Patterns of $^{11}$C-PIB cerebral retention in mild cognitive impairment patients

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**A B S T R A C T**

**Objective**: To evaluate the patterns of cerebral cortical distribution of $^{11}$C-PIB in patients with mild cognitive impairment (MCI).

**Material and methods**: The study included 69 patients (37 male, age range 42–79 years) with MCI, sub-classified as 53 with amnestic-MCI (A-MCI), and 16 with non-amnestic-MCI (NA-MCI). Patients underwent $^{11}$C-PIB PET/CT scan 60 min after intravenous injection of the radiotracer. A visual analysis of the images was performed by 2 experienced physicians. $^{11}$C-PIB-positive studies were considered when gray matter uptake was equal to or greater than white matter. According to the regions involved, $^{11}$C-PIB-positive studies were classified into A-pattern (predominant retention in frontal, anterior cingulate, lateral temporal, and basal ganglia) and B-pattern (generalized retention).

**Results**: Thirty-nine of the 69 (56%) patients with MCI showed $^{11}$C-PIB retention. Of the 53 A-MCI patients, 36 (68%) showed $^{11}$C-PIB retention. Eleven of 36 (30%) positive scans in A-MCI patients showed A-pattern, and 25 out of 36 (70%) patients had a B-pattern. Positive $^{11}$C-PIB was observed in 3 out of 16 (19%) patients with NA-MCI. Regional distribution in these 3 patients showed A-pattern in 1, and B-pattern in 2 patients.

**Conclusion**: Cortical retention of $^{11}$C-PIB was more frequent in A-MCI than in NA-MCI patients, and also B-pattern than A-pattern in the $^{11}$C-PIB positive group. The recognition of $^{11}$C-PIB distribution patterns allows MCI patients to be classified, and the A-pattern may offer a therapeutic window for potential future treatments.

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**Patrones de retención cerebral de $^{11}$C-PIB en pacientes con deterioro cognitivo leve**

**RESUMEN**

**Objetivo**: Evaluar los patrones de distribución cortical cerebral de $^{11}$C-PIB en pacientes con deterioro cognitivo leve (DCL).

**Material y métodos**: El estudio incluyó 69 pacientes (37 varones, rango de edad 42–79 años) con DCL, que fueron clasificados en 53 DCL amnésico (DCL-A) y 16 DCL no amnésico (DCL-NA). Se obtuvo una PET/TC $^{11}$C-PIB 60 min después de la inyección intravenosa del radiotrazador. Se realizó un análisis visual de las imágenes por 2 médicos con experiencia. Los estudios $^{11}$C-PIB se consideraron positivos cuando la captación en la sustancia gris fue igual o superior a la captación en la sustancia blanca. Dependiendo de las regiones afectadas, los estudios $^{11}$C-PIB positivos se clasificaron en patrón A (retención predominante en frontal, cingulado anterior, lateral temporal y ganglios basales) y patrón B (retención generalizada).

**Resultados**: De los 69 pacientes con DCL, 39 (56%) mostraron retención de $^{11}$C-PIB. De los 53 pacientes DCL-A, 36 (68%) tuvieron retención cerebral de $^{11}$C-PIB. Once de los 36 (30%) estudios positivos en los pacientes DCL-A mostraron un patrón A y 25 de los 36 (70%) pacientes presentaron un patrón B. Se observaron estudios $^{11}$C-PIB positivos en 3 de los 16 (19%) pacientes con DCL-NA. En estos 3 pacientes la distribución regional mostró patrón A en uno y patrón B en 2 pacientes.

**Conclusión**: La retención cortical de $^{11}$C-PIB fue más frecuente en pacientes con DCL-A que en pacientes con DCL-NA, y, asimismo, el patrón B que el patrón A en el grupo $^{11}$C-PIB positivo. La identificación de los patrones de distribución de $^{11}$C-PIB permite una caracterización de los pacientes con DCL; el patrón A puede ofrecer una ventana para potenciales tratamientos en el futuro.

