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Original Article

Reduction in amyloid β deposition on ^{18}F-florbetapir positron emission tomography with correction of cerebral hypoperfusion after endarterectomy for carotid stenosis

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Abstract: The process of amyloid β (Aβ) deposition in sporadic Alzheimer's disease remains unclear. However, hypoperfusion due to vascular pathology may precede Aβ deposition, as suggested by data from animal models and autopsy tissue from Alzheimer's disease patients. In this exploratory study, we examined the hypotheses that chronic cerebral hypoperfusion due to severe atherosclerotic stenosis of the internal carotid artery (ICA) increases Aβ deposition in the affected cerebral hemisphere and that correction of cerebral hypoperfusion after carotid endarterectomy (CEA) in such patients reduces Aβ deposition. Four patients with cerebral hemispheric hypoperfusion due to unilateral ICA stenosis (≥80%) and without episodes of carotid territory ischemic symptoms or infarcts in the bilateral cerebral hemispheres underwent brain perfusion single-photon emission computed tomography (SPECT) and Aβ deposition positron emission tomography (PET) with ^{18}F-florbetapir before and after CEA. The asymmetry ratio of the radioactive counts in the affected cerebral hemisphere relative to that in the contralateral cerebral hemisphere was calculated on SPECT and PET images. In all four patients, the SPECT-perfusion asymmetry ratio was ≤0.81 before surgery and ≥0.90 after surgery. The PET-Aβ deposition asymmetry ratio ranged from 0.98 to 1.01 before surgery. The value in two patients remained at ≥0.97 after surgery, and in the other two patients, the value decreased to ≤0.91 after surgery. These findings suggested that chronic cerebral hypoperfusion due to severe atherosclerotic stenosis of the ICA does not increase Aβ deposition in the affected cerebral hemisphere, but correction of cerebral hypoperfusion after CEA often reduces Aβ deposition.

Keywords: Carotid artery stenosis, amyloid-beta, ^{18}F-florbetapir, hypoperfusion, carotid endarterectomy

Introduction

Plaques containing amyloid β (Aβ) are one of the main pathological characteristics of Alzheimer's disease, which is the main cause of dementia [1-4]. Accumulation of Aβ in the cerebral cortex, a primary mechanism of Alzheimer's disease pathology, likely begins many years before the onset of clinical symptoms [1-4]. However, the mechanisms triggering Aβ accumulation in sporadic Alzheimer's disease remain unsolved. Observations of animal models and autopsy tissue from Alzheimer's disease patients suggest that hypoperfusion due to vascular pathology may precede Aβ accumulation [1-4]. If this hypothesis is correct, chronic cerebral hypoperfusion due to severe atherosclerotic stenosis of the internal carotid artery (ICA) likely increases Aβ deposition in the affected cerebral hemisphere. Furthermore, correction of cerebral hypoperfusion after revascularization surgery may reduce Aβ deposition if this deposition is reversible.

To examine these hypotheses, we performed an exploratory study in which we assessed brain perfusion and Aβ deposition using single-photon emission computed tomography (SPECT) and positron emission tomography (PET), respectively, before and after carotid endarterectomy (CEA) in a small patient population with cerebral hypoperfusion due to severe stenosis of the unilateral cervical ICA.

Material and methods

Inclusion criteria

Inclusion criteria for this prospective exploratory study were: 1) unilateral cervical ICA stenosis ≥80% on angiography with magnetic resonance, computed tomography, or arterial catheterization; 2) age ≥65 years but <75 years; 3) modified Rankin disability scale score 0; 4) absence of episodes of carotid territory ischemic symptoms; and 5) absence of cortical infarcts in the bilateral cerebral hemispheres on magnetic resonance imaging. After obtaining written informed consent, each patient who satisfied the above inclusion criteria underwent brain perfusion SPECT. Only patients who were determined to have hypoperfusion in the cerebral hemisphere ipsilateral to the ICA stenosis on brain perfusion SPECT then underwent Aβ PET. Each patient who underwent CEA was finally included in the present study. Due to the exploratory nature of the study, we planned to enroll five patients in the present study.

