

Long-term Trial of Corticosteroid Therapy for the Recurrence of Cerebral Amyloid Angiopathy-related Hemorrhages : A Case Study Using [11C] BF-227 Amyloid-PET

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Aim : To clarify a long-term preventive effect of corticosteroid therapy for the recurrence of cerebral amyloid angiopathy (CAA)-related hemorrhages.

Subjects and methods : Cases consisted of one male and two females, being consistent with the diagnosis of G3 to G4 in Boston validation criteria of CAA. To detect cerebral A β amyloidosis, they underwent positron emission tomography combined with a novel amyloid specific tracer, BF-227, all showing positive brain shadow. A 66-year-old man (case 1) with a diagnosis of G3 was given an initial dose of prednisolone at 50 mg/day. The dose was gradually reduced and was tapered off 6 months later, but after the next 6 months cerebral hemorrhage recurred. He again received similar corticosteroid therapy. A 69-year-old woman (case 2) with a diagnosis of G3 was given dexamethasone 16 mg/day after suffering recurrent cerebral hemorrhages. A week later dexamethasone was switched to prednisolone 30 mg/day and the dose of this corticosteroid was gradually reduced, until being kept at 8 mg/day. Another 75-year-old woman (case 3) with a diagnosis of G4 was given an initial dose of prednisolone at 30 mg/day and the dose of this corticosteroid was gradually reduced and has been kept at 8 mg/day.

During the observation periods they were evaluated by clinical manifestations and T2* MR images : the total area of microbleeds was assessed by computer-assisted morphometry. After treatment two cases received a second PET scan and the regional standard uptake value ratio (SUVR) of BF-227 at the occipital lobe was compared with the previous one.

Results : Case 1 suffered a small hemorrhage in the left frontal lobe at 20 months after receiving the corticosteroid therapy and steroid pulse therapy was added. During the remaining 33 months he has been free of cerebral hemorrhages. SUVR in his PET scan showed 2.0 to 2.2 in a 14-month follow-up period and the total area of microbleeds extended from 410.2 to 445.5 mm² during the 48-month observation period. Case 2 showed two simultaneous small hemorrhages at 29 months after starting the corticosteroid therapy and her dose of prednisolone was temporally increased. During the remaining 17 months she has not had any strokes and SUVR in her PET showed 1.5 to 1.4 in an 18-month follow-up period. The total area of microbleeds extended from 512.5 to 560.8 mm² during the 27-month observation period. Case 3 has been free of cerebral hemorrhages for 22 months after this corticosteroid therapy and the total area of microbleeds ranged from 152.5 to 154.1 mm² during the 13-month observation period.

Conclusions : Corticosteroid therapy seems to be clinically effective for the long-term prevention of recurrences of CAA-related hemorrhages but current brain image data are inadequate to lead to this conclusion. This is the first report showing that domestically developed BF227 PET scan is useful in visualizing CAA lesions. *Shinshu Med J 62 : 155–165, 2014*

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Key words : cerebral amyloid angiopathy, cerebral hemorrhage, A β amyloid, corticosteroid, amyloid-imaging, positron emission tomography

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I Introduction

Cerebral amyloid angiopathy (CAA) is caused by the accumulation of A β amyloid fibrils on cere-

brovascular walls and is well known to be a cause of cerebral hemorrhages in the elderly¹²⁾. This disease manifests as recurrent or multiple simultaneous subcortical hematomas, occasionally leading to fatal lobar hemorrhages³⁾: in a cohort study of 71 consecutive survivors with CAA-related hemorrhages, the two-year cumulative recurrence rate of this hemorrhage was reported to be 21 percent, indicating a very high risk of recurrence⁴⁾. Additionally, it is noteworthy that CAA-related hemorrhages can develop in individuals aged around 50 years⁵⁾. For the prevention of the recurrence of CAA-related hemorrhages, the usefulness of corticosteroid was described in a number of reported cases⁶⁾⁷⁾. However, this therapy has not been widely accepted since there is limited evidence supporting this strategy.