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Introduction

Based on biomarkers criteria, the prevalence of amyloid pathology in persons with and without dementia has been recently published. The authors have conducted two meta-analysis to evaluate the presence of cerebral amyloid by PET imaging in persons with risk factors for developing Alzheimer disease (AD) and in a variety of dementia syndromes. They concluded that the PET detection of amyloid cerebral deposition in persons with normal cognition supports the hypothesis that the presence of amyloid defines the first stage of AD. Moreover, in the clinical practice, the authors emphasize the role of PET imaging for the demonstration of amyloid in the diagnosis of AD in patients with different degrees of cognitive impairment.

Mild cognitive impairment (MCI) is currently considered an intermediate phase of cognition decline that precede the clinical onset of AD. In the clinical setting, MCI patients can be categorized as amnestic MCI (A-MCI) and non-amnestic MCI (NA-MCI). It is well known that patients with A-MCI have a risk to develop dementia. However, clinical evolution of each MCI subgroup (A-MCI and NA-MCI) is different in terms of risk of conversion to AD. The progress to AD of patients with A-MCI is about 12% per year, and up to 80% of these patients will develop AD in a period of 6 years. In previous studies, we have reported a different behavior of 11C-PIB accumulation between A-MCI and NA-MCI patients. All the NA-MCI patients presented negative 11C-PIB PET/CT scans. Nevertheless, 74% of the A-MCI patients demonstrated 11C-PIB cerebral retention. This observation allowed us to suggest an elevated risk of conversion to AD in A-MCI patients.

Normally, 11C-PIB PET/CT scans are reported in terms of dual-report. Negative scan if only unpecific uptake in the white matter is observed, and positive scan if cortical amyloid deposition is detected regardless of its distribution. In the study of patients with cognitive impairment, we have observed several 11C-PIB cerebral patterns. Among them the most frequently and commonly found were either predominant retention in anterior regions of the brain (frontal, anterior cingulate, lateral temporal, basal ganglia) and the generalized retention in all cerebral regions.

To the best of our knowledge, this issue has not been addressed before. Thus, we have carried out this work to present the distribution patterns of cerebral amyloid detected by 11C-PIB PET/CT scan in A-MCI and NA-MCI patients.

Material and methods

Study population

All MCI patients were submitted by the Cognitive Impairment Unit of the hospital. The study included 69 patients, 37 male and 32 female. The average age was 67.5 years (range 42–79 years). All patients underwent a complete neurological evaluation, including medical history, physical examination, blood chemistry measurements, and neuroimaging (CT or MR). Neurological study of the cognitive function included screening tests (MMSE, TgM, and clock test) and neurophysiological evaluation of different cognitive areas (verbal and visual episodic memory, semantic knowledge, language, attention, executive function, praxis, and visuospatial abilities). Signed informed consent was obtained from each patient. All procedures were approved by the ethical committee of the University Hospital.

According to the clinical and neurophysiological evaluations, MCI patients were sub-classified as A-MCI (53 patients) and NA-MCI (16 patients). Patients with A-MCI had just one impairment in the memory domain or impairment in the memory domain associated with one or more impairment in other domains, such as attention, language, executive function, and visuospatial processing. Patients with NA-MCI had impairment in one or more nonmemory domains and no memory deficits.

11C-PIB synthesis

The radiosynthesis of 11C-PIB was performed in the Department of Nuclear Medicine of the hospital. 11C-PIB was synthesized using the one-step 11C-methyl triflate approach. The full process of synthesis has been described elsewhere. The final administered product contained 0.8 ± 1.28 μg of PIB. The specific activity was 138 ± 35 GBq/μmol and the radiochemical purity was higher than 99%.

Image acquisition

11C-PIB PET/CT scans were acquired on a Siemens Biograph LSO Pico 3D equipment (Siemens Healthcare Molecular Imaging, Hoffman Estates, IL, USA). Twenty minutes before the intravenous administration of the radiotracer, the patients rested in supine position in a quiet room, dimly lit. All patients underwent a 30 min static scan at 60–90 min after injection. The information provided by CT was used for the attenuation correction of the PET scan. Iterative reconstruction of the images was performed using an ordered subsets expectation maximization algorithm. The axial slices were reoriented parallel to the frontal–occipital axis.

