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## Original Research Article

# The Pattern of Brain Amyloid Load in Posterior Cortical Atrophy Using $^{18}\text{F}$ -AV45: Is Amyloid the Principal Actor in the Disease?

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## Key Words

Biomarker · Posterior cortical atrophy · Alzheimer's disease · Positron emission tomography · Amyloid

## Abstract

**Background:** Posterior cortical atrophy (PCA) is characterized by progressive higher-order visuospatial dysfunction and praxis declines. This syndrome is related to a number of underlying diseases, including, in most cases, Alzheimer's disease (AD). The aim of this study was to compare the amyloid load with  $^{18}\text{F}$ -AV45 positron emission tomography (PET) between PCA and AD subjects. **Methods:** We performed  $^{18}\text{F}$ -AV45 PET, cerebrospinal fluid (CSF) biomarker analysis and a neuropsychological assessment in 11 PCA patients and 12 AD patients. **Results:** The global and regional  $^{18}\text{F}$ -AV45 uptake was similar in the PCA and AD groups. No significant correlation was observed between global  $^{18}\text{F}$ -AV45 uptake and CSF biomarkers or between regional  $^{18}\text{F}$ -AV45 uptake and cognitive and affective symptoms. **Conclusion:** This  $^{18}\text{F}$ -AV45 PET amyloid imaging study showed no specific regional pattern of cortical  $^{18}\text{F}$ -AV45 binding in PCA patients. These results confirm that a distinct clinical phenotype in amnesic AD and PCA is not related to amyloid distribution.

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## Introduction

Posterior cortical atrophy (PCA) is a syndrome characterized by a progressive decline in higher-order visuospatial function, associated with a decline in praxis, although memory and insight are relatively spared [1, 2]. In this kind of clinical presentation with progressive

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cognitive alteration, neuroimaging studies usually show focal atrophy and/or hypoperfusion in the posterior regions of the brain [3].

While the clinical presentation is dominated by higher-order visuospatial dysfunction, neuropathological studies report that PCA is typically associated with underlying Alzheimer's disease (AD) [4, 5]. Less frequently, this clinical presentation has been shown to be associated with corticobasal degeneration diseases, Creutzfeldt-Jakob disease, dementia with Lewy bodies, or subcortical gliosis [6].

The core neuropsychological features of PCA are Balint's syndrome, Gerstmann's syndrome, alexia, visual object agnosia, visuospatial neglect, prosopagnosia, environmental disorientation and apraxia [6]. Associated neurological signs have also been reported, including extrapyramidal motor signs, limb dystonia, visual hallucinations and myoclonus. Early affective symptoms, especially anxiety, are frequently observed [6].

Both chemical and imaging biomarkers are indicators of specific changes that characterize AD in vivo [7]. Consequently, they can help identify the underlying aetiology of PCA [8]. Few reports have described cerebrospinal fluid (CSF) biomarker profiles in PCA [9–14]. Most of them fulfilled the biological criteria for typical AD with an increase in the T-tau and p-tau levels and a decrease in the A $\beta$ <sub>42</sub> level.

Positron emission tomography (PET) imaging with amyloid probes now offers us the opportunity to investigate brain amyloid deposition in vivo [15]. Among the candidate probes, tracers labelled with carbon 11 have been extensively studied, especially the PIB compound [16]. Few <sup>11</sup>C-PIB studies have been conducted in PCA patients [11, 12, 17–24], and the results obtained have been contradictory. Increased <sup>11</sup>C-PIB uptake in the occipital cortex has been reported in single cases and small-series studies [12, 17–19], whereas larger-group studies have found no differences in <sup>11</sup>C-PIB patterns between PCA and amnesic AD [11, 21, 23] patients. However, the <sup>11</sup>C-PIB compound has a radioactive half-life of 20 min, which is a serious limitation for the widespread use of this biomarker for routine clinical purposes.

Fluorine-labelled compounds have a half-life of 110 min, allowing plenty of time for the centralized production and locoregional delivery of the compounds. Several fluorine-18-labelled radioligands have already shown that they can be very useful in AD patients, such as florbetapir (<sup>18</sup>F-AV45) [25]. This radiotracer has recently been validated as a useful biomarker for distinguishing AD and mild cognitive impairment patients from healthy control subjects [26, 27].

