Relationship between comprehensive geriatric assessment and amyloid PET in older persons with MCI

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Abstract

Background.
The association between amyloid deposition and cognitive, behavioral and physical performance in mild cognitive impairment (MCI) due to Alzheimer's disease (AD) has been poorly investigated, especially in older persons.

Methods.
We studied the in vivo correlation between the amyloid deposition at Positron Emission Tomography (amyloid-PET) and the presence of memory loss, reduced executive function, physical performance and neuropsychiatric symptoms in older persons with MCI due to AD. Amyloid-PET was performed with 18F-flutemetamol and quantitavely analyzed.

Results.
We evaluated 48 subjects, including 21 men and 27 women older than 65 years old. We performed in each patient a comprehensive geriatric assessment including MMSE, Clock Drawing Test, ADL, IADL, NPI, SPPB and Hand Grip strength. Then, each patient underwent amyloid-PET. The mean scores obtained at the MMSE by the subjects under examination was 24.97 ± 3.90 with a median NPI of 4. PET scan revealed brain amyloid deposition in 21 persons. Participants with positive amyloid scans exhibited a higher prevalence of pathological clock drawing test (p=0.0009). We did not find a significant association between MMSE score and beta amyloid plaque burden. When amyloid deposition was present, we observed that the deposition was diffuse, involving cortex in a widespread manner, as showed by alterations of CDT.

Conclusion.
Our findings support the recent hypothesis that amyloid deposition could be associated with multiple cerebral dysfunction, such as executive dysfunction and other cognitive impairment.

Introduction
Dementia in industrialized countries affects about 8% of over sixty and rises in up to 20% after the eighties [1]. According to some perspectives, dementia may triple in the next 30 years in Western countries. Therefore, dementia has been defined from the World Health Organization (WHO) a
"worldwide public health priority". Globally, dementia affected about 46 million people in 2015 [2] and the number is estimated to double in 2030. In view of the high social and economic burden of the disease, all countries should include dementia in their public health programs, and coordinated strategies are needed to reduce the clinical impact of this disease and relative complications [3]. Alzheimer’s disease (AD) is the most common type of dementia in which early clinical manifestations are characterized by a number of cognitive and behavior symptoms [4–5]. With the progression of the disease, more cognitive and behavior changes are observed, causing a progressive loss of autonomy and, in advanced stages, also compromising motor functions with the appearance of hypokinetic-hypertonic syndrome.

Recently, the in vivo evaluation of amyloid deposition with Positron Emission Tomography (PET) has been useful to anticipate the diagnosis of dementia, before symptoms become clinically evident [7–9]. However, there is a lack of evidence in AD especially how PET findings correlate with cognitive, motoric and behavioral functions. In this study, we therefore studied the correlation between amyloid deposition and the presence of memory loss, reduced cognitive and physical performance, and neuropsychiatric symptoms.

Materials And Methods
We selected 48 elderly subjects (older than 65 years) with “mild cognitive impairment (MCI) due to AD” [10] evaluated at the Cognitive and Mobility Disorders Lab of the Department of Medicine, Geriatrics and Rehabilitation of the University-Hospital of Parma, and enrolled in the prospective observational T.R.I.P. Study (Traumatic Risk Identikit Parma Study) [11]. Briefly, patients at risk for falling were normally assessed by Comprehensive Geriatric Assessment (CGA) and those with MCI due to AD were enrolled in this study. In details, we consecutively selected subjects fulfilling the MCI “core” criteria as defined by the recommendations from the National Institute on Aging-Alzheimer’s Association (NIA-AA) workgroups on diagnostic guidelines for Alzheimer’s disease [10]. Inclusion criteria were a) MMSE score ≥ 24/30 in order to exclude demented persons [12] and b) concerns about cognitive modifications, expressed as subjective complaints by the subject or by impression by a close acquaintance or an expert clinician. Finally, participants with any memory complaint
objectively confirmed or with the presence of a pathological Neuropsychiatric Inventory (NPI) questionnaire were considered. Neuropsychiatric symptoms represent a common feature in addition to the full cognitive changes in dementia even in the mild cognitive impairment (MCI) setting [13]. Participants with established dementia, severe depression, or severe limitations in basic activities of daily living were excluded. Each patient had a recent brain computed tomography (CT) and/or magnetic resonance (MR) that excluded any secondary cause of cognitive impairment (e.g., hydrocephalus, cerebral expansive lesions and stroke). Each patient was evaluated by a geriatrician with expertise in the administration of Comprehensive Geriatric Assessment and in particular of Mini Mental State Examination (MMSE), Clock Drawing Test (CDT), Activity Daily Living (ADL), Instrumental Activity of Daily Living (IADL), Neuropsychiatric inventory (NPI) questionnaire, Geriatric Depression Scale (GDS), Short Physical Performance Battery (SPPB) and hand grip strength. All the selected subjects underwent amyloid-PET scan with 18F-flutemetamol to verify the presence cerebral amyloid deposits of (Aβ), in accordance with the indication provided by the Italian Ministry of Health.

