with a higher rate of decline in those with SUVr above a threshold of 1.21. Detection of early amyloid positivity may help in selecting the target population for preventive therapeutic interventions and in designing treatment trials (Trial number, EudraCT 2015-001184-39).

Keywords Mild cognitive impairment · PET imaging · Beta-amyloid · Cognitive trajectory · Longitudinal study

This article is part of the Topical Collection on Neurology.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00259-019-04409-1) contains supplementary material, which is available to authorized users.

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Introduction

In the preventive treatment of dementia, one of the major open issues today remains identifying subjects affected by cognitive impairment and most likely to develop Alzheimer's disease (AD). In fact, patients with mild cognitive impairment (MCI) show an increased risk of progression to advanced stages of dementia, with a conversion rate between 10% and 15% [1, 2].

Yet there are no predictors to discriminate MCI patients in whom disease will progress to AD or advanced stages of dementia from those in whom the disease will remain stable over time.

Studies have shown that one key aspect in the neurodegenerative process underlying AD is the overproduction or inadequate clearance of the extracellular protein beta-amyloid and the formation of intraneuronal neurofibrillary tangles, the increased accumulation of which is considered to be associated particularly with the development of AD [3]. The presence of amyloid deposits in the brain of patients with amnestic MCI (aMCI) and probable AD has also been supported by post-mortem findings in brain tissue. Although high levels of amyloid have also been observed in the brain of normal elderly individuals, it is the increase in deposited amyloid or amyloid-induced tau hyperphosphorylation that accelerates progression towards neurodegeneration and cognitive impairment [4–7].

In recent years, PET imaging studies have contributed to the quantification of amyloid levels in specific brain regions by enabling the measurement of tracer standardized uptake value ratios (SUVr), and thresholds for the identification of pathological levels of amyloid deposition defined by a semi-quantitative approach have been proposed [8–11]. Pike et al. demonstrated that SUVr greater than 1.6 is able to differentiate between AD patients and normal controls [12]. A slightly different SUVr threshold of 1.5 was proposed by Jack et al., although these authors included subjects with MCI as well as controls and patients with AD [13]. However, the amyloid positivity thresholds applied in these studies, identified individuals with impairment close to the disease onset zone who already show advanced permanent structural brain changes and neuronal damage (overt or prodromal phase of AD). Accordingly, the diagnostic potential of amyloid PET must now be fine-tuned to focus on the earlier stages of amyloid deposition when pharmacological interventions are still effective and yield more favourable patient outcomes.

In a recent study, we investigated amyloid deposition in terms of brain uptake of [^{18}F]florbetaben (FBB) in subjects with MCI. MCI subjects with SUVr above 1.3 showed significantly greater cognitive impairment than individuals with SUVr below this threshold. Specifically, 80% of subjects with significant cognitive impairment were amyloid-positive (Aβ+) compared with the 21% of patients without cognitive impairment. Moreover, amyloid load was significantly correlated with episodic memory scores. In consideration of these findings, we wanted to assess whether early amyloid deposition is also associated with a higher rate of disease progression.

The primary aim of this study was therefore to investigate whether early amyloid deposition measured in terms of brain uptake of FBB in subjects with MCI may be predictive of cognitive decline over 1 year. The secondary objective was to compare the rate of cognitive decline in subjects with and without early amyloid deposition.

Materials and methods

Design

This was a longitudinal study in subjects with aMCI. The aims of the study were to determine the extent to which amyloid burden was associated with cognitive impairment and to test the relationship between amyloid accumulation and memory and cognitive impairment. Full descriptions of the subject selection procedure and the study protocol have been reported previously [14].

Setting

The follow-up reported here was carried out between December 2017 and January 2019 at the same facilities as in the original study, that is the Nuclear Medicine Unit and Neurology Unit (patient recruitment and PET imaging), and the Memory Laboratory and Memory Clinics (clinical and neuropsychological evaluation) of S. Andrea Hospital.