Brain perfusion SPECT and Aβ deposition PET

Brain perfusion and Aβ deposition were assessed using SPECT (GCA-9300R; Toshiba Medical Systems, Tochigi, Japan) with *N*-isopropyl-*p*-[^{123}I]-iodoamphetamine [5] and PET (SET-3000GCT/M scanner; Shimadzu, Kyoto, Japan) with ^{18}F-florbetapir [6], respectively, as reported previously. *N*-isopropyl-*p*-[^{123}I]-iodoamphetamine nonspecifically binds sites for amines according to the distribution of brain perfusion [5]. ^{18}F-florbetapir, like Pittsburgh compound B, binds to Aβ and has a half-life of 109.75 min, in contrast to Pittsburgh compound B's radioactive half-life of 20 min [6]. The longer life reportedly allows significantly more tracer accumulation in human brains, particularly in the regions with beta-amyloid deposits [6]. Brain perfusion SPECT was performed within 14 days before surgery, and Aβ deposition PET was performed between 3 and 7 days after brain perfusion SPECT. These SPECT and PET studies were also performed 6 months after surgery.

Imaging analysis

For anatomic standardization, SPECT and PET images were transformed into the standard brain template with linear and nonlinear transformation using SPM2 software (Wellcome Trust Center for Neuroimaging, London). Also using SPM2, 318 constant regions of interest (ROIs) were automatically set in the cerebral and cerebellar hemispheres using a three-dimensional stereotaxic ROI template (FUJIFILM RI Pharma, Tokyo) [7]. Eight regions (callosomarginal, pericallosal, posterior, precentral, central, parietal, angular, and temporal) in each hemisphere were combined and defined as a hemispheric ROI. The mean radioactive counts on SPECT and PET images were measured in the hemispheric ROIs in each cerebral hemisphere. An asymmetry ratio was then calculated for the hemispheric ROI as follows: value of the affected cerebral hemisphere/value of the other hemisphere. Patients with hypoperfusion in the affected cerebral hemisphere, which was defined as a preoperative SPECT-perfusion asymmetry ratio <0.93 [8], were enrolled in this study.

Pre- and intraoperative management

Clopidogrel was administered to all patients until the morning of the CEA procedure. CEA was performed while the patient was under general anesthesia. The systolic blood pressure before surgery was maintained throughout the operation. No intraluminal shunts or patch grafts were used in any patients. Prior to clamping of the ICA, a 5000-IU bolus of heparin was administered.

Results

Patient inclusion

Over the course of 36 months, five patients satisfied the inclusion criteria including hypoperfusion in the affected cerebral hemisphere. Of these five patients, four underwent CEA and postoperative SPECT and PET studies. The remaining patient who underwent CEA but did not undergo the postoperative PET study was excluded from the present study.

Clinical characteristics

The clinical characteristics of the four patients studied are described in **Table 1**. All four patients underwent successful CEA, and the postoperative course was uneventful. No new ischemic lesions were identified on magnetic resonance imaging performed after surgery.

Table 1. Clinical characteristics and SPECT-perfusion and PET-Aβ deposition asymmetry ratios of the four patients studied

Case	Age (years)	Sex	Diabetes mellitus	Dyslipidemia	Hypertension	Side of lesion	Degree of ICA stenosis (%)	SPECT-perfusion asymmetry ratio		PET-Aβ deposition asymmetry ratio	
								Preop.	Postop.	Preop.	Postop.
1	68	F	No	Yes	Yes	Right	95	0.72	0.95	0.98	0.89
2	74	M	No	Yes	No	Left	95	0.71	0.93	1.01	0.91
3	66	M	No	Yes	Yes	Right	90	0.81	0.90	1.00	0.97
4	69	M	No	Yes	Yes	Left	90	0.80	0.92	1.00	0.98

SPECT, single-photon emission computed tomography; PET, positron emission tomography; Aβ, amyloid β; ICA, internal carotid artery; preop., preoperative; postop., postoperative; F, female; M, male.