In details, all patients were first evaluated by trained geriatrician with a standard clinical evaluation [14] and, if necessary, also referred to a neuropsychologist with long-term experience in clinical and experimental neuropsychology of degenerative diseases [15]. The diagnosis of MCI due to AD, was established using a standard evaluation protocol based on the new NIA-AA criteria [10]. Cognitive function was evaluated by Mini Mental State Examination and Clock Drawing Test. Mini Mental State Examination (MMSE) [16] consists of thirty items that refer to seven different cognitive areas: orientation in time and space, word recording, attention and calculation, re-evocation, language and executive function. The total score ranges between a minimum of 0 and a maximum of 30 points. The score is adjusted for age and the subject's education. Clock Drawing Test (CDT) was used to assess executive cognitive dysfunction [17]. Many variants of the test are used in clinical practice: each variant proposes a different error detection with different scores that quantify them. In this study, it was chosen the clock test version in Camdex (watch dial to adjust = 1 point, all the numbers and hours correct position = 1 point, exact time = 1 point) [18]. Depressive symptoms were assessed by the 15-item Geriatric Depression Scale (GDS-15) which
detects changes in depressive symptoms after a major negative life event [19]. Physical performance was assessed by the Short Physical Performance Battery (SPPB) [20], while hand grip strength was measured by manual dynamometer [21]. Neuropsychiatric symptoms were recorded by the neuropsychiatry inventory (NPI) scale. Weight and height were assessed for having body mass index (BMI). All patients underwent a brain CT or MR scan in the previous 3 months. Chronic drug treatment was recorded. Missing data were integrated by checking original clinical sheets.

18F-Flutemetamol PET

Amyloid PET scans was performed using a whole-body hybrid system Discovery IQ (GE Healthcare) operating in three-dimensional detection mode. Head holder was used to restrict patient movement. Head movement was checked on a regular basis. All cerebral emission scans began 90 minutes after a mean injection of 2 MBq/kg weight (150-250 MBq) of 18F-flutemetamol. For each subject, 10-minute frames were acquired to ensure movement-free image acquisition. All PET sinograms were reconstructed with a 3-D iterative algorithm, with corrections for randomness, scatter, photon attenuation and decay, which produced images with an isotropic voxel of 2 × 2 × 2 mm and a spatial resolution of approximately 5-mm full-width at a half-maximum at the field of view center.

PET images were assessed visually by two trained, independent readers blinded each other with a previously described technique [22-24].

[18F] Flutemetamol binding was analyzed using a regional semi-quantitative technique described by Thurfjell et al., in which where described an automated quantification of 18F-flutemetamol PET activity after comparison with visual image reads [25]. In this technique, semi-quantitative regional (prefrontal, anterior cingulate, precuneus/posterior cingulate, parietal, mesial temporal, lateral temporal, occipital, sensorimotor, cerebellar grey matter, and whole cerebellum) and global composite standardized uptake value ratios (SUVRs) in the cerebral cortex were generated automatically and normalized to the pons using the CortexID Suite software (https://www.gehealthcare.co.uk/-/media/13c81ada33df479ebb5e45f450f13c1b.pdf ). This software uses a threshold z score of 2.0 to indicate abnormally increased regional amyloid
burden that corresponds to a composite SUVR of approximately 0.59 to 0.62 when normalized to the pons, providing a 99.4% concordance with visual assessment [25]. The study images were compared to the intrinsic software database control group (of > 100 amyloid negative flutemetamol healthy controls from GE Healthcare) as a whole to calculate the z scores compared to clinically negative amyloid scans.