A recent in vitro study has demonstrated that $A\beta$ -induced cerebrovascular smooth muscle cell death is significantly suppressed by dexamethasone⁸⁾. We also have reported the postmortem findings of a CAA patient treated by corticosteroid in which diminishing of the cerebrovascular amyloid deposits was noted in comparison with the previous biopsy findings⁹⁾¹⁰⁾. To address the long-term preventive effect of corticosteroid therapy for CAA-related hemorrhages we studied three cases with this disorder by quantitative analyses of brain images including positron emission tomography (PET) combined with a novel tracer, (11)C-labeled-(2-[2-dimethylaminothiazol-5-yl]ethenyl)-6-(2-[fluoro]ethoxy) benzoxazole ([11C]BF-227). [11C]BF-227 is a tracer having specific binding to amyloid fibrils including $A\beta$ amyloid fibrils¹¹⁾, and the usefulness of this [11C]BF-227 amyloid-PET was previously reported for the evaluation of cerebral amyloid deposits in patients with Alzheimer's disease¹²⁾ and transthyretin-derived amyloid deposition on myocardium¹³⁾. The present case study aimed to obtain evidence that corticosteroid therapy is effective for the prevention of recurrence of CAA-related hemorrhages, paying special attention to the usefulness of [11C]BF-227 amyloid-PET in evaluating cerebrovascular amyloid deposits in

patients non-invasively.

II Subjects and Methods

The subjects were the following three cases who were diagnosed as having probable (G3) or possible (G4) CAA on the basis of validation of the Boston criteria¹⁴⁾.

III Case Reports

Case 1 was a 66-year-old male when he first visited us. During the previous 2 years he had gradually suffered from cognitive decline including speech disturbance and memory loss. He underwent magnetic resonance imaging (MRI) at another hospital, which showed bilateral white matter degeneration with multiple microbleeds, and he was hospitalized in March 2008. Cerebral angiography was normal and revised Hasegawa dementia scale (HDS-R) was 17 out of 30. He was discharged with oral administration of cilostazole 200 mg/day but three months later he developed intractable headache and CT showed two small hematomas in the left parietal and occipital lobes (**Fig. 1A**). He was suspected to be suffering from CAA-related hemorrhages. Thus, cilostazole was stopped and he was given an initial dose of prednisolone at 50 mg/day in August 2008. The dose of prednisolone was gradually reduced and was tapered off six months later. Six months after from cessation of corticosteroid therapy he suffered hemorrhages in the left fronto-parietal lobe (**Fig. 1B**). Prednisolone 40 mg/day was, therefore, started again in August 2009 and he was referred to us: he was 162.3 cm tall and weighted 56.5 kg. His pulse rate was 63 per minute and was regular, and blood pressure was 135/76 mmHg. His general condition was good and showed no neurological disability. Routine laboratory data were all normal. PET with BF227 showed positive shadow mainly in the bilateral occipital lobes (**Fig. 2A**). Prednisolone was gradually reduced, until being kept at 10 mg/day. In April 2011 he developed slight paresis in the right leg and a small hematoma in the left frontal lobe was seen on CT (**Fig. 1C**). He received an additional steroid pulse therapy (methylpred-

