

## Original article

**<sup>11</sup>C-PIB retention patterns in white and grey cerebral matter in idiopathic normal pressure hydrocephalus patients. A visual analysis**

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## ABSTRACT

**Objective:** Cortical cerebral amyloid disease, a hallmark of Alzheimer's disease, has also been observed in idiopathic normal pressure hydrocephalus (iNPH). The aim of this study was to compare the <sup>11</sup>C-PIB PET/CT retention pattern in iNPH patients and healthy subjects.

**Material and methods:** A comparison was made of the <sup>11</sup>C-PIB PET/CT retention pattern in 13 iNPH patients selected for surgical deviation, compared to a normal control population. Images were visually analyzed and scored for gray matter and white matter (WM) from 1 to 4 (slight to very high PIB retention). The scoring was analyzed in both groups separately for infra- and supra-tentorial regions. A comprehensive clinical report was presented in terms of positive, negative, or equivocal.

**Results:** <sup>11</sup>C-PIB PET/CT scan were reported as negative in 8, positive in 3, and equivocal in 2. Five of 13 patients showed at least one cortical area with PIB retention with an intensity higher than that observed in the control group. Overall, white matter (WM) PIB retention of iNPH scored lower than in the control group, showing a statistically significant difference in the infratentorial WM (92/104 vs 54/56;  $P < 0.05$ ) and a tendency to be lower in the supratentorial regions (70/84 vs 122/156,  $P = 0.327$ ), in particular in the upper periventricular region (25/28 vs 40/52;  $P = 0.134$ ).

**Conclusions:** The PIB retention pattern seems to be different in NPH, compared to normal subjects. PIB retention in WM of NPH appears less intense than in healthy subjects, and they show a higher degree of PIB retention in cortical regions. This deserves to be taken into account.

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### Patrones de retención de <sup>11</sup>C-PIB en la sustancia blanca y en la sustancia gris cerebral de pacientes con hidrocefalia a presión normal idiopática. Un análisis visual

## RESUMEN

## Palabras clave:

Hidrocefalia a presión normal

PET amiloide

<sup>11</sup>C-PIB

PET/TAC

Sustancia blanca

**Objetivo:** El depósito cortical de amiloide, una señal de identidad de la enfermedad de Alzheimer, se ha observado en la hidrocefalia a presión normal (HPN). Nuestro objetivo fue comparar el patrón de retención de <sup>11</sup>C-PIB PET/TAC en pacientes con HPN y sujetos sanos.

**Material y métodos:** Hemos comparado el patrón de retención de <sup>11</sup>C-PIB en 13 casos de HPN seleccionados para cirugía derivativa con una población control normal. Las imágenes se analizaron visualmente y puntuaron de 1-4 (de ligera a muy alta retención de PIB) tanto en la sustancia gris como en la sustancia blanca (SB). La puntuación se analizó por separado en las regiones infra y supratentoriales de ambos grupos. Se emitió un informe clínico en términos de positivo, negativo o dudoso/equívoco.

**Resultados:** Ocho <sup>11</sup>C-PIB PET/TAC se informaron como negativos, 3 positivos y 2 dudosos. Cinco de 13 pacientes mostraron al menos una región cortical con retención de PIB de intensidad mayor que la observada en el grupo control. En general, la retención de PIB en la SB de los pacientes con HPN tuvo puntuaciones menores que en el grupo control, mostrando una diferencia estadísticamente significativa en la SB infratentorial (92/104 vs. 54/56,  $p < 0,05$ ) y una tendencia a ser menor en las regiones supratentoriales (70/84 vs. 122/156,  $p = 0,327$ ), en particular en la región periventricular superior (25/28 vs. 40/52,  $p = 0,134$ ).

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**Conclusiones:** Los patrones de retención de  $^{11}\text{C}$ -PIB parecen ser diferentes en los pacientes con HPN comparados con sujetos normales. La retención de PIB en la SB de la HPN aparece menos intensa que en sujetos sanos y estos muestran un mayor grado de retención de PIB en las regiones corticales. Esto merece ser tomado en consideración.

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## Introduction

Carbon-11 ( $^{11}\text{C}$ ) labeled Pittsburgh Compound B (PIB) was the first amyloid radiotracer for in vivo detection of cerebral amyloid deposition in patients with Alzheimer's disease (AD) dementia.<sup>1–3</sup> Currently, its value as a biomarker of AD is similar to the  $\beta$ -amyloid 1–42 peptide detected in cerebral spinal fluid (CSF). The majority of the  $^{11}\text{C}$ -PIB PET studies has been targeted to patients with cognitive impairment, in order to detect the presence of AD and in this sense, a qualitative visual analysis has been well validated for this purpose in the clinical setting.<sup>4–7</sup>

Idiopathic normal-pressure hydrocephalus (iNPH) is a potentially treatable cause of cognitive impairment by surgical ventricular diversion. In these patients, the CSF dynamics are altered,<sup>8</sup> and in addition, some cerebral structural abnormalities have been described in gray and in white matters.<sup>9,10</sup> On the other hand, an important comorbidity with AD has been noted in this kind of patients.<sup>11,12</sup> Due to the altered CSF dynamics, it could be that the cerebral  $^{11}\text{C}$ -PIB distribution could be influenced without relation to AD. This potential influence may add some difficulties to the visual reading of images in a binary report for AD diagnosis, making it necessary to take them into account when we approach the study of a potential cerebral amyloid deposition in iNPH patients assessed by  $^{11}\text{C}$ -PIB PET/CT.