Highly positive amyloid-PET was defined when amyloid deposition involved at least one brain areas with a z score > 2.0. Normal tracer distribution at qualitative analysis with a threshold z score of 2.0 on all examined regions identified a negative amyloid-PET. Mild results were considered as PET scans with a z score of 1.0 at least one brain areas.

The data were treated in agreement with Italian legislation on Data Protection. A detailed informed consent was obtained from all patients. The study was approved by the Ethical Committee of the University Hospital of Parma (ID 17262 del 12/05/2017). It was conducted in compliance with the Good Clinical Practice.

**Statistical Analysis**

Data are reported as means and standard deviations, or median and interquartile (IQR) or percentages. To test the relationship between global cognitive performance, evaluated by MMSE and CDT, and deposition of the amyloid detected in the brain regions, we schematically divided into frontal, temporal and parietal areas. Each of the three cerebral areas examined by amyloid PET was considered pathologically affected by amyloid deposition if the Z-score of the amyloid deposition in each area was greater than at least three times the normal reference population. Furthermore, a parameter was considered to be the pathological deposition of amyloid in all three brain areas examined (frontal and parietal and temporal), an expression of a global amyloid brain deposition, and this parameter was examined by multivariate logistic regression with cognitive tests of the subject. All p-values were considered significant for p < 0.05. The statistical processing was carried out using the Statistical Analysis System (SAS) 8.2 software.

**Results**

The patients included in the study were 48, including 21 males (43.75%) and 27 females (56.25%).
Mean age of the enrolled subjects was 74.58 ± 7.6 years (range 54–90 years) (Table 1).
Of these subjects, 59.26% showed conservation of cognitive functions at MMSE (score corrected for age and education > 24), while 40.74% had a mild deficit. Mean value of MMSE score obtained by the subjects under examination was 24.97 ± 3.90. The clock drawing test was performed incorrectly by 35 subjects (64.81%).
The mean value of SPPB score was 9.04 ± 2.61, while the average muscle strength of the upper extremities measured by hand grip was 25.68 ± 7.68 Kg.
The average scores obtained in the ADL (Katz’s scale) was 5.25 ± 1.31, while in instrumental activities IADL (Lawton’s scale) equaled 5.12 ± 2.63. Finally, the mean NPI score was 4.2 ± 2.38 CT/MRI images showed cortical atrophic changes in 26 of the 48 examined subjects (54.2%), while cerebrovascular modifications were present in 31 subjects (64.8%).
High burden of amyloid deposits was detected in 25 of 48 (45.8%) patients included in the study, with a mean value of global z score of 2.8. Amyloid-PET was negative in 21 (43.7%) subjects and mild amyloid deposition was present in 2 (0.5%) subjects.
In Fig. 1 we show an example of negative and positive amyloid-PET results. Taken into account the only subjects with pathological PET examination emerges from the mean of the uptake values of 18F-Flutemetamol, albeit in the presence of a widespread and pathological deposition of amyloid, a lower involvement of sensory-motor regions of the right and left (average values of z-score of 3.25 ± 2.44 and 3.01 ± 2.42, respectively), occipital left and right (average values of z-score of 3.83 ± 3.75 and 3.15 ± 3.08, respectively) and right and left medial temporal region which remain the cortical area less involved by amyloid pathology (mean values of z-score of 0.83 ± 1.59 and 0.47 ± 1.60, respectively).
Table 2a shows the relationship between abnormal amyloid deposits, MMSE score, the clock drawing test results and the presence of atrophic changes at CT/ MRI scans. Only changes in CDT were significantly higher in subjects with positive amyloid-PET (p = 0.0009).
Furthermore, there was no significant relationship between the presence of atrophy or cerebrovascular alterations in CT/MRI and an altered or normal MMSE score (Table 2b).
Table 3a shows the percentage of subjects with more than one altered test, expression of cognitive, psychic symptoms, behavioral alterations or physical performance (Table 3a). Stratifying subjects in subclasses of alterations, only the association between abnormally increased deposition of amyloid at PET scan and the concomitant alteration of both MMSE and CDT was positive and statistically significant (p = 0.03). However, altered MMSE and NPI (p = 0.87), altered CDT and NPI (p = 0.39), altered MMSE, CDT and NPI (p = 0.84) were not significantly associated. Similarly, alterations in cognitive (MMSE) and motoric (SPPB) performance (p = 0.32) and MMSE and Muscle strength impairment (p = 0.94) were not significantly correlated (Table 3a).