Participants

Follow-up was anticipated in all 66 patients of the original sample. However, follow-up was discontinued in 25 subjects, and these subjects were excluded (two died, three were lost to follow-up, seven withdrew at their own request or the request of their family, five changed residence, six missed appointments, and two had incomplete neuropsychological evaluations). Subject inclusion/exclusion criteria remained the same as those for the first part of the study as described in detail elsewhere [14]. Briefly, subject inclusion criteria according to the Petersen definition for aMCI [1] consisted of Mini-Mental State Examination (MMSE) uncorrected score of ≥24, Clinical Dementia Rating (CDR) score of 0.5, absence of dementia and preserved basic activities of daily living [15]. The exclusion criteria were the presence of disease potentially related to memory impairment, including (in agreement with the NINDS–AIREN criteria [16]) a clinical history of depression within the past year, ongoing treatment with psychotropic medication (e.g. antidepressants, neuroleptics), and drug or alcohol abuse.

Standard patient consent, protocol approval and registration

All participants had given written informed consent. This study was approved by the regional medical Ethics Committee, authorized by the Italian Competent Authority (AIFA) and registered in the EudraCT database as a nonprofit phase III clinical trial (EudraCT number 2015-001184-39).

Clinical assessment

Neuropsychological and clinical assessments

All participants underwent neurological examinations and neuropsychological assessment. Neuropsychological evaluation was carried out during the 2 weeks prior to the PET scan by a certified clinical psychologist who was blinded to the subject's cognitive status. The age of onset of the first signs of cognitive impairment was tracked back by means of a semistructured interview with family members. The MMSE was used as a measure of global cognitive performance [17]. Scores were adjusted for age and years of education according to Italian norms [18]. Clinical severity was determined using the CDR scale and CDR Sum of Boxes (CDR-SOB) [19–21]. The Mattis Dementia Rating Scale (MDRS) was used to assess clinical longitudinal changes in cognitive impairment [22–24]. To account for age and years of education, MDRS scores were corrected for Italian norms [25]. Episodic Memory Composite score (EMCs) and Non-Memory Composite score (NMCs) were measured as previously described [14] and used as indexes of cognitive performance.

PET imaging and preprocessing procedures

PET/CT images were acquired in 3D mode 88 ± 10 min after intravenous injection of 307 ± 30 MBq FBB (Neuraceq™) on a Discovery 710 PET/CT scanner (GE Medical Systems. Milwaukee, WI). PET projection data were iteratively reconstructed using a 3-D OSEM algorithm with eight iterations and 48 subsets, postsmoothing with a gaussian filter of 3 mm FWHM, and CT-based attenuation correction. Images were processed using SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) implemented under Matlab 8.6 (MATLAB R2015b; Mathworks Inc., Natick, MA). Image transformation into standard anatomical space, estimation of regional SUVr from standardized uptake values (SUV) and calculation of amyloid cortical burden have been described fully elsewhere [14].

Visual assessment and threshold generation

Images were independently rated by three blinded, certified readers according to the methodology described by Seibyl at al. [26]. Visual assessment (VA) was based on agreement between at least two readers. For the calculation of sensitivity (SE) and specificity (SP) based on visual classification, ROC analysis was used to determine the optimal SUVr cut-off value, identified as the maximum value of Youden's statistic (Se + Sp − 1) [27].

Imaging and clinical follow-up

All subjects with MCI underwent imaging and clinical tests 1 year after baseline examination. The mean follow-up times were 391 ± 47 days and 389 ± 47 days for Aβ+ and amyloid-negative (Aβ−) subjects, respectively.

Statistics

Data were analysed with the JMP statistical software package (SAS Institute, Cary, NC). The assumption of normality was tested using the Kolmogorov–Smirnov statistic. Based on the amyloid burden estimated in terms of SUVr, subjects were grouped as low amyloid deposition (Aβ−) and high amyloid deposition (Aβ+) by applying the cut-off value derived from VA. Demographic variables and amyloid status were compared between included and excluded subjects using the two-sided *t* test for age and years of education and the chi-squared test for gender and amyloid status. The chi-squared test was used for categorical variables. The differences in the mean scores of neuropsychological tests between Aβ+ and Aβ− groups were determined using one-way independent analysis of variance (ANOVA). Repeated-measures ANOVA (RM ANOVA) with amyloid load and neuropsychological scores as main effects was used to test group, time and group-by-time interactions. Tukey post-hoc analyses were performed for all significant interactions.