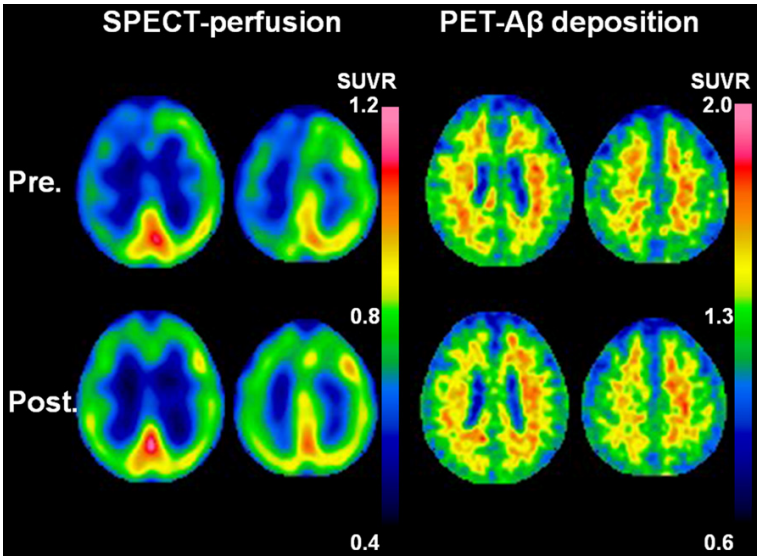

Figure 1. Brain perfusion single-photon emission computed tomography (SPECT) and amyloid β (Aβ) deposition positron emission tomography (PET) images in Case 1. Perfusion was preoperatively (pre.) reduced in the right cerebral hemisphere compared with the left cerebral hemisphere (upper), and this reduction was corrected after surgery (lower). Aβ deposition appeared similar between the bilateral cerebral hemispheres before surgery (upper) and was postoperatively (post.) reduced in the right cerebral hemisphere compared with the left cerebral hemisphere (lower). Color scale bars denote standardized uptake value ratio (SUVR) relative to a mean value of bilateral cerebellar hemispheres.

Pre- and postoperative data of brain perfusion SPECT and Aβ deposition PET

The SPECT-perfusion asymmetry ratio and the PET-Aβ deposition asymmetry ratio before and after surgery in each patient are also shown in **Table 1.** In all four patients, the SPECT-perfusion asymmetry ratio was ≤0.81 before surgery and increased to ≥0.90 after surgery. The PET-Aβ deposition asymmetry ratio ranged from 0.98 to 1.01 before surgery; in two patients, this value remained at ≥0.97 after surgery, and in the other two patients, the value decreased to ≤0.91 after surgery. Brain perfusion SPECT and Aβ deposition PET images in two patients with a PET-Aβ deposition asymmetry ratio ≤0.91 after surgery are shown in **Figures 1** and **2**.

Discussion

The present exploratory study using a small patient population investigated a possible role for chronic hypoperfusion in Aβ deposition. To exclude influences of focal or global ischemic insults on Aβ deposition, only patients without episodes of carotid territory ischemic symptoms and cortical infarcts in any cerebral hemispheres were enrolled. Furthermore, only patients with a preoperative SPECT-perfusion asymmetry ratio <0.93 were enrolled. In a cerebral hemisphere with severe steno-occlusive disease of the cerebral arteries, misery perfusion is defined as a blood supply that is barely adequate for the metabolic needs and is suggestive of severe hypoperfusion [9]. In a patient with unilateral ICA steno-occlusive disease, the affected hemisphere exhibits misery perfusion when the SPECT-perfusion asymmetry ratio is <0.93 [8]. The affected hemispheres in our four patients thus may have had no ischemic insults despite misery perfusion. The present study including patients with such homogeneous conditions showed that chronic cerebral hypoperfusion does not increase Aβ deposition in the affected cerebral hemisphere. These results were comparable with findings of