The main aim of this study was to quantify the amyloid load with <sup>18</sup>F-AV45 in PCA subjects, with and without associated neurological signs, and then compare the results to AD patients. In addition, we aimed at assessing (1) the correlations between <sup>18</sup>F-AV45 uptake and CSF biomarker concentrations and (2) the correlations between <sup>18</sup>F-AV45 uptake and cognitive (memory, language, visuoconstructional skills and gestural praxis) and affective symptoms in PCA subjects.

## Materials and Methods

### Subjects

We recruited PCA patients from the memory clinic in Tours, France. PCA was diagnosed according to the following clinical diagnostic criteria [28]: (1) insidious onset and gradual progression; (2) presentation with visual complaints despite intact primary visual functions; (3) evidence of predominant complex visual disorder on examination; (4) proportionally less impaired memory and verbal fluency, and (5) relatively preserved insight with or without depression.

All PCA patients underwent a thorough neurological and neuropsychological examination. Higher-order visuoperceptual dysfunctions were specifically documented with the Visual Object and Space Perception Battery [29] and the Visual Gnosia Evaluation Protocol [30]. In addition, associated neurological signs and symptoms such as myoclonus and extrapyramidal motor signs were specifically looked for and assessed by the motor subscale of the Unified Parkinson's Disease Rating Scale. The Mini-Mental State Examination was performed in order to rate global cognitive ability [31]. The neuropsychological battery was designed to assess several cognitive functions including short-term memory and working memory with the Digit Span Subtest [32], verbal episodic memory with the Buschke Selective Reminding Test [33, 34], visual memory with the 48-item Delayed Matching-to-Sample task [35], language with naming (DO 80) [36], literacy and semantic fluency [37], writing comprehension and logic and reasoning with the Boston Diagnostic Aphasia Examination [38], visuoperceptual skills with the BEC96 figure copy [39], a French neuropsychological battery, and gestural praxis with the Praxis Evaluation Battery [40]. Behavioural and affective symptoms were also assessed using the Neuropsychiatric Inventory Scale [41] and the Hamilton Depression Rating Scale [42].

For diagnostic purposes, all PCA patients underwent structural MRI and brain perfusion with <sup>99m</sup>Tc-ECD or <sup>99m</sup>Tc-HMPAO single-photon emission CT (SPECT), which showed focal atrophy and/or perfusion changes in the posterior brain regions. Lumbar puncture with CSF biomarker analysis was performed for diagnostic purposes several months ( $16 \pm 9$  months) before the beginning of the study, according to French health recommendations (HAS 2011). The results had to fulfil the biological criteria for typical AD (defined by T-tau >350 pg/ml, p-tau >60 pg/ml, A $\beta_{42}$  <500 pg/ml and/or A $\beta_{42}$ /A $\beta_{40}$  <0.05) or for atypical AD due to abnormalities of either tau or amyloid protein levels.

Patients with typical AD underwent amyloid PET imaging with <sup>18</sup>F-AV45. The results have been published in a previous study performed in the memory clinic in Tours [27]. AD patients met the NINCDS-ADRDA criteria for probable AD dementia [43]. Unlike for PCA subjects, lumbar puncture to analyse CSF biomarkers was not conducted for diagnostic purposes in all AD subjects, but only in the youngest ones, in accordance with the French health recommendations.

In order to meet French regulations and laws on biomedical research, the study was approved by the Local Ethics Committee in Tours and the French Agency for Safety and Security for Medical Devices.

