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Original Article

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

I. Banzo[a,*], J.F. Jiménez-Bonilla[a], I. Martínez-Rodríguez[a], R. Quirce[a], M. de Arcocha-Torres[a], Z. Bravo-Ferrer[a], C. Lavado-Pérez[a], P. Sánchez-Juan[b], E. Rodríguez[b], M. Jiménez-Alonso[a], J. López-Defilló[a,b], J.M. Carril[a]

[a] Department of Nuclear Medicine, Molecular Imaging Group (IDIVAL), Marqués de Valdecilla University Hospital, University of Cantabria, Santander, Spain
[b] Department of Neurology, IDIVAL, Marqués de Valdecilla University Hospital, University of Cantabria, Santander, Spain

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ABSTRACT

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 out 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.

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

Palabras clave:
Deterioro cognitivo leve
Enfermedad de Alzheimer
Demencia
Imagen amiloide
^{11}C-PIB
Tomografía por emisión de positrones

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.

* Corresponding author.
E-mail address: mnubmj@humv.es (I. Banzo).

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Introduction

Based on biomarkers criteria, the prevalence of amyloid pathology in persons with and without dementia has been recently published.[1,2] 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.[2] 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.[1]

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.[3] 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.[4] In previous studies, we have reported a different behavior of ^{11}C-PIB accumulation between A-MCI and NA-MCI patients.[5,6] All the NA-MCI patients presented negative ^{11}C-PIB PET/CT scans. Nevertheless, 74% of the A-MCI patients demonstrated ^{11}C-PIB cerebral retention. This observation allowed us to suggest an elevated risk of conversion to AD in A-MCI patients.

Normally, ^{11}C-PIB PET/CT scans are reported in terms of dual-report.[7–9] Negative scan if only unspecific 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 ^{11}C-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 ^{11}C-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, T@M, 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.

^{11}C-PIB synthesis

The radiosynthesis of ^{11}C-PIB was performed in the Department of Nuclear Medicine of the hospital. ^{11}C-PIB was synthesized using the one-step ^{11}C-methyl triflate approach. The full process of synthesis has been described elsewhere.[5] 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

^{11}C-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 ^{11}C-PIB study were displayed with a color and gray scales. The cerebral distribution of ^{11}C-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. ^{11}C-PIB images were considered positive when cortical retention of the radiotracer was observed. ^{11}C-PIB images were considered negative if only nonspecific white matter uptake was observed. According to regions involved, ^{11}C-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 $p \leq 0.05$.

Results

Overall, 39 of the 69 patients (56%) showed a positive ^{11}C-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 ^{11}C-PIB scans, whereas 17 (32%) had negative scans ($p < 0.001$). Regarding the distribution of the ^{11}C-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 ^{11}C-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 ^{11}C-PIB scans showed A-pattern in 1 (33%) and B-pattern in 2 cases (67%).