

Assessment of β -Amyloid in a Frontal Cortical Brain Biopsy Specimen and by Positron Emission Tomography With Carbon 11–Labeled Pittsburgh Compound B

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Objective: To compare carbon 11–labeled Pittsburgh Compound B (^{11}C PiB) positron emission tomography (PET) findings in patients with and without Alzheimer disease lesions in frontal cortical biopsy specimens.

Design: Cross-sectional study of ^{11}C PiB PET findings in patients with or without β -amyloid (A β) aggregates in frontal cortical biopsy specimens.

Setting: Two university hospitals in Finland.

Patients: Ten patients who had undergone intraventricular pressure monitoring with a frontal cortical biopsy (evaluated for A β aggregates and hyperphosphorylated tau) for suspected normal-pressure hydrocephalus.

Interventions: ^{11}C PiB PET and evaluation for cognitive impairment using a battery of neuropsychological tests.

Main Outcome Measures: Immunohistochemical evaluation for A β aggregates and hyperphosphorylated tau in the frontal cortical biopsy specimen and ^{11}C PiB PET.

Results: In patients with A β aggregates in the frontal cortical biopsy specimen, PET imaging revealed higher ^{11}C PiB uptake ($P < .05$) in the frontal, parietal, and lateral temporal cortices and in the striatum as compared with the patients without frontal A β deposits.

Conclusions: Our study supports the use of noninvasive ^{11}C PiB PET in the assessment of A β deposition in the brain. Large prospective studies are required to verify whether ^{11}C PiB PET will be a diagnostic aid, particularly in early Alzheimer disease.

Arch Neurol. 2008;65(10):1304-1309

AGGREGATES OF β -AMYLOID (A β) in the neuropil together with hyperphosphorylated tau (HP τ) seen in neurons and neuronal processes are considered diagnostic hallmark lesions of Alzheimer disease (AD).¹ Based on current knowledge, at the first phase presumably A β deposits in neocortical regions; at the second phase, in the allocortex; at the third phase, addition-

ally in the diencephalic nuclei and striatum; at the fourth phase, additionally in distinct brainstem nuclei; and, finally, at the fifth phase, also in the cerebellum and additional brainstem nuclei.² Variation in this pattern of deposition has been reported in subjects carrying the presenilin 1 mutation.³ So far, the only confident method to assess A β aggregates and HP τ

in the brain is the histological analysis of tissue samples obtained either during life or at autopsy,^{1,2} a major methodological obstacle considering clinical drug trials of early AD.

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Imaging of A β aggregates by Pittsburgh Compound B (PiB) positron emission tomography (PET) seems a promising method for noninvasive evaluation of patients with suspected AD.³⁻⁸ A case report described that a patient with dementia with Lewy bodies showed a positive correlation between carbon 11–labeled (^{11}C) PiB PET findings during life and postmortem assessment of A β aggregates 3 months later.⁹

Cognitive impairment, the leading symptom of AD, is also included in the clinical triad of normal-pressure hydrocephalus (NPH).¹⁰ In NPH, the diagnostic accuracy is increased by intracranial pressure (ICP) monitoring,¹¹ and a tiny cortical biopsy

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Table 1. Case Characteristics and IHC Findings of Frontal Cortical Biopsy Specimens

Case/Sex/ Age at Biopsy, y	Score				NPH ^b	Time From Biopsy to PET, mo	HP τ	No. of Amyloid β Aggregates ^c (4G8)	No. of Diffuse/Neuritic Plaques ^d (Bielschowsky Silver Stain)
	CDR	CDR SOB	CERAD Total ^a	MMSE					
1/F/68	0.5	0.5	78	30	+	36	-	0	0/0
2/F/75	0	1	73	26	+	23	-	0	0/0
3/M/70	0	0.5	82	29	+	15	-	0	0/0
4/F/72	1	6	53	22	-	2	-	0	0/0
5/F/72	1	2.5	67	24	+	5	-	1 (only fleecy)	0/0
6/F/72	1	5.5	62	19	+	20	-	39	0/1
7/F/71	1	3.5	57	28	+	12	-	42	2/0
8/F/75	0.5	1	60	27	+	26	+	45	11/2
9/F/66	2	9.0	49	22	-	27	+	66	20/3
10/M/70	1	5	74	23	-	28	+	80	20/0