#### *<sup>18</sup>F-AV45 PET Imaging*

<sup>18</sup>F-AV45 was prepared by nucleophilic substitution of a tosylate precursor (E)-2-(2-(2-(5-(4-(tert-butoxycarbonyl(methyl)amino)styryl)pyridin-2-yloxy)ethoxy)ethoxy)ethyl 4-methylbenzene sulfonate provided by Avid Radiopharmaceuticals, Inc. (Philadelphia, Pa., USA) on an automatic synthesizer, according to the method already described in the literature [44]. The radiochemical purity and specific activity were approximately 98% and  $180 \pm 70$  GBq/ $\mu$ mol (mean  $\pm$  SD values of 20 experiments). The radiochemical yields were 40–45%. Subjects were examined using whole-body hybrid PET-CT scanners: a Dual Gemini (Philips Medical Systems) and a Discovery RX VCT 64 (General Electric). All the acquisitions were performed in the 3D detection mode. Acquisition data were processed by adapting the reconstruction parameters to those of the tomograph having the lowest spatial resolution (Dual Philips Gemini) so that the images could be matched. All PET sinograms were reconstructed with an iterative 3D algorithm, with corrections for random, scatter, photon attenuation and decay into images with an isotropic voxel size of  $2 \times 2 \times 2$  mm<sup>3</sup> and a spatial resolution of approximately 5 mm full width at half maximum at the centre of the field of view. Acquisition data were processed with the standard package delivered with each acquisition system. All

**Table 1.** Demographic characteristics of the PCA and AD groups

	PCA (n = 11)	AD (n = 12)	p value
Age at lumbar puncture, years	64.45 ± 7.33	69.44 ± 4.93	0.074
Sex (male/female)	6/5	6/6	0.827
Education, years	10.91 ± 2.88	–	–
Disease duration, years	3.82 ± 1.72	3.5 ± 1.96	0.885

cerebral emission scans were started 50 min after <sup>18</sup>F-AV45 injection. The mean ± SD injected radioactivity was 237 ± 51 MBq. For each subject, two frames of 10 min were acquired but only the first one was analysed qualitatively and quantitatively.

### Image Analysis

The <sup>18</sup>F-AV45 PET images were co-registered to the <sup>18</sup>F-AV45 template, proposed by Wong et al. [45], in the Talairach space by PMOD<sup>®</sup> version 3.2 (PMOD Technologies) using a mutual-information similarity function. Standardized uptake values were obtained by normalizing tissue concentrations to the injected dose and patient body weight. Regions of interest were defined in several cerebral regions (precuneus, anterior cingulate, posterior cingulate, frontal, temporal, parietal and occipital) according to the MNI-AAL atlas. Cortical-to-cerebellum standardized uptake value ratios were calculated and used for intersubject comparison, since the cerebellum has been reported to be a region free of amyloid plaques in the AD brain. We obtained right and left standardized uptake value ratios as well as the corresponding means in each cerebral region.

### Statistical Analysis

We described data separately in each PCA and AD group. Values were expressed as means ± SD or as frequency. Due to a skewed distribution and unequal variances, we used non-parametric tests for the analyses. We compared continuous data between the two groups using the Mann-Whitney test and gender ratios using the  $\chi^2$  test. In PCA patients, we used Spearman rank correlations to detect associations between <sup>18</sup>F-AV45 uptake and cognitive and affective symptoms or with CSF biomarker concentrations. Finally, we used the Wilcoxon signed-rank test to determine the binding symmetry in abnormal versus intact sides of regional <sup>18</sup>F-AV45 uptake. All the tests were two-sided. The significance level was set at  $p < 0.005$  and the statistical analyses were performed using R version 2.12.2 [46].

## Results

### Characteristics of the Study Subjects

We enrolled 11 patients with PCA (5 females and 6 males; aged 64.5 ± 7.3 years) and 12 patients with typical AD (6 females and 6 males; aged 69.3 ± 4.9 years). The demographic characteristics of the study sample are reported in table 1. The two groups were similar with respect to age, gender distribution and disease duration. No significant differences were found between the two groups regarding levels of global cognitive efficiency (Mini-Mental State Examination), verbal and visual memory (Buschke Selective Reminding Test, 48-item Delayed Matching-to-Sample task) and naming (DO 80) (table 2).