Finally, Table 4 shows the multiple logistic regression analysis testing the relationship between clinical, cognitive and motor characteristics of the enrolled subjects and positive amyloid-PET (Table 4). Only CDT alteration was associated with an increased risk of having pathological deposition of cerebral amyloid deposits (p = 0.01).

Discussion

This study shows that patients with MCI due to AD and cerebral amyloid deposition have a high amount of amyloid plaques in brain cortical structures, not only in the temporal lobes. This feature could explain some of MCI clinical manifestations that may be attributable not only to the disturbance of memory. MCI could affect different cognitive domains and the global brain involvement demonstrated by amyloid-PET is associated with the impairment of several higher brain activities, and in particular executive functions, attention, memory and praxis.

These findings support recent data showing that pathological amyloid deposition could be present at least several years before the appearance of clinical manifestation of the AD [26]. Amyloid-PET could be used together with anamnestic, clinical and objective neuropsychological tests for early diagnosis of MCI due to AD [27], even if MMSE expression of global cognitive function is normal [28]. Our results are in accordance with previous studies showing that executive functions, evaluated by CDT [28] or Montreal Cognitive Assessment (MoCA) tests [28], could identify persons at risk of developing AD. Another interesting aspect emerging from our results is that CDT correlates with amyloid pathology within almost normal MMSE values and this could be explained by the fact that CDT requires
activation of various neuro-psychological functions, such as auditory perception, auditory memory, abstraction ability, visual memory, visual perception, visual-spatial functions, planning capacity, visual motor and executive functions [29–30]. This association could be related to the globality of the amyloid deposition in the central nervous system and supports the evidence that the cerebral amyloid angiopathy (CCA) could be the result of a deficit of the protein clearance pathways [31]. Recently, Morris et al. [32] proposed that an impairment of the cerebral vascular basement membranes by which fluid passes into and out of the brain explain the accumulation of the amyloid in the central nervous system with an imbalance between production and its clearance.

Our data also suggest that if amyloid deposit if present, the amount of deposition should be relevant for being detected clinically and the process could influence different brain area and not only the medial temporal lobe where important memory related circuits are located. This aspect is in line with other studies [33]. In fact, the hierarchical amyloid deposition in the brain had already been suggested in the past by Thal and Braak [34] from pathological studies, suggesting that the onset of aggregates of β-amyloid initially cared areas of the neocortex as the frontal, parietal and temporal area and only in more advanced stages the hippocampus would be affected by the amyloid pathology. It could be speculated that in the early phase of the disease the deposition of amyloid should involve globally the cortex, and this process could require several years. Recently, a longitudinal study realized in cognitively normal older persons, showed that higher amyloid beta burden was associated with increasing anxious-depressive symptoms over time [35], and these results are consistent with our data showing that amyloid brain deposition produces a behavior modification, particularly evident in the atypical forms of dementia.

Then, probably only when the amount of amyloid is high enough, Tau deposits are produced from amyloid in areas such as the medial temporal lobe, with clinical picture of loss of long-term memory. This hypothesis is in accordance with recent results reported by Donohue et al. [36], showing that there is a time window of at least five years between the initial deposition of amyloid and a clear reduction of cognitive performance detected by MMSE. More recently, even findings reported by Sepulcre J et al. [37] confirm this hierarchical organization of Tau and Amyloid deposits in the cerebral
cortex. In particular, these authors suggest that several years before AD dementia manifestations, abnormal accumulations of tau and Aβ insoluble proteins are visible in the temporal lobe and association cortex. Tau and Aβ deposits show some degree of spatial specificity as well as some overlapping in convergent zones [38].