Reliable change index (RCI) analysis was used to assess the clinical relevance of changes in MDRS scores at the subject level between the baseline and retest evaluations. RCI was calculated by multiplying the standard error of the difference by 1.65, which gave the RCI value for a critical change threshold with a one-tailed *P* value of 5% [28–30]. According to this criterion, subjects with and without a significant decrease in score at the retest evaluation were classified as MDRS+ and MDRS−, respectively.

The association between amyloid SUVr and cognitive decline was tested by comparing the Aβ+ and Aβ− groups using the chi-squared test. SE, SP, positive predictive value (PPV), negative predictive value (NPV), likelihood ratio (LR) and their 95% confidence intervals were calculated to test the magnitude of the associations. For all tests, significance was assumed for *P* values <0.05.

Results

Baseline

Of the 66 patients from the initial patient sample, 41 completed the 1-year follow up. Of these patients, three more were excluded due to motion artifacts on PET images, leaving 38 subjects who completed neuropsychological evaluation and

Table 1 Demographics and SUVr in all subjects with MCI and in the Aβ+ and Aβ− groups separately

	All subjects	Aβ+	Aβ−	*P* value
Number of subjects	38	18	20	
Male	17	6	11	
Female	21	12	9	NS[b]
Age (years)	73.9 ± 7	75.6 ± 5.8	72.4 ± 5.8	NS[c]
Education (years)	10.8 ± 4.3	10.5 ± 4	11.1 ± 4	NS[c]
Time from baseline to retesting (days)	390 ± 45	390.9 ± 46.8	389.2 ± 46.8	NS[c]
SUVr[a]	1.21 ± 0.23			
Baseline		1.41 ± 0.11	1.02 ± 0.12	
Retest		1.42 ± 0.11	1.07 ± 0.12	

The data presented are means ± SD

NS not significant, *SUVr* standardized uptake value ratio

[a] From amyloid imaging with [^{18}F]florbetaben PET

[b] Chi-squared test

[c] Student's *t* test

PET imaging for analysis. Demographic characteristics of the whole cohort of MCI subjects and in the Aβ+ and Aβ− groups separately are presented in Table 1. No significant differences in demographic features or amyloid status were found between included and nonincluded patients (mean ± standard deviation: age 73.9 ± 7.0 vs. 73.4 ± 7.9 years, P = 0.79; years of education 10.8 ± 4.3 vs. 11.4 ± 4.4, P = 0.58; gender P = 0.58; amyloid status P = 0.79). The Kolmogorov–Smirnov test showed that the data were normally distributed (P > 0.05). Plots of the Kolmogorov–Smirnov statistic are shown in Fig. 1 of the Supplementary Material.

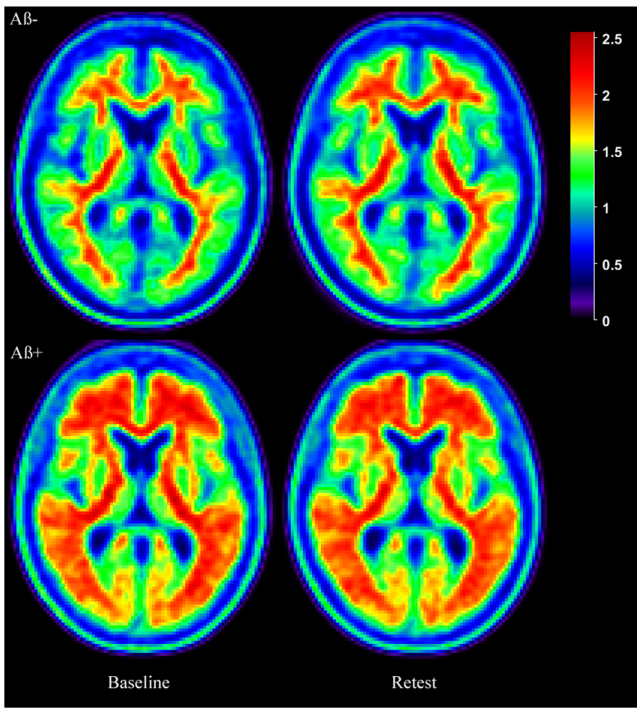

Fig. 1 Average axial [^{18}F]florbetaben PET images in subjects with mild cognitive impairment (*top* Aβ−, *bottom* Aβ+; *left* baseline images, *right* retest images). Signal intensity in the grey matter regions is significantly lower in the images from Aβ− subjects (*top*) than in those from Aβ+ subjects (*bottom*; P < 0.0001), but there are no significant differences between the baseline and retest images for either group