Image analysis

Axial slices of 11C-PIB study were displayed with a color and gray scales. The cerebral distribution of 11C-PIB on sagittal and coronal slices was not evaluated. Visual analysis of the studies was performed by two experienced nuclear medicine physicians. The observers were unaware of diagnosis and any other clinical data. 11C-PIB images were considered positive when cortical retention of the radiotracer was observed. 11C-PIB images were considered negative if only nonspecific white matter uptake was observed. According to regions involved, 11C-PIB cortical retention was classified into A-pattern and B-pattern. The A-pattern described a predominant retention in frontal, anterior cingulate, lateral temporal, and basal ganglia. On the other hand, the B-pattern was assigned when a generalized cortical retention was detected (Fig. 1).

Statistical analysis

Categorical differences were expressed as frequencies and were compared with the Fisher exact test for independent samples. Statistical analysis was performed using SPSS, version 15 for windows. Statistical significance was established at p ≤ 0.05.

Results

Overall, 39 of the 69 patients (56%) showed a positive 11C-PIB PET/CT scan; the remaining 30 patients (44%) presented a negative scan. Based on the clinical assessment, 53 out of 69 patients had a diagnosis of A-MCI and the other 16 patients were NA-MCI (Fig. 2).

Of the 53 A-MCI patients, 36 (68%) showed positive 11C-PIB scans, whereas 17 (32%) had negative scans (p < 0.001). Regarding the distribution of the 11C-PIB cortical retention, 11 out of 36 (30%) positive scans in the group of A-MCI showed A-pattern and in the remaining 25 (70%) patients, B-pattern was detected.

For the 16 patients with a diagnosis of NA-MCI, positive 11C-PIB scans were observed in 3 patients (19%) and negative scans in the other 13 patients (81%) (p < 0.001). Regional distribution in the 3 positive 11C-PIB scans showed A-pattern in 1 (33%) and B-pattern in 2 cases (67%).
Therefore, A-pattern was found in 12 out of 39 (31%) positive \(^{11}\)C-PIB scans and B-pattern in the remaining 27 (69%) positive scans.

When the group of A-MCI patients was compared with the group of NA-MCI patients, statistically significant differences in \(^{11}\)C-PIB brain retention were found (36/53 vs. 3/16; \(p<0.001\)).

**Discussion**

In the present study we found that 56% of patients with MCI had cortical retention of \(^{11}\)C-PIB in the brain. This finding is similar to previous reports\(^4\) and represents the prevalence of amyloid deposition detected by \(^{11}\)C-PIB PET in patients with MCI. Many studies have documented that AD showed higher cortical retention of \(^{11}\)C-PIB than healthy controls.\(^9\) All this cumulative evidence with amyloid imaging led to recommend its use in the clinical decision-making process by the current guidelines on diagnostic criteria for studying dementia patients.\(^13\)

In MCI patients, \(^{11}\)C-PIB PET has demonstrated in vivo an increased cerebral amyloid burden.\(^3\) This fact is remarkable. Forsberg et al. documented that 33% (7/21) of MCI patients with positive \(^{11}\)C-PIB PET converted to AD during clinical follow-up (8.1 ± 6.0 months).\(^17\) In another study, Okello et al. reported that 82% of patients with MCI and positive \(^{11}\)C-PIB converted to AD within 3 years of baseline PET study; and, in addition, they observed a fast conversion to AD within 1 year in half (47%) of the \(^{11}\)C-PIB positive patients.\(^3\) Thus, the demonstration of cerebral amyloid using \(^{11}\)C-PIB in MCI patients can identify a group of patients at increased risk of developing AD.\(^16\) On the other hand, we have obtained negative \(^{11}\)C-PIB studies in 44% of MCI patients included in our study. This observation would mean that AD could be excluded almost in half of the population with MCI.