Abbreviations: CDR, Clinical Dementia Rating Scale; CDR SOB, CDR sum of boxes; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; HP τ , hyperphosphorylated tau; ICP, intracranial pressure; IHC, immunohistochemical; MMSE, Mini-Mental State Examination; NPH, normal-pressure hydrocephalus; PET, positron emission tomography; +, present; -, absent.

^aCERAD total score was constructed as suggested by Chandler and colleagues.¹⁵

^b+ Indicates NPH according to clinical symptoms and ICP monitoring and the patient has a shunt.

^cCount of diffuse and dense aggregates independent of size in a visual field (3.14 mm²) in magnification \times 100.

^dCount of diffuse and neuritic plaques in a visual field (3.14 mm²) in magnification \times 100. None of the neuritic plaques were labeled with HP τ .

Table 2. Antibodies Used in IHC Evaluation of Frontal Cortical Samples

Antigen	Pretreatment	Type	Clone	Code	Company	Dilution
β -Amyloid	80% formic acid 1 h	Monoclonal	6F/3D	M0872	Dako (Glostrup, Denmark)	1:100
HP τ	None	Monoclonal	4G8	9220	Signet Laboratories (Dedham, Massachusetts)	1:2000
		Monoclonal	AT8	³ Br-3	Innogenetics (Gent, Belgium)	1:30

Abbreviations: HP τ , hyperphosphorylated tau; IHC, immunohistochemical.

specimen can be obtained through the bur hole for differential diagnosis. The risk of complications associated with this invasive procedure has been low. In fact, 22% to 42% of the patients with symptoms suggestive of NPH showed AD pathological lesions in frontal cortical samples.¹²⁻¹⁴

In this study, our objectives were to assess A β aggregates both applying noninvasive [¹¹C]PiB PET and invasive surgery. We compared [¹¹C]PiB PET results in 10 patients with known histopathological features (ie, the presence or absence of A β aggregates and HP τ in frontal cortical samples obtained during ICP monitoring).

participate in the [¹¹C]PiB PET study (**Table 1**). Based on the neuropathological findings in the frontal cortical biopsy specimen, patients were divided into 2 groups. Six patients had A β (3 of them had also HP τ) pathological lesions in the biopsy specimen, whereas 4 patients had no AD-related pathological lesions in the biopsy specimen (Table 1). Close to the PET investigation, the patients were evaluated for cognitive impairment using the Clinical Dementia Rating Scale (CDR),¹⁶ CDR sum of boxes, Mini-Mental State Examination,¹⁷ Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological test battery,¹⁸ and total score of CERAD constructed as suggested by Chandler and colleagues.¹⁵

METHODS

BASIC SERIES

Altogether, 125 patients underwent ICP monitoring with frontal cortical biopsy for suspected NPH at the Department of Neurosurgery, Kuopio University Hospital, between January 2004 and February 2007.

PRESENT SERIES

Medical records of the patients, who were 75 years or younger, were first screened according to the medical history by an independent neurologist. Exclusion criteria included poor general health, severe dementia, or severe concomitant diseases affecting the ability to cooperate in the PET examination or contraindication for magnetic resonance imaging. Approximately 50 patients fulfilled the study criteria. These patients were contacted by telephone and only 10 patients agreed to par-

ICP MONITORING AND FRONTAL CORTICAL BIOPSY

A right frontal 12-mm bur hole was made under local anesthesia. The standard site was 2 cm right from the midline ahead of the coronary suture. Prior to insertion of the intraventricular monitoring catheter, cylindrical cortical brain biopsy specimens of 2 to 5 mm in diameter and 3 to 7 mm in length were obtained through the bur hole. The samples were placed in buffered formalin and, after overnight fixation, were embedded in paraffin.