No significant differences were found between the Aβ+ and Aβ− groups in terms of age, gender or years of education. As expected, the study sample included a slightly higher percentage of women. The SUVr cut-off value of 1.21 was determined using VA as the reference for amyloid status classification. According to the SUVr cut-off value measured on baseline scans, 47% of the aMCI patients were classified as Aβ+ with SUVr ranging from 1.21 to 1.57 and 53% as Aβ− with SUVr ranging from 0.85 to 1.12 (Table 1). The agreement between scan classification based on VA and SUVr cut-off values was 92%. Figure 1 shows average axial FBB PET images at the level of the basal ganglia in all subjects in the Aβ+ and Aβ− groups obtained at baseline (left) and retest (right).

Mean neuropsychological test scores in all subjects and in the Aβ+ and Aβ− groups separately are given in Table 2. Significant differences were found between Aβ+ and Aβ− subjects in baseline CDR-SOB scores, EMCs and NMCs (2.4 ± 1.6 vs. 1.4 ± 1.0, P = 0.017; −0.43 ± 0.73 vs. 0.33 ± 0.73, P = 0.003; −0.26 ± 0.45 vs. 0.18 ± 0.51, P = 0.008, respectively), whereas no significant differences were found for CDR, MMSE and MDRS scores at baseline (Supplementary Table 1).

Follow-up

Mean follow-up times are shown in Table 1. During the 13-month follow-up, 2 of 38 subjects with aMCI showed clinical conversion to AD. These two converters were Aβ+ on their baseline PET scan. RM ANOVA indicated

Table 2 Neuropsychological test results in all subjects with MCI and in the Aβ+ and Aβ− groups separately

Test	All subjects	Aβ+		Aβ−	
		Baseline	Retest	Baseline	Retest
CDR	0.5 ± 0.1	0.5 ± 0.1	0.7 ± 0.5	0.5 ± 0	0.6 ± 0.3
CDR-SOB	1.9 ± 1.4	2.4 ± 1.6	3.2 ± 2.7	1.4 ± 1	1.5 ± 2.6
MMSE	26 ± 2.4	25.5 ± 2.5	23.1 ± 4.7	26.5 ± 2.2	26.3 ± 2.1
MDRS	127.9 ± 9.4	126.6 ± 9.9	115.3 ± 15.1	129.1 ± 9.1	129.9 ± 11.3
EMCs	−0.03 ± 0.82	−0.43 ± 0.73	−0.82 ± 0.6	0.33 ± 0.73	0.15 ± 0.69
NMCs	−0.02 ± 0.53	−0.26 ± 0.45	−0.52 ± 0.7	0.18 ± 0.51	0.08 ± 0.67

The data presented are means ± SD

Neuropsychological scores are based on age and years of education according to Italian norms obtained from a prior validation study

CDR Clinical Dementia Rating, *CDR-SOB* Clinical Dementia Rating Scale Sum of Boxes, *MMSE* Mini-Mental State Examination, *MDRS* Mattis Dementia Rating Scale, *EMCs* Episodic Memory Composite score, *NMCs* Non-Memory Cognition Composite score

a significant group-by-time interaction effect for MDRS score ($F = 15.7$, $P = 0.0003$) and MMSE score ($F = 6$, $P = 0.019$). The results of the RM ANOVA are presented in Table 3. In the Tukey post-hoc analysis, the MDRS score in Aβ+ subjects was the only result that showed a significant decrease between the baseline and follow-up evaluations (Table 4).

There were no significant increases in amyloid load in either the Aβ− or the Aβ+ group between the baseline and follow-up assessments (Supplementary Table 1). Figure 2 shows the differences between baseline and retest MDRS scores in the Aβ+ and Aβ− groups.

RCI showed significant decreases in cognitive performance in 14 of the 38 subjects with aMCI over 1 year and these subjects were in the MDRS+ group. By contrast MDRS scores were stable over time in 24 subjects who were in the MDRS− group. Among the 14 subjects with cognitive deterioration, 86% were Aβ+ and 14% were Aβ−; among the MDRS− group, 25% were Aβ+ and 75% were Aβ− ($\chi^2 = 13$; $P = 0.0003$). SUVr above 1.21 identified individuals who would show significant clinical progression over 1 year with a SE of 86%, SP of 75% and LR of 7, as compared to Aβ− subjects. The PPV was 67% and NPV was 90% (Table 5).