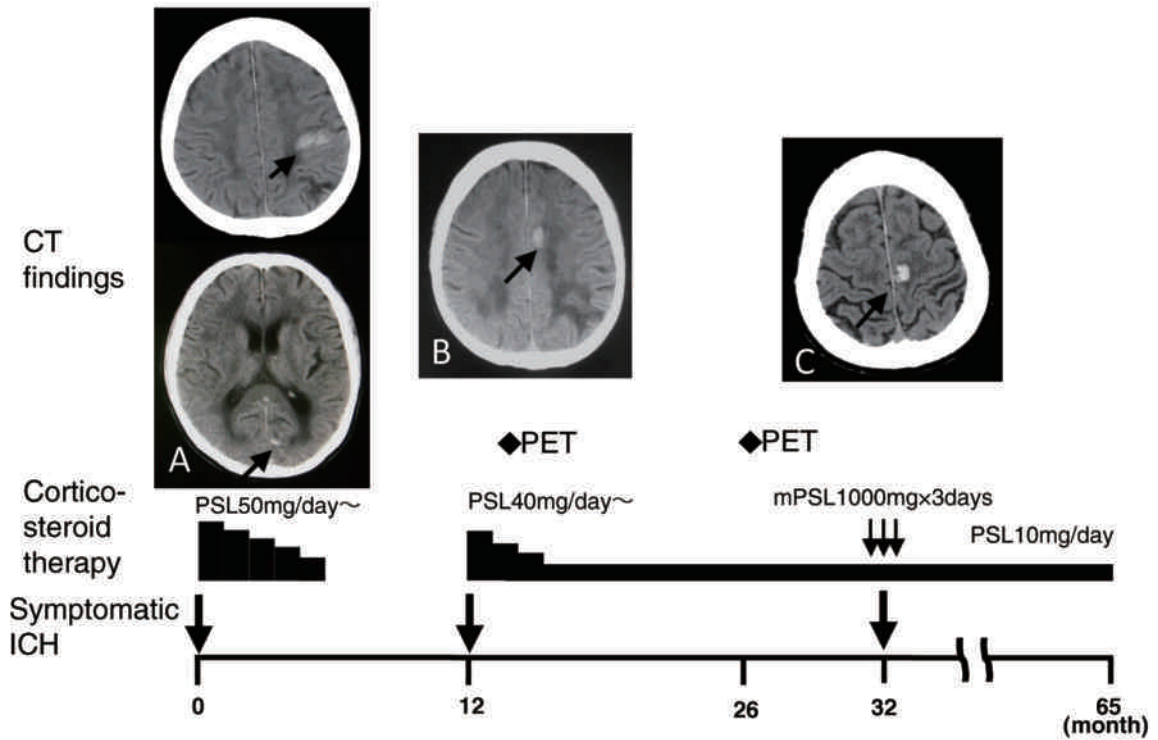


Fig. 1 CT findings and clinical course of case 1.

A : CT finding of initial cerebral hemorrhages, B : recurrent cerebral hemorrhage after cessation of prednisolone, C : recurrent cerebral hemorrhage even when taking a small dose of prednisolone. All arrows indicate hematomas on CT images. Abbreviations : PSL : prednisolone, ICH : intracranial hemorrhage.

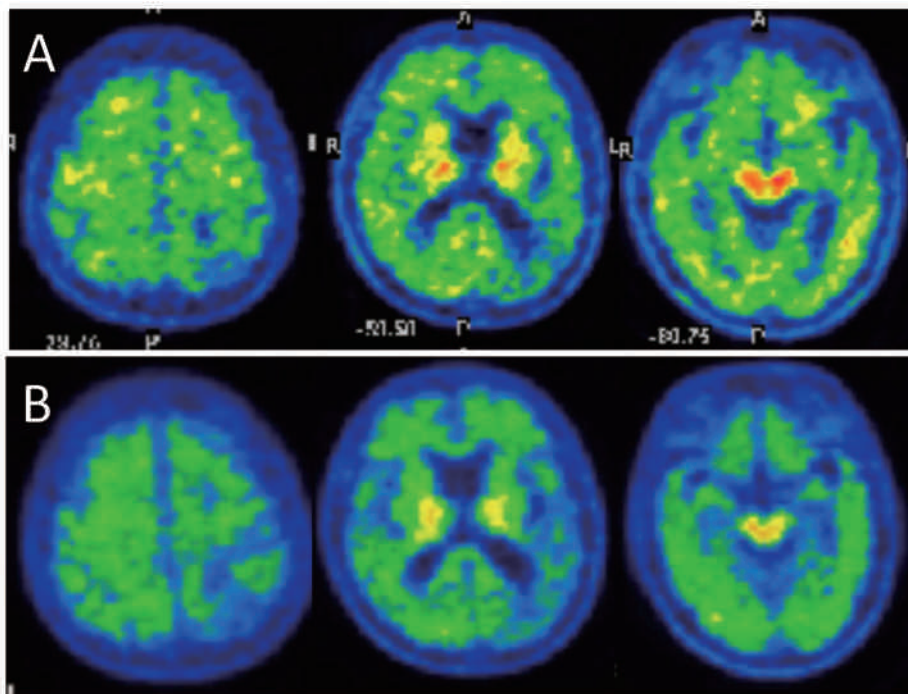


Fig. 2 BF227 PET findings in case 1.

A : before corticosteroid treatment, B : after that. In panel A patchy distribution of increased uptake of a tracer is seen mainly in frontal and occipital lobes, while in panel B this finding is less impressive.