HISTOCHEMICAL AND IMMUNOHISTOCHEMICAL STAINING

Consecutive 7- μ m-thick sections were stained with hematoxylin-eosin, Bielschowsky silver impregnation technique, and immunohistochemical (IHC) methods. Briefly, deparaffinized sections were manually immunostained with antibodies directed

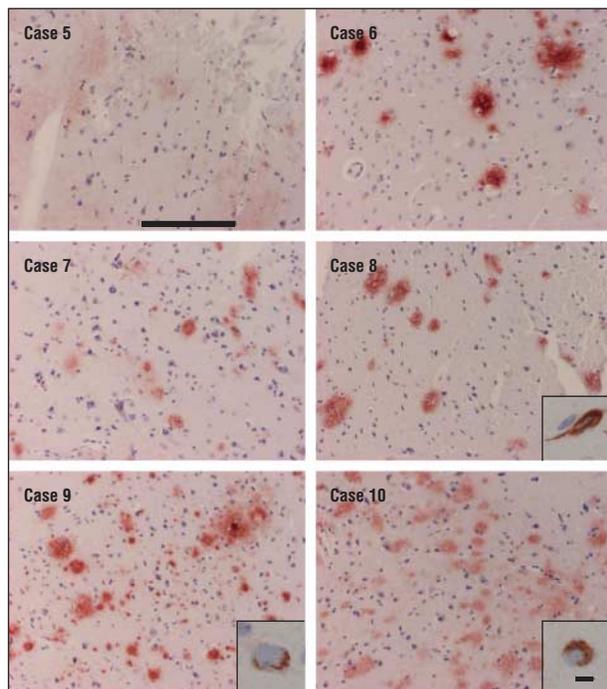


Figure 1. Immunohistochemical examination of protein aggregates in the frontal cortex biopsy specimens using β -amyloid antibody (clone 4G8). Insets show cytoplasmic labeling with hyperphosphorylated tau antibody (clone AT8). Large panels, original magnification $\times 100$, scale bar, 200 μm ; insets, original magnification $\times 400$, scale bar, 10 μm . In case 5, there is pale staining of fleecy aggregates, and in cases 6 and 8, predominantly dense plaques are seen. In the remaining cases, all types (ie, fleecy, diffuse, and dense plaques) were noted. Cytoplasmic hyperphosphorylated tau labeling was seen in 3 cases (8, 9, and 10) and even then only in occasional neurons.

to HPr and A β (**Table 2**). β -amyloid antibodies included both 6F/3D (reactive to amino acid residue 10-15), labeling both parenchymal aggregates (ie, plaques) as well as cerebral amyloid angiopathy, and 4G8 (residue 18-22), labeling primarily parenchymal A β aggregates and especially fleecy and diffuse aggregates seen at early stages. The labeled streptavidin-biotin method (Histostain-Plus Kit; Zymed, San Francisco, California) was used with romulin 3-amino-9-ethylcarbazole chromogen (Biocare Medical, Walnut Creek, California). The sections were counterstained with Harris hematoxylin (Merck, Darmstadt, Germany), dehydrated, and mounted in DePex (BDH Laboratory Supplies, Poole, England). Omission of primary antibodies revealed no detectable staining.

HISTOLOGICAL EXAMINATION

The assessment of stained sections was carried out under light microscopy at magnifications $\times 100$ to $\times 200$. Cellular or neuritic HPr structures were sought and rated as negative or positive. In Bielschowsky silver-stained and in A β -IHC-stained sections, fleecy, diffuse, and dense plaques were counted in magnification $\times 100$ within the whole visual field (3.14 mm^2) composed of gray matter.