Table 3 Repeated measures analysis of variance of SUVr values and neuropsychological test scores in Aβ+ and Aβ− groups in relation to group, time and group-by-time interaction. assessed at baseline and after 1 year

	Group		Time		Group × time	
	F	*P* value	*F*	*P* value	*F*	*P* value
Neuropsychological tests						
CDR	0.6	NS	3	NS	0.3	NS
CDR-SOB	5.6	0.023	1.9	NS	1	NS
MMSE	5.6	0.024	7.4	0.01	6	0.019
MDRS	6.3	0.0166	10.4	0.0027	15.7	0.0003
EMCs	16.56	0.0002	16.13	0.0003	2.25	NS
NMCs	7.82	0.008	11.87	0.001	2.31	NS
SUVr[a]	117.38	<0.00001	3.8	NS	1.63	NS

The data presented are means ± SD

CDR Clinical Dementia Rating, *CDR-SOB* Clinical Dementia Rating Scale Sum of Boxes, *MMSE* Mini-Mental State Examination, *MDRS* Mattis Dementia Rating Scale, *EMCs* Episodic Memory Composite score, *NMCs* Non-Memory Cognition Composite score, *NS* not significant, *SUVr* standardized uptake value ratio

[a] From amyloid imaging with [^{18}F]florbetaben PET

Table 4 Post-hoc analysis of SUVr values and neuropsychological test scores in Aβ+ and Aβ− groups assessed at baseline and after 1 year

	Difference between retest and baseline scores			
	Aβ+	*P* value[b]	Aβ−	*P* value[b]
Neuropsychological tests				
CDR	0.14 ± 0.41	NS	0.08 ± 0.34	NS
CDR-SOB	0.81 ± 2.07	NS	0.15 ± 2.01	NS
MMSE	−2.47 ± 3.35	0.079	−0.19 ± 2.35	NS
MDRS	−11.25 ± 11.34	0.023	0.81 ± 7.16	NS
EMCs	−0.39 ± 0.56	NS	−0.18 ± 0.28	NS
NMCs	−0.26 ± 0.36	NS	−0.1 ± 0.28	NS
SUVr[a]	0.01 ± 0.09	NS	0.05 ± 0.1	NS

The data presented are means ± SD

CDR Clinical Dementia Rating, *CDR-SOB* Clinical Dementia Rating Scale Sum of Boxes, *MMSE* Mini-Mental State Examination, *MDRS* Mattis Dementia Rating Scale, *EMCs* Episodic Memory Composite score, *NMCs* Non-Memory Cognition Composite score, *NS* not significant, *SUVr* standardized uptake value ratio

[a] From amyloid imaging with [^{18}F]florbetaben PET

[b] Tukey–Kramer post-hoc test

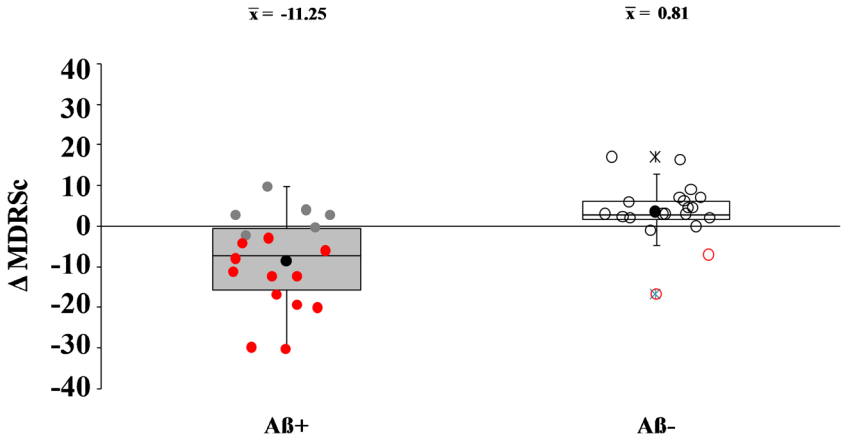

Fig. 2 Individual differences between baseline and retest MDRS scores in Aβ+ and Aβ− subjects with mild cognitive impairment. The box plots show the medians and 25th and 75th percentiles of the differences in MDRS scores, and the whiskers indicate the 90th and 10th percentiles. *Asterisks* indicate outliers, *black circles* are the average in each group, and *red circles* indicate clinically relevant changes as shown calculation of the reliable change index. The $\bar{x}$ values are the mean differences between baseline and retest scores