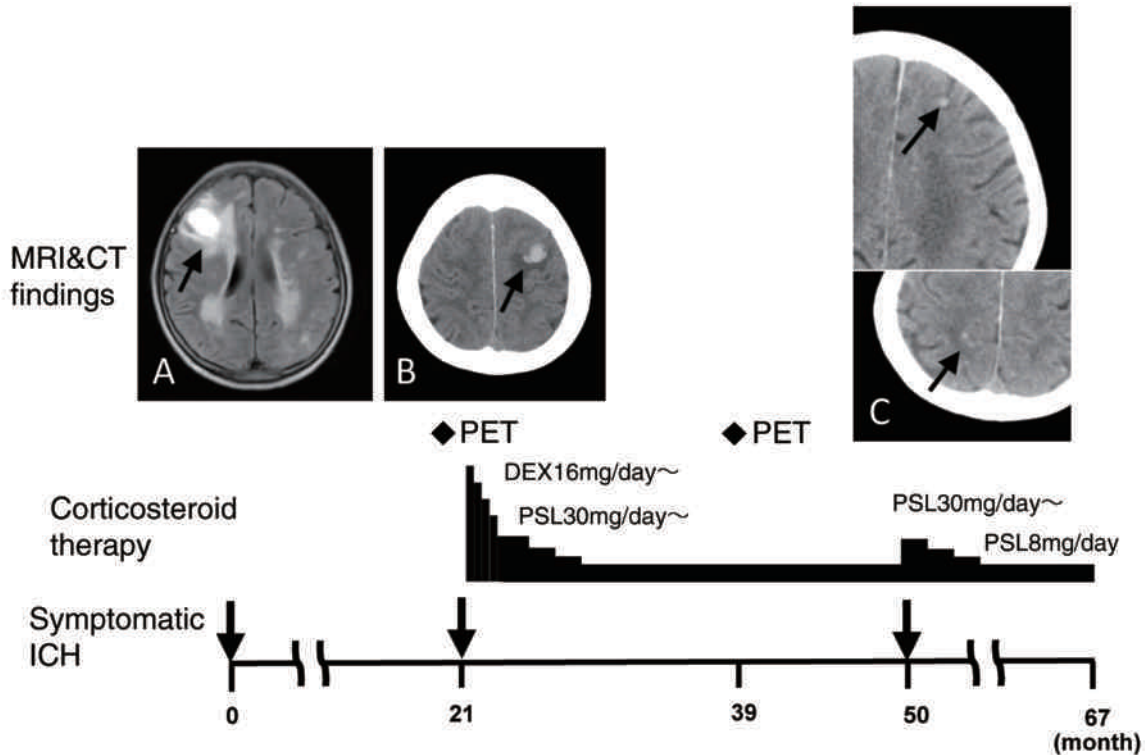


Fig. 3 MRI and CT findings, and clinical course of case 2.

A: MRI flair image of a subcortical hematoma, B: CT finding of recurrent cerebral hemorrhage, C: CT findings of two recurrent simultaneous small hemorrhages. All arrows indicate hematomas on MRI and CT images. Abbreviations: PSL: prednisolone, ICH: intracranial hemorrhage.

nisolone 1 g/day for three days) and his leg weakness improved. Since that event he has been free of cerebral hemorrhage for 33 months (**Fig. 1**).

Case 2 was a 69-year-old female who had a history of cerebral hemorrhages: in May 2008 she suddenly developed disorientation of time and day, and confused communication. MRI at another hospital revealed a subcortical hematoma in the right frontal lobe (**Fig. 3A**). Her symptoms gradually recovered but MRI showed multiple microbleeds in the bilateral temporal-occipital lobes. She was referred to us in February 2010. On examination she was 141.0 cm tall and weighted 42.2 kg. Her pulse rate was 67 per minute and was regular, and blood pressure was 126/80 mmHg. Since she had been suffering from severe osteoarthropathy of the thoracolumbar spine she used a stick when walking. Mini-mental state examination (MMSE) was 18 out of 30 and PET with BF227 showed positive shadow in the bilateral temporal-occipital lobes (**Fig. 4A**).

In March she complained of headache and difficulty in writing and CT disclosed a small hematoma in the left frontal lobe (**Fig. 3B**). In April 2010 she started to be treated with dexamethasone 16 mg/day, which was then switched to prednisolone 30 mg/day. The dose of this drug was gradually reduced, and has since been kept at 8 mg/day. She showed two simultaneous small hemorrhages at 29 months after starting the corticosteroid therapy, and her dose of prednisolone was temporarily increased to 30 mg/day (**Fig. 3C**) and then decreased to 8 mg/day. During the remaining 17 months she has not suffered any cerebral hemorrhages.