[¹¹C]PiB PET IMAGING

PET Imaging

[¹¹C]PiB was produced by the reaction of 6-OH-BTA-0 and [¹¹C]methyl triflate, as reported earlier.⁷ The radiochemical purity of the tracer was more than 98% in all [¹¹C]PiB studies. A mean (SD) 442.8 million (90.1 million) Bq (range, 255-530 mil-

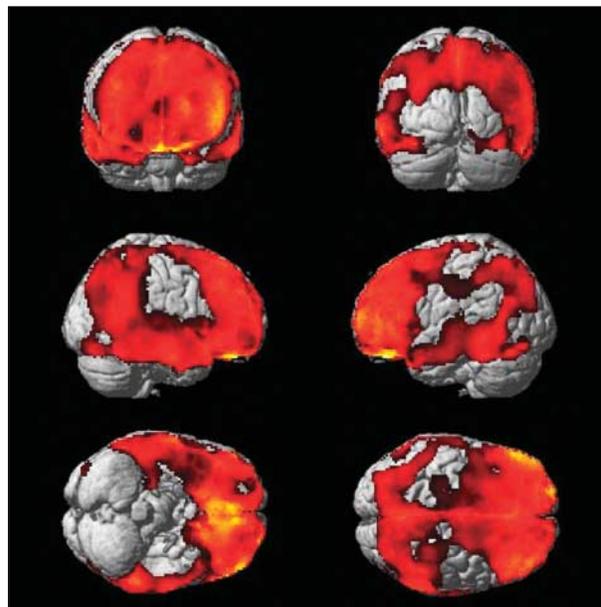


Figure 2. Visualization of the results of Statistical Parametric Mapping analysis. The regions with statistically significant increases (corrected *P* value at cluster level $< .01$) in carbon 11-labeled Pittsburgh Compound B uptake in patients with β -amyloid aggregates ($n=5$, cases 6-10) compared with patients without any β -amyloid aggregates ($n=4$, cases 1-4) in the cortical biopsy specimen are indicated with colors.

Table 3. Automated ROI Analysis of [¹¹C]PiB Uptake: Mean (SD) Region to Cerebellum Ratio in Patients With or Without A β Aggregates in the Frontal Cortical Biopsy Specimen

Brain Area	A β Aggregates (n=6)	No A β Aggregates (n=4)	<i>P</i> Value
Lateral frontal cortex	1.75 (0.59)	1.01 (0.11)	.03
Lateral temporal cortex	1.54 (0.45)	1.04 (0.07)	.04
Medial temporal lobe	1.36 (0.22)	1.15 (0.09)	.07
Inferior parietal cortex	1.57 (0.63)	1.10 (0.15)	.13
Anterior cingulate	1.95 (0.69)	1.15 (0.13)	.04
Posterior cingulate	2.08 (0.77)	1.19 (0.12)	.04
Caudate nucleus	1.71 (0.50)	1.18 (0.10)	.05
Putamen	1.78 (0.41)	1.54 (0.18)	.23
Occipital cortex	1.49 (0.28)	1.35 (0.08)	.29
White matter	1.93 (0.32)	1.75 (0.21)	.35
Thalamus	1.45 (0.18)	1.20 (0.31)	.15

Abbreviations: A β , β -amyloid; [¹¹C]PiB, carbon 11-labeled Pittsburgh Compound B; ROI, region of interest.

lion Bq) (to convert to curies, multiply by 2.7×10^{-11}) of [¹¹C]PiB was injected intravenously as a bolus and all patients underwent a 90-minute dynamic PET scan with a GE Advance PET scanner (General Electric Medical Systems, Milwaukee, Wisconsin) in the 3-dimensional scanning mode, as described earlier.⁷ Positron emission tomography imaging was performed without the knowledge of the neuropathological data of the patient.