Discussion

Although PET-based amyloid imaging is widely used in the research setting, the application is still of limited clinical relevance. Many studies have shown a significant relationship between a high brain amyloid load and the likelihood of progression to probable AD [12, 31–33]. However, the amyloid positivity thresholds applied in these studies identified individuals with impairment close to the disease onset zone who already show advanced structural brain changes. In the present study, the association between amyloid load in subjects with aMCI and progression to probable AD or clinical cognitive decline was investigated specifically in subjects with early amyloid retention. VA of FBB images was used as the reference to determine the SUVr threshold of 1.21 to define amyloid positivity. This threshold value was in the same range as that determined in our previous cross-sectional study [34], and similar to that identified by Villeneuve et al. in a study including 18 young adults and 154 cognitively normal elderly subjects [10].

In the present study, clinical assessment showed decreases in MDRS scores at 1 year in 37% of subjects with aMCI. Among subjects with clinical progression, 86% were Aβ+ at baseline and only 14% were Aβ−. Conversely, among subjects without evidence of cognitive decline, 75% were Aβ− and 25% were Aβ+ (Table 5). Moreover, according to previous studies [14, 35] Aβ+ subjects show greater decline in EMCs than Aβ− subjects. Previous studies have shown that increased amyloid deposition in the brain of subjects with MCI is associated with a greater likelihood of conversion to AD. In particular, Okello et al. found that 47% of subjects with MCI and increased ^{11}C-PIB retention at baseline showed clinical conversion to AD during a 1-year follow-up, which increased to 82% over 3 years [36]. By contrast, only 7% of Aβ− subjects with MCI converted to AD over 3 years. In that study, MCI subjects with a cortical SUVr of more than twice the standard deviation of mean in healthy controls in the frontal, parietal, temporal, occipital and cingulate cortices were Aβ+. In these cortical areas the mean SUVr values varied between 1.59 and 2.10 in MCI converters. Similar results were found by Doraiswamy et al. [37] who evaluated the prognostic role of PET-based amyloid brain assessment in MCI subjects over 18 months. In that study, images were visually classified as Aβ+ and Aβ−. Individuals Aβ+ at baseline showed higher amyloid retention (SUVr 1.52) and greater clinical deterioration on the Alzheimer's Disease Assessment Scale–Cognitive subscale than Aβ− subjects ($P < 0.01$).

However, in these studies, amyloid positivity was defined by VA or by comparing images from cognitively normal individuals (in whom the amyloid load would be expected to be low) with those from cognitively impaired patients (in whom the amyloid load would be expected to be high) [12, 13,

Table 5 Differences between SUVr and cognitive performance scores at baseline and 1 year in Aβ+ and Aβ− groups

Cognitive status[a]	Aβ+	Aβ−	χ^2	*P* value	Sensitivity (95% CI)	Specificity (95% CI)	Likelihood ratio (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
MDRS+	12 (86%)	2 (14%)							
MDRS−	6 (25%)	18 (75%)	13	0.0003	67% (46–83%)	90% (74–97%)	7 (5–10)	86% (70–94%)	75% (58–87%)

[a] Subjects with (MDRS+) and without (MDRS−) clinically relevant change in MDRS scores between baseline and 1 year

38–40]. Amyloid deposition is a lengthy process, which takes more than about a decade to move from SUVr values found in healthy controls to SUVr 1.5 used to identify amyloid positivity, and another 19 years to move from SUVr 1.5 to SUVr 2 observed in patients with AD. Several pieces of evidence indicate that the amyloid deposition increases to a plateau of around SUVr 2 [31, 32]. According to this model describing the temporal trajectory of cortical amyloid deposition, the threshold during the period with a low rate of accumulation preceding the increase in amyloid burden and progression of cognitive impairment in subjects at risk of AD conversion is lower than that used in the present study [31, 41].