All of the PCA patients presented focal atrophy or changes in perfusion (SPECT) in the posterior brain regions, which enhances the diagnostic probability. The clinical and biological

**Table 2.** Neuropsychological data of the PCA and AD groups

Test	PCA	AD	p value
MMSE score (range 0–30)	16.91 ± 6.66	20.64 ± 3.17 <sup>a</sup>	0.356
Buschke Selective Reminding Test			
Free recall (range 0–48)	5.67 ± 3.79 <sup>b</sup>	6.62 ± 5.68 <sup>c</sup>	1
Total recall (range 0–48)	25.33 ± 9.29 <sup>b</sup>	18.62 ± 13.18 <sup>c</sup>	0.3052
% sensitivity (range 0–100)	45.67 ± 23.86 <sup>b</sup>	31.88 ± 25.88 <sup>c</sup>	0.3063
48-Item Delayed Matching-to-Sample task			
Immediate recall, %	72.00 ± 10.35 <sup>c</sup>	71.43 ± 15.61 <sup>d</sup>	0.9069
Delayed recall, %	71.75 ± 16.26 <sup>c</sup>	65.29 ± 17.09 <sup>d</sup>	0.3833
Oral naming (DO 80)	68.56 ± 11.64 <sup>e</sup>	72.27 ± 4.36 <sup>a</sup>	0.8185

<sup>a</sup> n = 11; <sup>b</sup> n = 3; <sup>c</sup> n = 8; <sup>d</sup> n = 7; <sup>e</sup> n = 9.

findings of the 11 subjects with PCA are given in table 3. Six patients (patients 4, 5, 6, 7, 8 and 10) revealed associated neurological signs (myoclonus and/or extrapyramidal motor signs; Unified Parkinson's Disease Rating Scale score >5). Seven PCA patients (patients 2, 4, 5, 7, 8, 10 and 11) had typical AD CSF biomarker profiles, and all had a decreased Aβ<sub>42</sub>/Aβ<sub>40</sub> ratio.

#### *PET Imaging*

As reported in table 4, global and regional <sup>18</sup>F-AV45 uptake was similar in the PCA and AD groups. The global <sup>18</sup>F-AV45 uptake of each PCA and AD subject is presented in a boxplot (fig. 1). Examples of axial PET slices obtained for an AD and a PCA subject are shown in figure 2. Examples of axial SPECT and PET slices obtained for the same PCA subject are displayed in figure 3. Hypoperfusion was observed in the left parieto-occipital region, while no significant differences in <sup>18</sup>F-AV45 uptake were detected between the right and left cerebral posterior regions.

No correlation was observed between the global <sup>18</sup>F-AV45 uptake and the concentrations of CSF biomarkers (T-tau, p-tau, Aβ<sub>42</sub> levels and Aβ<sub>42</sub>/Aβ<sub>40</sub> ratio) and between the regional <sup>18</sup>F-AV45 uptake and cognitive and affective symptoms in the PCA subjects.

No significant differences in the global <sup>18</sup>F-AV45 uptake were found between PCA patients with or without associated neurological signs (1.51 ± 0.12 and 1.45 ± 0.15, respectively; p = 0.46) and between PCA patients with typical or atypical AD CSF biomarker profiles (1.49 ± 0.16 and 1.48 ± 0.09, respectively; p = 0.92).

In PCA subjects, no significant differences were observed between the corresponding right and left standardized uptake value ratios, in spite of the existence of an important lateralization of atrophy and/or hypoperfusion, in particular, in the occipital region.

## Discussion

In this prospective study, we investigated the deposition of amyloid with <sup>18</sup>F-AV45 in a cohort of 11 PCA patients who presented with either a typical or an atypical AD CSF profile. We then compared the density and topography of amyloid deposition between the PCA and AD patient groups.