Case 3 was a 75-year-old woman who developed cognitive decline two years ago. One year before her visit to us she experienced right hemiparesis and aphasia. She was transferred to another hospital where she was found to have a cerebral hemorrhage in her left frontal lobe (**Fig. 5A**). Although her motor disability gradually recovered, her cognitive

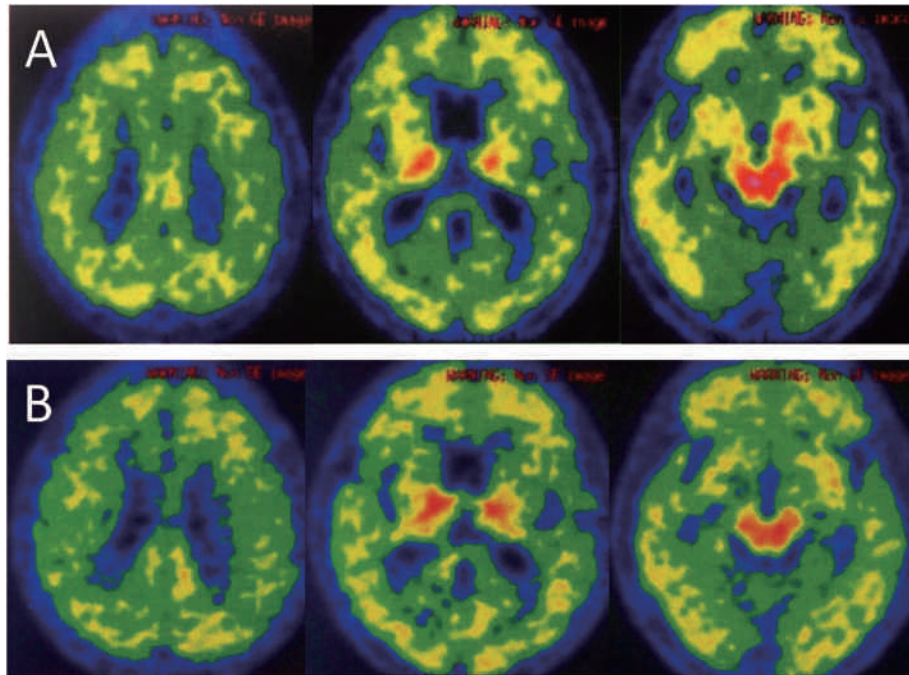


Fig. 4 BF227 PET findings in case 2.

A: before corticosteroid treatment, B: after that. Although both panels show patchy distribution of increased uptake of a tracer mainly in frontal and occipital lobes, panel B seems to be more highly visualized.

