Reduction in amyloid β deposition on 18F-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 18F-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, 18F-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.
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Table 1. Clinical characteristics and SPECT-perfusion and PET-Aβ deposition asymmetry ratios of the four patients studied

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

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.

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
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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