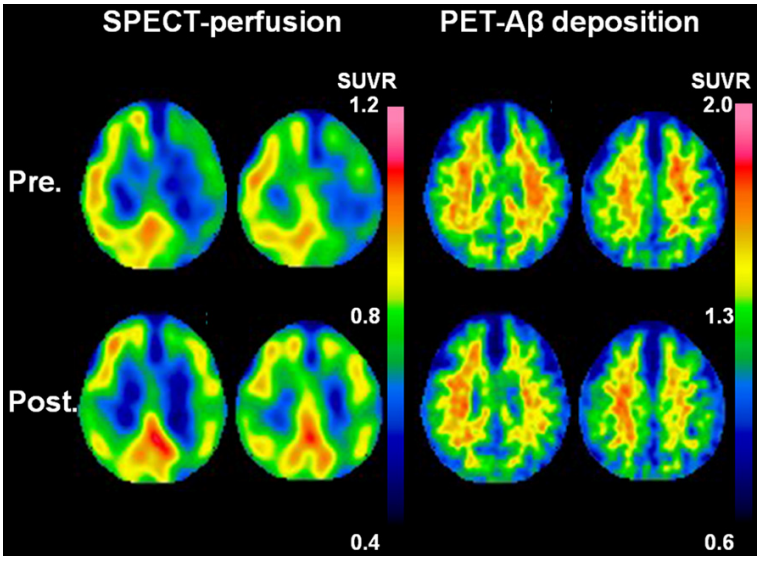

Figure 2. Brain perfusion single-photon emission computed tomography (SPECT) and amyloid β (Aβ) deposition positron emission tomography (PET) images in Case 2. Perfusion was preoperatively (pre.) reduced in the left cerebral hemisphere compared with the right cerebral hemisphere (upper), and this reduction was corrected after surgery (lower). Aβ deposition appeared similar between the bilateral cerebral hemispheres before surgery (upper) and was postoperatively (post.) reduced in the left cerebral hemisphere compared with the right cerebral hemisphere (lower). Color scale bars denote standardized uptake value ratio (SUVR) relative to a mean value of bilateral cerebellar hemispheres.

a previous study that included symptomatic patients with various degrees of ischemic insults [1].

Another finding in the present study was that correction of cerebral hypoperfusion after CEA often reduces Aβ deposition. Water-soluble monomeric Aβ peptides are initially transformed into Aβ oligomers. The oligomers then aggregate, resulting in formation of water-insoluble Aβ fibrils [10, 11]. Florbetapir, which was used as a PET tracer for Aβ detection in the present study, is thought to bind to fibrillar forms rather than monomeric or oligomeric forms of Aβ [12]. Our data thus suggested a reduction in Aβ fibrils following correction of cerebral hypoperfusion. Aβ accumulation in the brain may be due to reduced Aβ clearance rather than increased Aβ synthesis in the most prevalent, late-onset type of Alzheimer's disease [4]. Extracellular Aβ clearance is a result of the motive force from arterial pulsations [3]. Abrupt and long-term restoration of arterial pulsation after carotid revascularization may facilitate clearance of monomeric or oligomeric forms of Aβ. The oligomer-to-fibril transition may be irreversible, and carotid revascularization may not directly facilitate clearance of Aβ fibrils. Rather, microglial and astroglial cells degrade Aβ fibrils, leading to clearance of Aβ [2]. The degradation of Aβ fibrils along with increased clearance of monomeric or oligomeric Aβ may contribute to a reduction in Aβ fibrils.

A serious limitation in the present study is that, due to it being an exploratory study, our patient population was too small to analyze statistically. An effect of post-CEA reduction in Aβ deposition on cognitive function remains also unknown. This is another limitation. Cognitive function improves after CEA in approximately 10% of asymptomatic patients and this cognitive improvement is related to postoperative restoration of brain perfusion that was reduced before surgery [13]. Further studies to investigate relationship between post-CEA reduction in Aβ deposition and cognitive change in a larger patient population will be beneficial.

In conclusion, although chronic cerebral hypoperfusion due to severe atherosclerotic stenosis of the ICA does not increase Aβ deposition in the affected cerebral hemisphere, correction of cerebral hypoperfusion after CEA often reduces Aβ deposition.