Data Analysis

Before the voxel-based statistical analysis and automated region-of-interest (ROI) analysis, dynamic images were first computed into quantitative parametric images. Parametric images

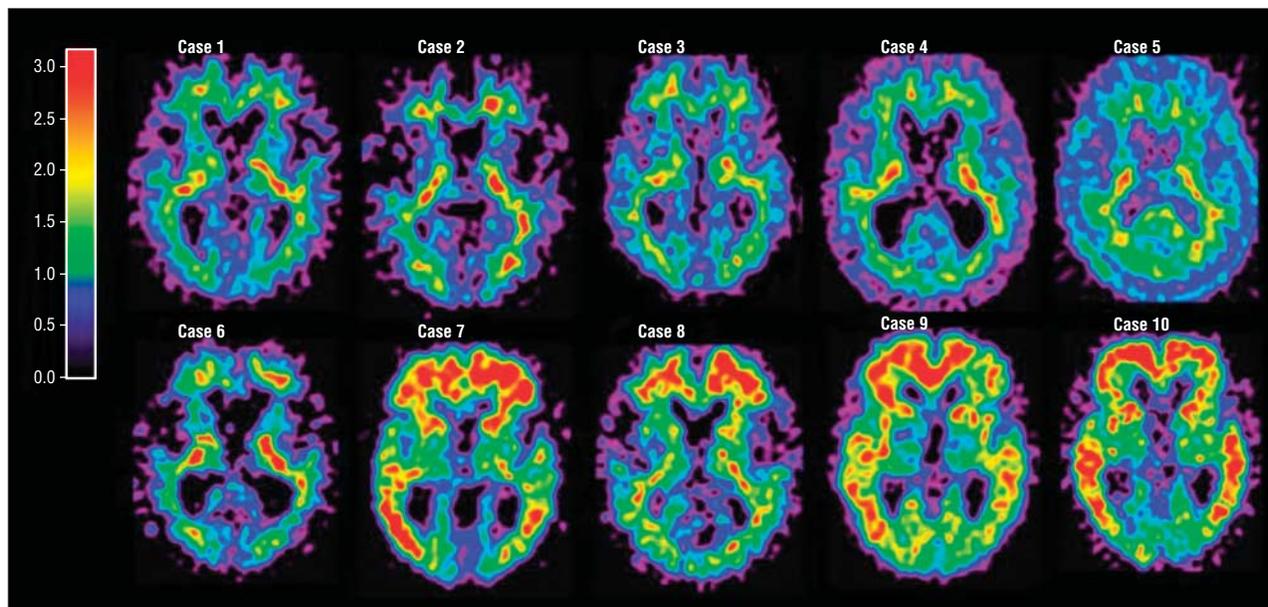


Figure 3. Transaxial slices of parametric carbon 11–labeled Pittsburgh Compound B images. The values represent ratios to cerebellar value. The case numbers refer to Figure 1 and Table 1.

representing [¹¹C]PiB uptake in each pixel were calculated as a region-to-cerebellum ratio of the radioactivity concentration over 60 to 90 minutes, as described earlier.⁷

Statistical Parametric Mapping Analysis

Voxel-based statistical analyses of [¹¹C]PiB data were performed using Statistical Parametric Mapping version 99 (SPM99) and MATLAB 6.5 for Windows (MathWorks, Natick, Massachusetts), using procedures described in detail earlier.⁷ Briefly, spatial normalization of parametric images was performed using a ligand-specific [¹¹C]PiB template.⁷ The between-group comparison equaling 2-sample *t* tests and testing the difference in ratio values was performed as an explorative analysis covering the whole brain. Multiple comparison–corrected *P* values <.01 were considered significant.