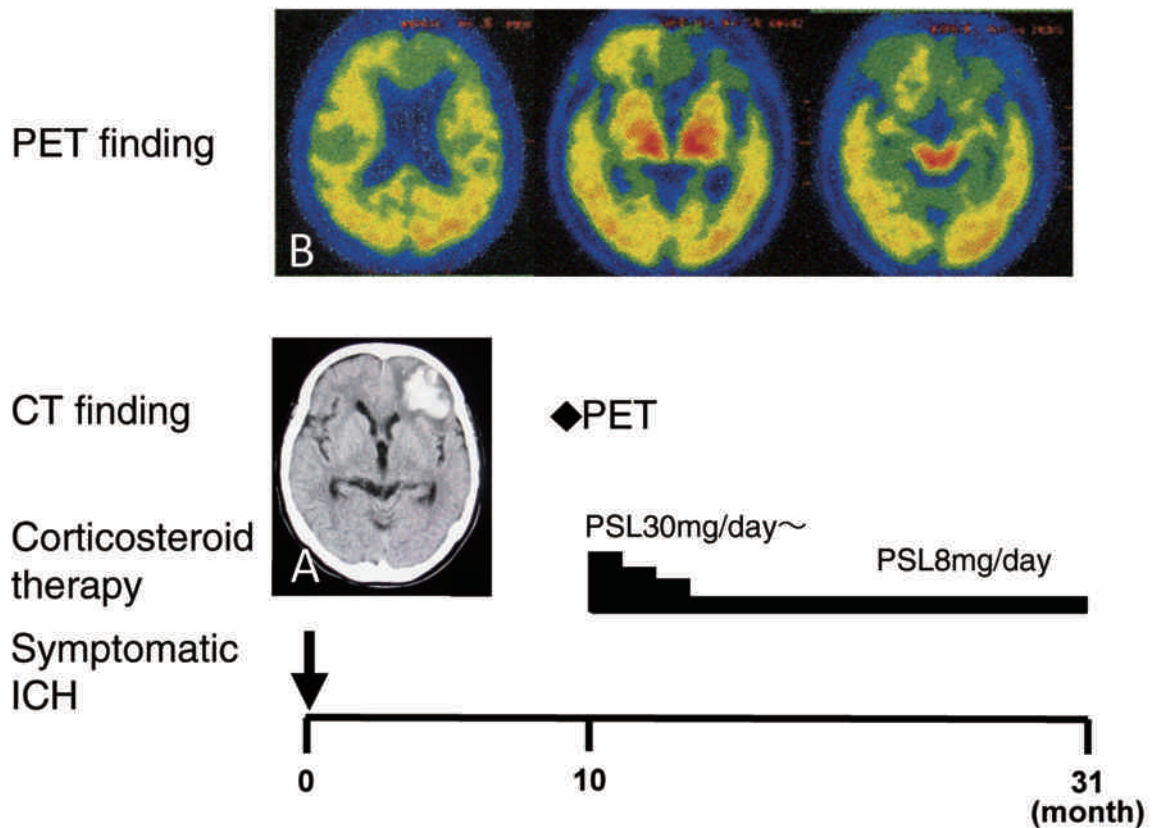


Fig. 5 BF227 PET and CT findings, and clinical course in case 3.

A: CT finding of a left frontal lobe hematoma, B: PET scan showing positive shadow mainly in bilateral occipital lobes.

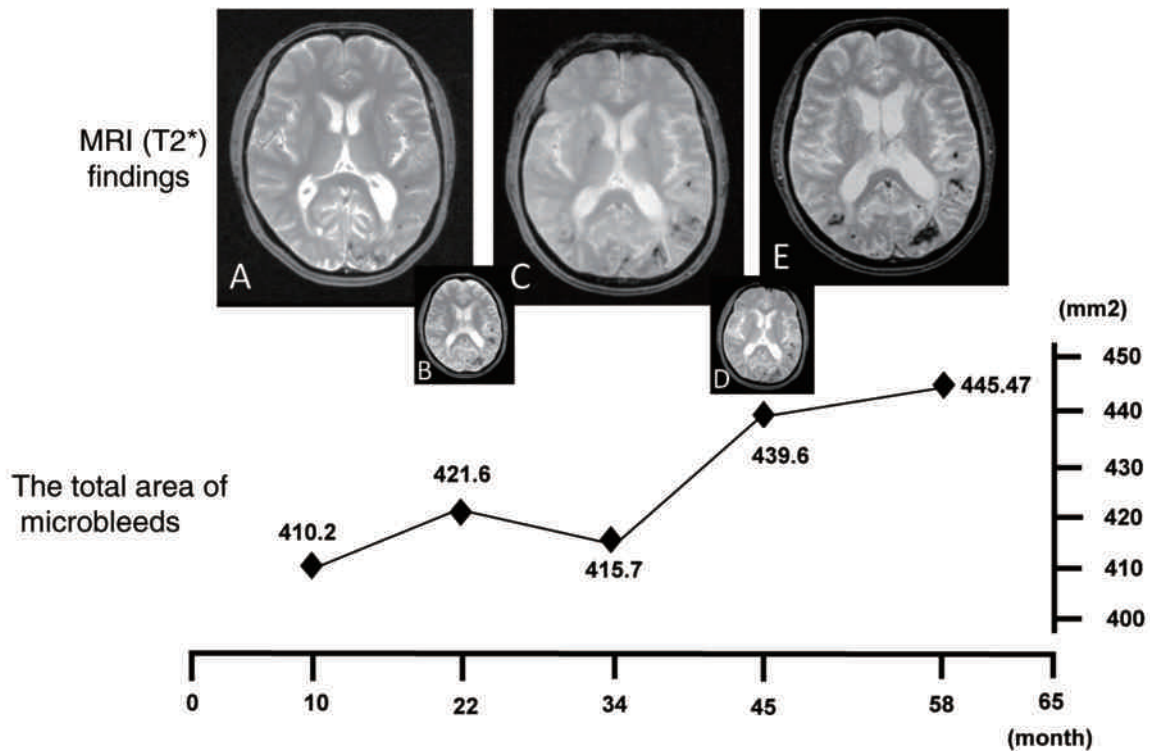


Fig. 6 Serial changes of MRI T2*-weighted images and calculated values indicating microbleed area in case 1.

Comparing between panels A and E microbleed-related lesions have apparently expanded in the latter.

state did not improve. She was, therefore, referred to our hospital in November 2011. At examination she was 148.7 cm and weighted 50.3 kg. Her pulse rate was 72 per minute and was regular, blood pressure being 128/76 mmHg. Her general condition was good and she looked apathetic, but lacked any specific neurological deficits. MMSE was 17 out of 30 and MRI showed an abnormal lesion in the left frontal lobe, indicating an old hematoma, while microbleeds were barely visible in the temporal lobes. A regimen of 8 mg of galantamine twice daily improved her cognitive function, raising her MMSE score to 25 out of 30. Then she underwent PET with BF227, showing marked uptake mainly in parietal and occipital cortical regions (Fig. 6B). She was diagnosed as having possible CAA (G4) and was given an initial dose of prednisolone at 30 mg/day in February 2012. The dose of prednisolone was gradually reduced, until being kept at 8 mg/day (Fig. 5). She has been free of cerebral hemorrhage for 22 months.