Our group has started a long-term study to investigate if the cerebral amyloid deposition assessed by  $^{11}\text{C}$ -PIB PET/CT could be a prognostic factor for the outcome of cognitive status after ventricular shunt placement in the brain. In the first step, we compared the  $^{11}\text{C}$ -PIB cerebral pattern distribution in a group of iNPH patients who were selected for derivative ventricular surgery and in a normal control population to study if there are any differences. We think this knowledge could contribute to a better understanding of the disease, and for a more accurate interpretation of this kind of brain scan. The aim of the study was to evaluate the cerebral  $^{11}\text{C}$ -PIB distribution pattern in iNPH patients in comparison with normal cognitive subjects.

## Materials and methods

### Study group

The study group included 13 patients, 6 men and 7 women, with a mean age of  $73 \pm 6$  years, selected for shunt surgery. The inclusion criteria were: clinical diagnosis of probable or possible iNPH according Relkin's criteria,<sup>13</sup> neuro-radiological findings of hydrocephalus without evidence of obstruction of CSF (Evans index  $>0.30$  and blurring convexity sulcus), CSF dynamic criteria for surgical treatment and no data suggesting secondary NPH. The exclusion criteria included a suspicion of secondary HPN (meningitis, subarachnoid hemorrhage, cerebral hemorrhage, brain trauma or tumor), aphasia or severe sensorial impairment and comorbidities which could compromise the evaluation of the post-surgical response to shunting. The patient clinical characteristics are shown in Table 1. None of the patients showed cognitive impairment clinically suggestive of AD.

### Control group

The control group included 7 healthy subjects, 3 men and 4 women, mean age of  $64 \pm 10$  years, with a normal neurological exam, submitted from the Cognitive Impairment Unit of our hospital.

The study has been approved by the Ethic Committee of our institution, and all subjects signed an informed consent form.

### $^{11}\text{C}$ -PIB synthesis

The radiosynthesis of  $^{11}\text{C}$ -PIB was performed in the Department of Nuclear Medicine of our hospital.  $^{11}\text{C}$ -PIB was synthesized using the one-step  $^{11}\text{C}$ -methyl triflate approach. The full process of synthesis has been described elsewhere.<sup>14</sup> The final administered product contained  $1.28 \pm 0.8 \mu\text{g}$  of PIB. The specific activity was  $138 \pm 35 \text{ GBq}/\mu\text{mol}$  and the radiochemical purity was higher than 99%.

### Image acquisition

In all patients and controls,  $^{11}\text{C}$ -PIB PET/CT scans were obtained using a Siemens Biograph LSO Pico 3D equipment (Siemens Healthcare Molecular Imaging, Hoffman Estates, IL, USA). Before performing the PET scans, all patients had an intravenous catheter placed in an arm. The patients were asked to lie in the supine position in a quiet room, dimly lit for 20 min before the radiotracer administration. They were injected with 555 MBq of  $^{11}\text{C}$ -PIB.  $^{11}\text{C}$ -PIB PET acquisition consisted of one static image acquired from 60 to 90 min after injection.

The information provided by CT was used to correct the attenuation of the PET scan. Images were reconstructed on a  $128 \times 128$  matrix using the ordered subsets expectation maximization iterative method (6 iterations and 16 subsets. Zoom 2.5, filter FWHM 2 mm and sinogram trim factor 1.5). The axial slices were reoriented parallel to the frontal–occipital axis.

### Analysis of images

Every study was analyzed by two experienced nuclear medicine physicians, who had no access to the patient clinical information during the informative step. The images were displayed in gray and microdelta color scales. Visual analysis of the images was carried out on a scale of PIB retention intensity from 1 to 4 for white and gray matter separately. Based on our previous experience reading  $^{11}\text{C}$ -PIB PET/CT scans, we assigned the maximal grade of intensity to the usual elevated PIB retention observed in cerebellar white matter of normal subjects. The other grades were assigned in comparison with it. Therefore, the intensity of PIB retention in gray and white cerebral matter was scored as follows: 1, slight retention (+); 2, mild retention (++); 3, high retention (+++); and 4, very high retention (++++).

The following topographic cortical regions were analyzed and scored: frontal, temporal, parietal and occipital in four axial slices, one infratentorial and three supratentorial: lower, middle and upper, in two sagittal slices, and in two coronal slices. White

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