In contrast to the neuropsychological signs, we found no specific regional pattern of cortical <sup>18</sup>F-AV45 binding in the PCA group. The observed pattern was indistinguishable from that shown in the AD group, especially in the posterior regions. These results are in agreement



**Table 3.** Clinical characteristics and CSF biomarker of PCA patients

Patient No.:	1	2	3	4	5	6	7	8	9	10	11
<i>Neurological examination</i>											
Myoclonus	-	-	-	+	+	+	+	+	-	+	-
Extrapyramidal motor signs with UPDRS score (/56)	0	1	5	10	3	8	12	20	1	1	1
<i>Behavioural and affective symptoms</i>											
Neuropsychiatric Inventory Scale (/144)	6	5	6	27	1	41	22	21	19	18	38
Hamilton Depression Rating Scale (/56)	5	10	3	7	8	27	10	11	4	32	6
<i>CSF concentrations of biomarkers and amyloid-β ratios</i>											
T-tau, pg/ml	224	392	259	723	661	951	457	474	439	573	538
p-tau, pg/ml	43	62	56	96	103	92	83	67	54	76	86
Aβ <sub>42</sub> , pg/ml	276	300	305	346	277	756	281	388	460	632	340
Aβ <sub>42</sub> /Aβ <sub>40</sub>	0.035	0.03	0.039	0.03	ND	0.058	0.02	0.03	0.042	0.04	0.03
CSF profile (typical AD/atypical AD)	AT	T	AT	T	T	AT	T	T	AT	T	T

UPDRS = Unified Parkinson's Disease Rating Scale; AT = atypical; T = typical.

**Table 4.** <sup>18</sup>F-AV45 uptake of PCA and AD groups

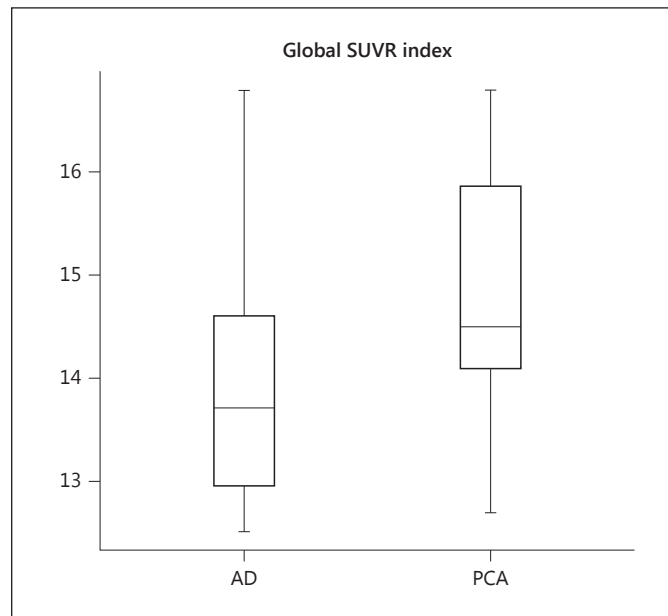
Neocortical <sup>18</sup> F-AV45 uptake value	PCA (n = 11)	AD (n = 12)	p value
Frontal	1.67±0.15	1.46±0.20	0.0097
Anterior cingulate	1.67±0.16	1.40±0.20	0.0051
Posterior cingulate	1.32±0.15	1.30±0.13	0.7580
Precuneus	1.43±0.14	1.35±0.15	0.2297
Temporal	1.43±0.14	1.35±0.12	0.1653
Parietal	1.44±0.16	1.43±0.11	0.7345
Occipital	1.44±0.12	1.41±0.12	0.5380
Global index	1.49±0.13	1.39±0.12	0.0789

The significance level was set at p < 0.005.

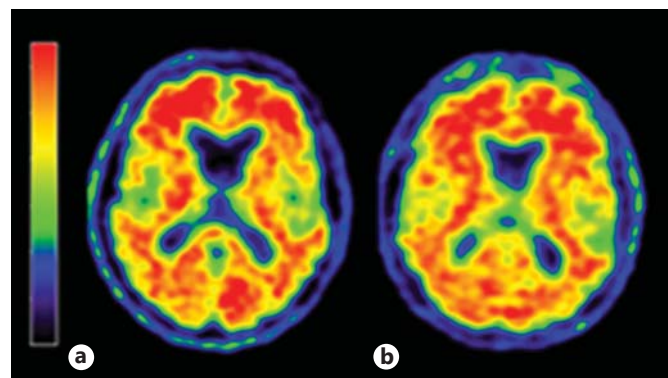
with previous <sup>11</sup>C-PIB studies using a similar sample size [11, 21, 23] and with neuropathological studies, which suggests that PCA is mostly associated with underlying AD [4, 5]. This result confirms the pertinence of the new diagnostic criteria for AD, which distinguish amnesic AD presentations from non-amnesic clinical AD forms, such as those seen in patients who present with only visuospatial anomalies [47].