The cerebral presence of \(^{11}\)C-PIB deserves an analysis when MCI patients are sub-classified into A-MCI and NA-MCI. We found higher proportion of positive \(^{11}\)C-PIB in A-MCI patients (68%) than NA-MCI patients (32%). Significant difference (\(p<0.001\)) between the 2 subgroups was obtained. This observation was in accordance with previous reports.\(^20\) In this sense, Lee et al. reported 62% \(^{11}\)C-PIB positive A-MCI patients.\(^20\) Meanwhile, Lowe et al. observed significant discrimination (\(p<0.05\)) between A-MCI and NA-MCI by \(^{11}\)C-PIB PET.\(^21\) Other authors have mentioned that the increased \(^{11}\)C-PIB uptake in prefrontal, cingulate and parietal regions is higher in AD compared to MCI or control subjects.\(^22\) Moreover, \(^{11}\)C-PIB uptake in MCI may be different than in controls only in prefrontal cortex.\(^3\)

In most of the published work\(^7\) the visual assessment of the \(^{11}\)C-PIB cortical retention was based on positive/negative criteria. However, we observed the frequent detection of two differentiated patterns of regional cerebral retention of \(^{11}\)C-PIB in the MCI population included. Taking into account these distribution patterns, and in accordance with other authors,\(^5\) our study shows a variable distribution of \(^{11}\)C-PIB cerebral retention in MCI patients, and this would allow to hypothesize on the value of these patterns for a better characterization of MCI patients.

The A-pattern of predominant cerebral retention in frontal, anterior cingulate, lateral temporal, and basal ganglia was detected in 31% of PIB-positive MCI patients (30% of A-MCI and 33% of NA-MCI). In the first human study using \(^{11}\)C-PIB PET in AD patients, Klunk et al. already observed, in his research work, a prominent increase of \(^{11}\)C-PIB retention in frontal, parietal, temporal and occipital cortex and in striatum.\(^15\) Posteriorly, other authors have reported similar findings.\(^23\) Interestingly, there is a correlation between the severity of dementia and the specific increased \(^{11}\)C-PIB retention in the anterior regions of the brain, including both putamina.\(^27\) In our experience, and excluding the \(^{11}\)C-PIB accumulation in the basal ganglia, the A-pattern would resemble the early neuropathological changes of cerebral amyloid deposits identified at autopsy from demented subjects.\(^28\) The B-pattern of generalized \(^{11}\)C-PIB cerebral retention was detected in 69% of PIB-positive MCI patients (70% of A-MCI and 67% of NA-MCI). This B-pattern was twice more frequently observed than A-pattern. The clinical relevance of this finding would be the identification of patients at an early stage of disease, represented by B-pattern, where treatments to control the disease progression would be desireable and potentially effective. From a pathological point of view, B-pattern is consistent with the extensive deposit of amyloid plaques in all cerebral cortical areas revealed in post-mortem studies and represent the end-stage of histological amyloid accumulation as mentioned by Braak et al.\(^29\) We think that both distribution patterns support the hypothesis of the clinical–pathological continuum of AD.
dementia. In the clinical setting of MCI patients, the A-pattern would represent a low and variable $^{11}$C-PiB uptake at the initial period of amyloid accumulation affecting heterogenous regions of the brain, whereas the B-pattern would represent a high and diffuse $^{11}$C-PiB uptake and, therefore, a more advanced stage of the disease.

Limitations

The work was conducted in a university hospital and the participants were clinically selected at a single cognitive impairment unit. This fact may limit the generalization of the results. The sample size of A-MCI group was relatively large. However, the sample size of NA-MCI patients was too small to detect significant differences between the 2 patterns of cerebral $^{11}$C-PiB deposition. We performed a visual analysis of images what it is accordance with the clinical daily practice. However, other authors used image co-registration with MR imaging to delineate regions of interest and automated or semi-automated software for data quantification. Although these methods allow the regional quantification of $^{11}$C-PiB retention, its use is not standardized and requires a previous process of validation. Further investigations and longitudinal studies may help to elucidate the clinical outcome and the possibility to detect changes in the cerebral $^{11}$C-PiB distribution of patients presenting A-pattern.

Conclusion

In positive $^{11}$C-PiB MCI patients, two distinctive patterns of distribution may be identified: predominant retention in the anterior cerebral regions and generalized retention. Positive $^{11}$C-PiB studies were more frequent in A-MCI than in NA-MCI patients. Negative $^{11}$C-PiB studies can be obtained in almost half of MCI patients. Visual assessment of $^{11}$C-PiB images allows a clear distinction between positive $^{11}$C-PiB patterns and negative $^{11}$C-PiB studies. The recognition of these distribution patterns of $^{11}$C-PiB cerebral retention provides a characterization of MCI patients.

Conflict of interest

The authors declare that they have no conflict of interest.

References