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Disclosure of conflict of interest

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References

[1] Hansson O, Palmqvist S, Ljung H, Cronberg T, van Westen D and Smith R. Cerebral hypoperfusion is not associated with an increase in amyloid β pathology in middle-aged or elderly people. Alzheimers Dement 2018; 14: 54-61.

[2] Maki T, Okamoto Y, Carare RO, Hase Y, Hattori Y, Hawkes CA, Saito S, Yamamoto Y, Terasaki Y, Ishibashi-Ueda H, Taguchi A, Takahashi R, Miyakawa T, Kalaria RN, Lo EH, Arai K and Ihara M. Phosphodiesterase III inhibitor promotes drainage of cerebrovascular β-amyloid. Ann Clin Transl Neurol 2014; 1: 519-533.

[3] Weller RO, Djuanda E, Yow HY and Carare RO. Lymphatic drainage of the brain and the pathophysiology of neurological disease. Acta Neuropathol 2009; 117: 1-14.

[4] Mawuenyega KG, Sigurdson W, Ovod V, Munsell L, Kasten T, Morris JC, Yarasheski KE and Bateman RJ. Decreased clearance of CNS beta-amyloid in Alzheimer's disease. Science 2010; 330: 1774.

[5] Ogasawara K, Ito H, Sasoh M, Okuguchi T, Kobayashi M, Yukawa H, Terasaki K and Ogawa A. Quantitative measurement of regional cerebrovascular reactivity to acetazolamide using ^{123}I-Nisopropyl-p-iodoamphetamine autoradiography with SPECT: validation study using $H_2{}^{15}O$ with PET. J Nucl Med 2003; 44: 520-525.

[6] Ikari Y, Akamatsu G, Nishio T, Ishii K, Ito K, Iwatsubo T and Senda M. Phantom criteria for qualification of brain FDG and amyloid PET across different cameras. EJNMMI Phys 2016; 3: 23.

[7] Takeuchi R, Matsuda H, Yoshioka K and Yonekura Y. Cerebral blood flow SPET in transient global amnesia with automated ROI analysis by 3DSRT. Eur J Nucl Med Mol Imaging 2004; 31: 578-589.

[8] Matsumoto Y, Ogasawara K, Saito H, Terasaki K, Takahashi Y, Ogasawara Y, Kobayashi M, Yoshida K, Beppu T, Kubo Y, Fujiwara S, Tsushima E and Ogawa A. Detection of misery perfusion in the cerebral hemisphere with chronic unilateral major cerebral artery stenoocclusive disease using crossed cerebellar hypoperfusion: comparison of brain SPECT and PET imaging. Eur J Nucl Med Mol Imaging 2013; 40: 1573-1581.

[9] Baron JC, Bousser MG, Rey A, Guillard A, Comar D and Castaigne P. Reversal of focal "misery-perfusion syndrome" by extra-intracranial arterial bypass in hemodynamic cerebral ischemia: a case study with ^{15}O positron emission tomography. Stroke 1981; 12: 454-459.

[10] Nag S, Sarkar B, Bandyopadhyay A, Sahoo B, Sreenivasan VK, Kombrabail M, Muralidharan C and Maiti S. Nature of the amyloid-beta monomer and the monomer-oligomer equilibrium. J Biol Chem 2011; 286: 13827-13833.

[11] Mulaj M, Foley J and Muschol M. Amyloid oligomers and protofibrils, but not filaments, self-replicate from native lysozyme. J Am Chem Soc 2014; 136: 8947-8956.

[12] Choi SR, Golding G, Zhuang Z, Zhang W, Lim N, Hefti F, Benedum TE, Kilbourn MR, Skovronsky D and Kung HF. Preclinical properties of 18 F-AV-45: a PET agent for AB plaques in the brain. J Nucl Med 2009; 50: 1887-994.

[13] Kojima D, Ogasawara K, Kobayashi M, Yoshida K, Kubo Y, Chida K, Oshida S, Yoshida J, Fujiwara S and Terasaki K. Effects of uncomplicated carotid endarterectomy on cognitive function and brain perfusion in patients with unilateral asymptomatic severe stenosis of the internal carotid artery by comparison with unoperated patients. Neurol Res 2016; 38: 580-586.