Similar to neuropathological studies, our results also confirm that the distinct clinical phenotype encountered in amnesic AD and PCA is not related to the amyloid distribution [22]. While this syndrome is defined by signs and symptoms of cortical visual dysfunction frequently associated with atrophy or hypoperfusion in the posterior cortical regions, we found similar patterns of <sup>18</sup>F-AV45 binding between the PCA and AD groups. We also found no significant correlation between regional <sup>18</sup>F-AV45 uptake and cognitive and affective symptoms in PCA subjects. Moreover, <sup>18</sup>F-AV45 uptake was relatively symmetrical as opposed to the important lateralization of atrophy and/or hypoperfusion frequently observed in PCA patients, especially in the occipital region.

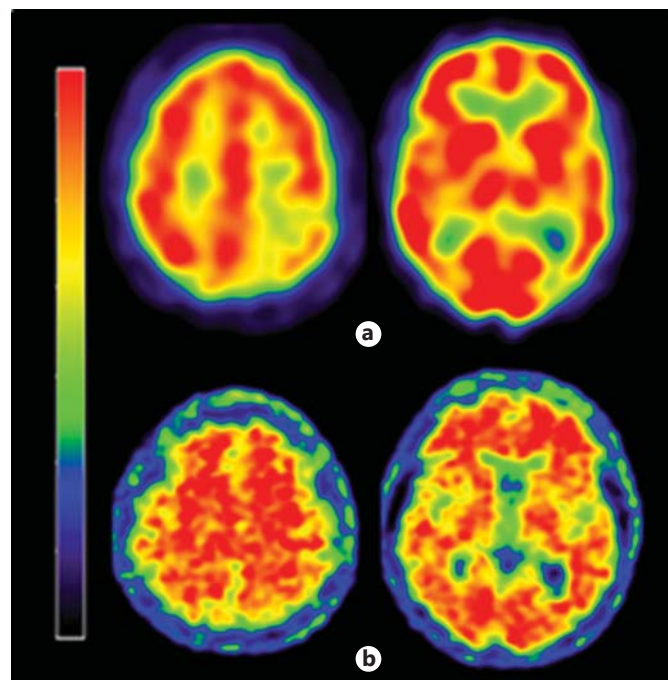
The distribution of the AD hallmarks seen in PCA varied in neuropathological studies, with some studies demonstrating a higher amyloid burden in the primary and associative visual cortex in PCA compared to typical amnesic AD [48, 49]. In contrast, previous studies



**Fig. 1.** Comparison of the global standardized uptake value ratio (SUVR) index distributions between AD and PCA subjects.



**Fig. 2.** Example of axial PET slices obtained for an AD (a) and a PCA subject (b). No significant differences on the  $^{18}\text{F}$ -AV45 uptake are observed between AD and PCA subjects.



**Fig. 3.** Example of axial SPECT (a) and PET (b) slices obtained for the same PCA subject. Hypoperfusion is observed in the left parieto-occipital region while no significant differences on the  $^{18}\text{F}$ -AV45 uptake are observed between the right and left cerebral posterior regions.

did not report any differences in the distribution of A $\beta$  pathologies [4, 5]. Amyloid imaging offers the opportunity of comparing in vivo neuropathological processes to the clinical symptoms. The results observed in neuropathological studies were confirmed by  $^{11}\text{C}$ -PIB PET studies [24]. Increased  $^{11}\text{C}$ -PIB uptake in the occipital cortex has been reported in single cases and studies [12, 17–19] containing small series, whereas larger-group studies have found no differences in  $^{11}\text{C}$ -PIB patterns between PCA and amnesic AD patients [11, 21, 23]. This study confirms that the amyloid burden cannot explain the differences in the clinical presentations of AD/PCA. Unlike amyloid deposition, a higher neurofibrillary tangle (NFT) burden is consistently seen in pathology studies [4, 5, 49] in PCA compared to AD, and in particular, a greater NFT density is observed in the primary visual and visual associative cortex. Clinicopathological studies have shown that NFT seems to be more closely related to clinical symptoms of AD than amyloid plaques [50, 51], but tracers with a specific affinity for NFT are still hard to find [52], and few have undergone any significant clinical development [53, 54].