IV Quantitative Analysis of Brain Images

A MRI analysis

To detect cerebral microhemorrhages or microbleeds T2*-weighted MR imagery was employed¹⁵⁾¹⁶⁾: this imagery was repeatedly obtained from 3 cases. For the three serial photographs including a large area of the fronto-temporo-occipital lobes the total area of microbleeds was calculated by computer-assisted morphometry with the use of Image J software (NIH, USA) and, the numbers obtained were serially compared before and after corticosteroid therapy.

B [(11)C]BF-227 amyloid-PET analysis

[(11)C]BF-227 amyloid-PET scan was performed at the Department of Radiology, Minami-Tohoku General Hospital, Kouriyama, Fukushima. The [(11)C]BF-227 PET study was carried out using a PET SET-2400 W scanner (Shimadzu Inc., Tokyo, Japan). After intravenous injection of 211–366 mBq of [(11)C]BF-227, dynamic serial PET images were obtained from 20 to 60 minutes with each subject's

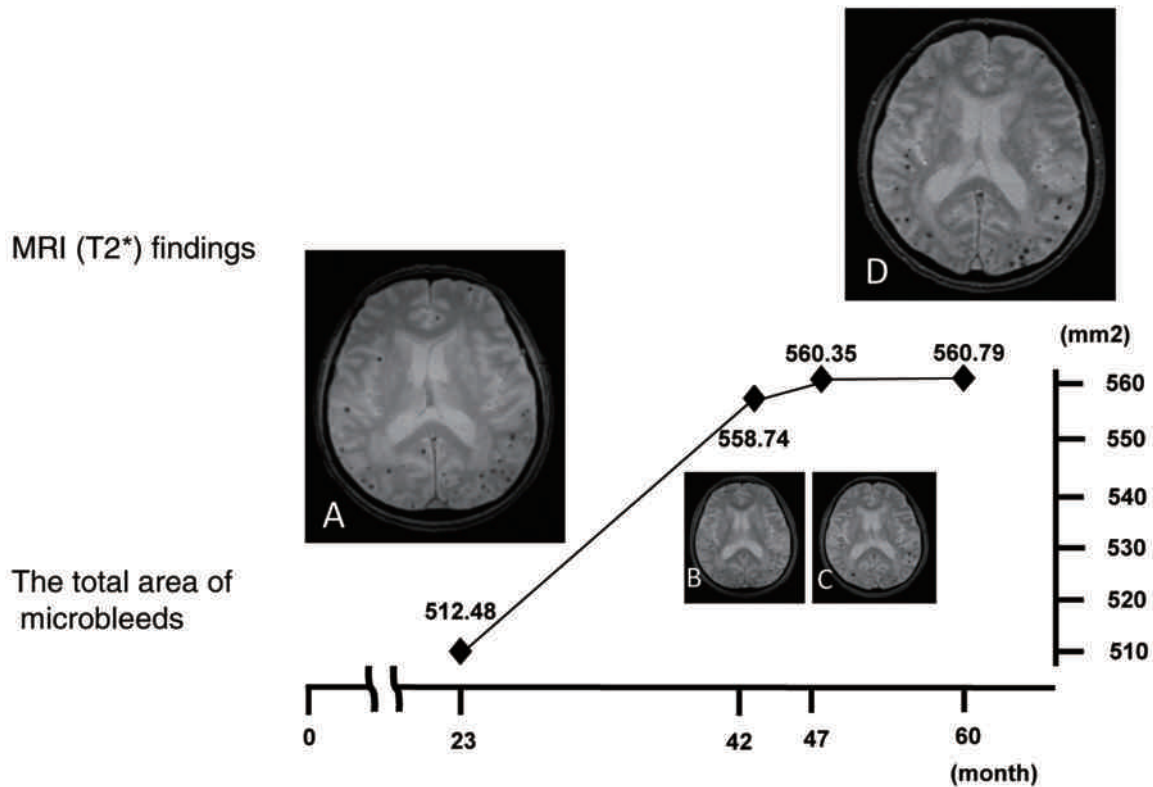


Fig. 7 Serial changes of MRI T2*-weighted images and calculated values indicating microbleed area in case 2.