Automated ROI Analysis

To obtain quantitative regional values of [¹¹C]PiB uptake, automated ROI analysis was performed, as described earlier.⁷ Briefly, the standardized ROIs were defined using Imadeus software (version 1.50; Forima Inc, Turku, Finland) on the magnetic resonance imaging template image representing brain anatomy in accordance with MNI space (Montreal Neurological Institute database). Because this method is based on a common stereotactic space (ie, spatial normalization of the images), the operator-induced error in defining ROIs individually for each subject can be avoided. The ROIs were positioned bilaterally on the frontal cortex, lateral temporal cortex, medial temporal lobe, inferior parietal lobe, occipital cortex, cerebellar cortex, and subcortical white matter.⁸ The average regional ratio values of [¹¹C]PiB uptake were calculated using these ROIs from spatially normalized parametric ratio images (see “Statistical Parametric Mapping Analysis” subsection) and subjected to statistical analysis conducted using SPSS for Windows (release 12.0.1; SPSS Inc, Chicago, Illinois).

The study was approved by the Kuopio University Hospital Research Ethics Board. All patients provided a written informed consent prior to their participation.

RESULTS

The cognitive status of the 10 patients (Mini-Mental State Examination score, CDR score, CDR sum of boxes, and CERAD total score) at the time of the [¹¹C]PiB PET scan and the histological and IHC findings in the frontal cortical biopsy specimens are presented in Table 1 and **Figure 1**. Occasional cytoplasmic HP τ was seen in only 3 of the 10 patients. No neuropil or plaque-associated neurites (ie, no HP τ -labeled neuritic plaques) were seen. No cerebral amyloid angiopathy was seen in any of our subjects either.

The between-group SPM analysis (**Figure 2**) showed significantly higher [¹¹C]PiB uptake in the frontal, parietal, and lateral temporal cortices (phase 1 of regional A β deposition) and striatum (phase 3) in patients with A β aggregates in the frontal cortex compared with those without notable A β aggregates in the brain biopsy specimen.

The automated ROI analysis showed that the patients with A β aggregates had higher [¹¹C]PiB uptake in the lateral frontal and lateral temporal cortices (phase 1), anterior and posterior cingulate gyri (phases 2-3), and caudate nucleus (phase 3) than the patients without A β aggregates (**Table 3**). The difference did not reach significance in the medial temporal lobe, inferior parietal and occipital cortices (phases 1-2), or putamen and thalamus (phase 3). **Figure 3** indicates representative transaxial slices of parametric [¹¹C]PiB images.

[¹¹C]PiB uptake in the right frontal cortex (ROI) correlated (Pearson $r=0.85$; $P=.002$) with the amount of A β aggregates in the right frontal cortical biopsy specimen (**Figure 4**).

COMMENT

This is, to our knowledge, the first study where living patients were assessed regarding their A β deposition in

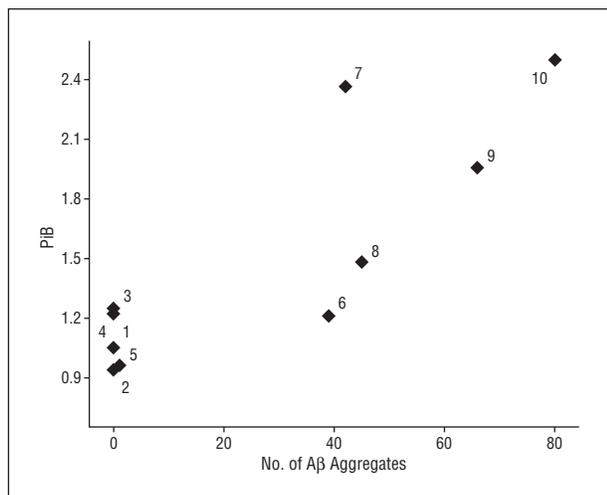


Figure 4. Scatterplot of carbon 11–labeled Pittsburgh Compound B (¹¹C)PiB uptake (region of interest) in the right frontal cortex. Aβ indicates the number of β-amyloid (clone 4G8) aggregates in the right frontal cortical biopsy specimen (count of diffuse and dense aggregates independent of size in a visual field). The diamonds are labeled by case numbers indicated in Figure 1 and Figure 3 and Table 1.

the brain both by means of surgery and imaging. Our results indicate that Aβ deposition in a frontal cortical biopsy specimen obtained during life is in line with the [¹¹C]PiB uptake found in PET imaging, suggesting that [¹¹C]PiB PET reflects brain Aβ deposition.