We tried to determine whether the presence of neurological signs (extrapyramidal motor signs, myoclonus) was associated with differences in the density or topography of amyloid deposition in PCA patients. Indeed, some studies have suggested that the presence of an extrapyramidal syndrome or hallucinations at the onset of the disease may indicate that PCA is associated with Lewy body disease or corticobasal degenerative disease [5]. However, we failed to find any differences in  $^{18}\text{F}$ -AV45 binding when we compared PCA patients with or without associated neurological signs. This result suggests that the presence of associated neurological signs in PCA is not predictive of the underlying neuropathological process and indicates that biomarkers could be helpful to identify the underlying aetiology of PCA.

Few studies have investigated the combination of CSF biomarker analysis and amyloid imaging in PCA patients [11, 12]. None has analysed both the profile of CSF biomarkers (T-tau, p-tau and A $\beta_{42}$ ) and the A $\beta_{42}$ /A $\beta_{40}$  ratio [14], which is particularly interesting when an atypical CSF profile is present. In our study, a decreased A $\beta_{42}$ /A $\beta_{40}$  ratio [14] was seen in all PCA patients including the 4 with atypical CSF profiles, thus confirming the amyloidogenic process. We found no differences in  $^{18}\text{F}$ -AV45 binding between PCA patients with a typical or atypical AD CSF profile. These results suggest that PCA patients with an atypical CSF profile do in fact have AD hallmarks just like patients with a typical AD CSF profile and no other neuropathological process like Lewy body disease or corticobasal degeneration disease. Moreover, we observed no correlation between global  $^{18}\text{F}$ -AV45 uptake and the concentrations of CSF biomarkers (T-tau, p-tau and A $\beta_{42}$  levels, A $\beta_{42}$ /A $\beta_{40}$  ratio). These results are not in accordance with previous studies conducted in typical AD patients [55] and warrant the standardization of CSF biomarkers in atypical AD presentations (PCA, primary progressive aphasia).

Our study has several limitations. First of all, the size of the study groups is small, but nonetheless comparable to the size of the study groups in other published series. Another limitation is the fact that we did not segment white and grey matter. Indeed, in these disease processes, we saw an increase in the amyloid burden in addition to its localization in the grey matter, which is considered specific. Since we did not apply a partial volume correction to the PET images, we chose to use the region of interest defined in the MNI-AAL atlas and incorporate both types of cerebral tissues. Another limitation is the fact that CSF biomarkers and brain perfusion with SPECT were not used in all AD subjects for their diagnosis. Finally, post-mortem verification would be helpful in order to confirm our findings, but this verification is obviously not possible.

The clinical criteria of PCA will thus continue to be the keystone for the diagnosis in clinical practice; however, in the future, confirmation of an AD pathology by  $^{18}\text{F}$ -AV45 PET imaging may provide an earlier diagnosis for PCA patients and consequently permit them to be included in therapeutic trials evaluating disease-modifying drugs and specific rehabili-



tation. Hypotheses other than amyloid deposition should be explored to try and explain the symptoms seen in the different clinical forms of AD. In light of the results of neuropathological studies, the implication of the tau pathology seems to be the most promising. Imaging studies using tracers with a specific affinity for NFT are needed in the future to help us gain a better understanding of atypical forms of AD.

### Acknowledgments

This work was conducted with the support of the ‘Fondation Thérèse et René Planiol pour l’étude du cerveau’, Cyclopharma laboratories and the ‘Centre pour l’Etude et la Recherche sur les Radiopharmaceutiques’. The authors are also grateful to C. Roussel, PhD, S. Dupont (CIC-IT INSERM 0806), A. Matysiak, M. Brachet and F. Brault for their contributions to the clinical investigation.

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