To date, research in the field of AD "causal" therapy is increasingly directed to identify subjects with AD in the pre-clinical stage, when amyloid deposits in the cortex are scarce and cognitive function not compromised. Hence, the possibility of having AD biomarkers in pre-clinical phase appears increasingly important and understanding the progression from MCI to dementia, identifying cluster of markers that intercept patients’ candidate for prescription of future drugs will be fundamental. Among these biomarkers of AD, the amyloid PET, could be useful for really identifying pre-mortem patients with high probability to be affected by AD. Our results support this hypothesis especially when the amyloid deposition is plentiful, as in our study, and higher than 3 times amount in age-matched older persons, it should not be considered as the “normal” effect of aging. Conversely, the presence of high amyloid burden with global diffusion in the cerebral cortex is associated with an increased risk of developing AD blown over time [39-40].

Supporting this evidence, more recently, a dose-response relationship between amyloid deposition and cognitive performance has been suggested [41]. The authors found that the magnitude of amyloid burden at baseline was associated with the rate of cognitive decline over 4-year follow-up period, suggesting a potential link between these two phenomena. Our findings may have important implications also for projecting clinical outcomes on amyloid-PET scan basis, as well as for understanding the effect of amyloid in preclinical AD.

The clinical significance of these results in the routine evaluation of AD patients is confirmed by a recent PET study which showed that, in almost a quarter of selected patients, [18F] flutemetamol PET changed the clinical diagnosis and altered the patient management plan. The authors concluded that amyloid-PET may have added value over the standardized diagnostic work-up in early-onset dementia patients with uncertain clinical diagnosis, providing evidence for the recommendations put forward in the appropriate use criteria for amyloid PET in clinical practice [41-43].
The main limitation of our study is the small number of patients that should be considered to draw definitive conclusions. Furthermore, selection of older persons with MCI could produce a significant "ceiling effect" reducing diagnostic accuracy of cognitive impairment. Despite these limits, this study supports the idea that even MCI due to AD is a multidomain disease that affects the cognitive sphere, neuropsychiatric and functional aspects of the persons affected with loss of autonomy initially in performing instrumental activities of daily living. All these aspects could be of importance in the initial evaluation of the patients. Through this study, we reinforce the hypothesis of a hierarchical deposition of amyloid aggregates, and the role of major cortical involvement of amyloid pathology in determining greater cognitive and functional impairment.

Declarations

**Ethics approval and consent to participate** The Ethics Committee of the University of Parma approved the study (ID 17262). A details informed consent was prepared and proposed to all patients. Consent to publish A consent to report individual patient data was obtained from all participants

**Availability of data and material** The datasets used and/or analyzed during the current study are available from the corresponding author on request.

**Competing interests** None to declare.

**Funding** None.

**Authors’ contributions** All authors of this manuscript have made substantial contributions to conception and design of the manuscript, have been involved in drafting and revising and have given final approval.

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Tables
Due to technical limitations, the tables are only available as a download in the supplemental files section.
Figures
Figure 1 showing an example of normal and pathological PET results. Taken into account the only subjects with pathological PET examination emerges from the mean of the uptake values of 18F-Flutemetamol, albeit in the presence of a widespread and pathological deposition of amyloid, a lower involvement of sensory-motor regions of the right and left (average values of z-score of 3.25 ± 2.44 and 3.01 ± 2.42, respectively), occipital left and right (average values of z-score of 3.83 ± 3.75 and 3.15 ± 3.08, respectively) and right and left medial temporal region which remain the cortical area less involved by amyloid pathology (mean values of z-score of 0.83 ± 1.59 and 0.47 ± 1.60, respectively).

**MMSE:** 30/30  
**NPI:** 0  
**CDR:** 0  
**SPPB:** 12/12  
**BALANCE:** no deficit  
**4-M WS:** 1.2 m/sec  

**MMSE:** 24.4/30  
**NPI:** 4  
**CDR:** 1  
**SPPB:** 9/12  
**BALANCE:** yes deficit  
**4-M WS:** 1.0 m/sec
Supplementary Files

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