In suspected NPH, we routinely monitor intraventricular ICP and obtain a small right frontal cortical biopsy specimen to exclude or verify a specific neurodegenerative process.^{11,12,14} Alzheimer disease–related lesions (ie, HPT) are primarily seen in the temporoparietal regions,¹ whereas the deposition of Aβ starts from the neocortex, proceeding via central structures to the subcortical structures.² Thus, a frontal cortical biopsy specimen with Aβ aggregates without HPT would suggest early AD.² Six of our patients displayed AD-related pathological lesions in the cortical biopsy specimen, but none of them had severe dementia.

In our study, the most significant differences in [¹¹C]PiB uptake between patients with Aβ immunoreactivity in the frontal cortical biopsy specimen and those without were seen in the frontal cortex (phase 1), the lateral temporal cortex (phase 1), the anterior and posterior cingulate gyri (phases 2-3), and the caudate nucleus (phase 3). The patients with the highest Aβ load in the biopsy specimen had also the highest [¹¹C]PiB uptake in PET imaging. The correlation and SPM analysis showed that the [¹¹C]PiB uptake increased with increasing Aβ load in the biopsy specimen. Our findings are congruent with the previous PET data from patients with AD^{4,7} or mild cognitive impairment^{8,19} and from healthy controls.

The study groups with or without frontal cortical Aβ aggregates were similar in age, sex, and time from the cortical biopsy to PET imaging. Thus, the patients were suitable for the main objective of the study: methodological comparison of the [¹¹C]PiB PET imaging findings and cortical biopsy specimen to indicate Aβ deposition in the brain independently from the cognitive status of the patients. Case 5 was excluded from the SPM analysis because there was

only 1 fleecy plaque in the biopsy specimen, and the presence or absence of that case did not change the result. The interval between the surgery and imaging (Table 1) might to some extent skew the interpretation of our results. In parallel with the increase of IHC/Aβ labeling, an increase in the plaque count was noted while using silver stain. The surgically obtained cortical biopsy sample was small and thus false-negative results are possible, and the absence of Aβ aggregates in the frontal cortex does not securely reflect the Aβ deposition in other isocortical brain regions. Also, the false-positive result of sampling of a very small area of high plaque load is possible. To validate the clinical significance of the surgically obtained frontal cortical biopsy specimen in diagnosing brain amyloidosis, further systematic assessment, preferably by post-mortem verification of brain pathological lesions in subjects in whom a biopsy specimen has been taken during life, needs to be carried out. However, all the patients with normal biopsy results also had negative PiB results despite the interval between biopsy and PET imaging. On the other hand, along with the potential technical errors of PET imaging and labeling of the histological samples, case 6 (IHC positive but PiB negative) emphasizes the potential that there might be types of Aβ deposits that PiB does not detect. Diagnosis of NPH was based on clinical symptoms and intraventricular ICP monitoring. Four of the 7 patients with NPH also had concomitant AD-related lesions (Aβ) in the cortical biopsy specimen. This is in line with the previous findings of notable comorbidity of NPH and AD-related pathological lesions.¹²⁻¹⁴

This study supports the use of [¹¹C]PiB PET in the evaluation of Aβ deposition in, for example, mild cognitive impairment, AD, or NPH. Large and prospective studies are required to verify whether [¹¹C]PiB PET will become a tool in diagnosing AD. Another potential use of [¹¹C]PiB would be the quantitative monitoring of Aβ deposits in the brain in subjects under treatment in pharmaceutical trials of early AD targeting amyloid accumulation.