Despite the low amyloid deposition levels in our study, Aβ+ subjects showed significantly greater global cognitive decline over 1 year than Aβ− subjects. Moreover, two Aβ+ subjects showed conversion to AD (13%), which is consistent with the conversion rate found in previous studies [1, 2]. By contrast, none of the Aβ− subjects showed clinical signs of prodromal dementia over 1 year.

In the aMCI subjects in this study there were no significant differences in SUVr values between the baseline and follow-up PET scans. The same results was obtained in the whole population and in the Aβ+ and Aβ− groups separately. The lack of significant SUVr changes found in this study can probably be explained by the short time between the baseline and follow-up scans [31, 41]. Our results indicate that subjects with aMCI with FBB SUVr above the threshold of 1.21, who are presumably still far from the onset of dementia, reveal a greater global cognitive decline than individuals with an amyloid load below SUVr 1.21. Moreover, the LR of 7 suggests that MDRS+ subjects have an approximately sevenfold higher chance of having an amyloid load greater than the threshold than MDRS− subjects. This also suggests that the SUVr threshold of 1.21 used to detect early amyloid deposition provides a diagnostic tool to identify aMCI subjects with a higher probability of progression to advanced disease.

In accordance with the temporal trajectory of amyloid deposition reported by several authors [31, 42, 43], the identification of a low threshold for amyloid positivity could be used to identify the period of slow accumulation that precedes the onset of the disease as a therapeutic window for secondary prevention interventions or to design treatment trials. Although amyloid positivity has been considered useful in vivo for the detection of pathological changes in patients with probable AD, the clinical relevance of this biomarker when positivity is detected at high amyloid loads might be reduced because of structural brain changes occurring at disease onset [31, 42] which contribute to disease severity, making it too late for effective therapeutic interventions.

Over the last decades there has been much effort exploring the potential of several MRI, PET, CSF and blood parameters as possible markers of neurodegeneration, amyloid deposition and tau-related pathology [44]. However, studies conducted so far have not led to conclusive results on the superiority of any of these over another, nor have they provided sufficient evidence for validation and application in practice [45]. However, it is likely that a single parameter would not be able to improve the diagnosis of AD, and it is conceivable that once validated a combination of neuroimaging and CSF markers will be able to fulfil the criteria needed to ensure an early and accurate diagnosis of AD [46].

The major limitation of this study lies in the relatively small sample size that did not allow definitive conclusions to be drawn from the analysis.

The results of this study showed that subjects with aMCI with an SUVr above the threshold of 1.21, who presumably are still far from the onset of dementia, showed greater global cognitive decline than subjects with an SUVr below this threshold. In conclusion, an amyloid burden represented by SUVr 1.21 in subjects with MCI identifies those at high risk of global cognitive decline over 1 year. In these subjects there is an opportunity for successful therapeutic interventions aimed at delaying disease onset and limiting further neuronal damage.

Acknowledgements We thank all patients who took part in this trial. We also acknowledge the excellent support of the team from the Nuclear Medicine Department. We are also grateful to Professor Alberto Pupi for critical reading of the manuscript. Assistance with editing the manuscript was provided by Manuella Walker (Pisa, Italy).

Author contributions A.C. conceived the study, participated in its design and coordination, drafted the manuscript and made the final revisions.

E.G. and V.D. carried out the PET experiments, participated in critical review of the data analysis and approved the final version of the manuscript.

O.F. performed PET scanner quality control and image analysis, participated in critical review of the data analysis and approved the final version of the manuscript.

G.G. performed statistical analysis, participated in critical review of the data analysis and approved the final version of the manuscript.

M.R. performed the radiochemistry, participated in critical review of the data analysis and approved the final version of the manuscript.

L.M. participated in the study design, participated in critical review of the data analysis and approved the final version of the manuscript.

A.T. participated in patient enrolment and contributed to revision of the manuscript.

A.M., C.P., E.C., M.DeB. recruited the patient, administered the neuropsychological tests, participated in critical review of the data analysis and approved the final version of the manuscript.

Funding The study was supported by ASL5 – Regione Liguria and Piramal imaging S.A which kindly provided the radiopharmaceutical for PET imaging.

Compliance with ethical standards

Conflicts of interest None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the principles of the

1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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