Accepted for Publication: February 5, 2008.

Published Online: August 11, 2008 (doi:10.1001/archneur.65.10.noc80013).

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Financial Disclosure: None reported.

Funding/Support: The study was supported by grant 5772720 from the Kuopio University Hospital, the Academy of Finland (project 205954), and the Sigrid Juselius Foundation.

REFERENCES

1. Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol.* 1991;82(4):239-259.
2. Thal DR, Rum U, Orantes M, Braak H. Phases of A β -deposition in the human brain and its relevance for the development of AD. *Neurology.* 2002;58(12):1791-1800.
3. Klunk WE, Price JC, Mathis CA, et al. Amyloid deposition begins in the striatum of presenilin-1 mutation carriers from two unrelated pedigrees. *J Neurosci.* 2007;27(23):6174-6184.
4. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol.* 2004;55(3):306-319.
5. Nordberg A. PET imaging of amyloid in Alzheimer's disease. *Lancet Neurol.* 2004;3(9):519-527.
6. Archer HA, Edison P, Brooks DJ, et al. Amyloid load and cerebral atrophy in Alzheimer's disease: an 11C-PIB positron emission tomography study. *Ann Neurol.* 2006;60(1):145-147.
7. Kemppainen NM, Aalto S, Wilson IA, et al. Voxel-based analysis of PET amyloid ligand [11C]PIB uptake in Alzheimer disease. *Neurology.* 2006;67(9):1575-1580.
8. Kemppainen NM, Aalto S, Wilson IA, et al. PET amyloid ligand [11C]PIB uptake is increased in mild cognitive impairment. *Neurology.* 2007;68(19):1603-1606.
9. Bacskai BJ, Frosch MP, Freeman SH, et al. Molecular imaging with Pittsburgh Compound B confirmed at autopsy: a case report. *Arch Neurol.* 2007;64(3):431-434.
10. Devito EE, Pickard JD, Salmond CH, Iddon JL, Loveday C, Sahakian BJ. The neuropsychology of normal pressure hydrocephalus (NPH). *Br J Neurosurg.* 2005;19(3):217-224.
11. Savolainen S, Hurskainen H, Paljarvi L, Alafuzoff I, Vapalahti M. Five-year outcome of normal pressure hydrocephalus with or without a shunt: predictive value of the clinical signs, neuropsychological evaluation and infusion test. *Acta Neurochir (Wien).* 2002;144(6):515-523.
12. Savolainen S, Paljarvi L, Vapalahti M. Prevalence of Alzheimer's disease in patients investigated for presumed normal pressure hydrocephalus: a clinical and neuropathological study. *Acta Neurochir (Wien).* 1999;141(8):849-853.
13. Golomb J, Wisoff J, Miller DC, et al. Alzheimer's disease comorbidity in normal pressure hydrocephalus: prevalence and shunt response. *J Neurol Neurosurg Psychiatry.* 2000;68(6):778-781.
14. Holm A, Savolainen S, Alafuzoff I. Brain biopsy prior to treatment of Alzheimer's disease. *Minim Invasive Neurosurg.* 2003;46(3):161-164.
15. Chandler MJ, Lacritz LH, Hynan LS, et al. A total score for the CERAD neuropsychological battery. *Neurology.* 2005;65(1):102-106.
16. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *Br J Psychiatry.* 1982;140:566-572.
17. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12(3):189-198.
18. Morris JC, Heyman A, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD), part I: clinical and neuropsychological assessment of Alzheimer's disease. *Neurology.* 1989;39(9):1159-1165.
19. Forsberg A, Engler H, Almkvist O, et al. PET imaging of amyloid deposition in patients with mild cognitive impairment [published online May 10, 2007]. *Neurobiol Aging.* doi:10.1016/j.neurobiolaging.2007.03.029.

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