The distribution of microbleeds seen on panels A and D is typical for CAA and the number of these lesions increased at an advanced stage.

eyes closed. The regional standardized uptake value ratio (SUVR), which reflected the ratio of regional cerebral SUV to cerebellar, was calculated as an index of BF-277 binding. Actually in Cases 1 and 2, SUVR for amyloid plaque deposition on the temporal-occipital area was evaluated before treatment and about a year after that. The study protocol was approved by the local ethics committee.

V Results

In case 1 the total area of microhemorrhages on T2*-weighted MR images extended from 410.2 to 445.5 mm² during the 48-month observation period (Fig. 6A, 6E) and SUVR in his PET scan showed 2.0 to 2.2 in a 14-month follow-up period (Fig. 2A, 2B). In case 2 the total area of microhemorrhages extended from 512.5 to 560.8 mm² during the 27-month observation period (Fig. 7A, 7D) and SUVR in her PET revealed 1.5 to 1.4 in a 17-month follow-up period (Fig. 4A, 4B). In case 3 the total area of

microhemorrhages ranged from 152.5 to 154.1 mm² during the 13-month observation period (Fig. 8A, 8B). SUVR of amyloid plaque deposition on BF227PET before therapy was 1.44 (Fig. 5B), but the next PET scan using this machine could not be performed because of the Great East Japan Earthquake.

VI Discussion

CAA usually involves small and medium-sized vessels of the cerebral cortex, subcortex, and leptomeninges¹⁾²⁾¹⁷⁾. This finding can be confirmed only by histopathological examination of brain tissues¹⁸⁾, but recent advances in brain imaging can provide very reliable information on cerebrovascular amyloid deposits in living individuals: a CT finding of intracerebral hemorrhage with a distinctive cortical-subcortical distribution is the first clue for the possibility of CAA¹⁶⁾ and this suspicion becomes more confident if the patients are aged and

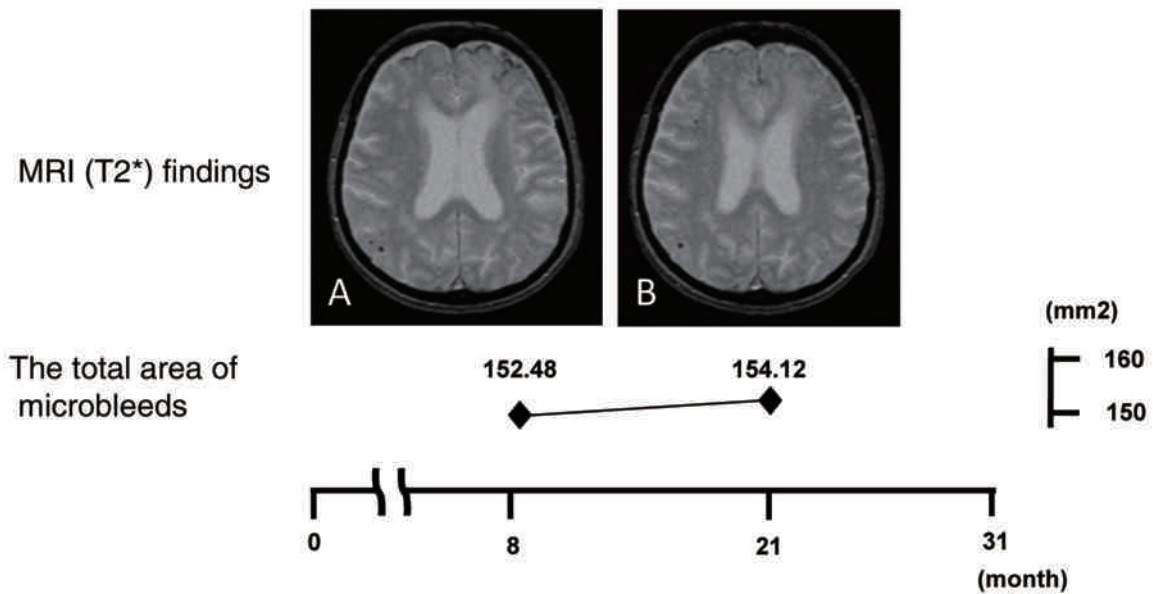


Fig. 8 Two panels of MRI T2*-weighted images and calculated values indicating microbleed area in case 3.

There is no significant change in microbleed-related areas between panels A and B.

have no history of hypertension. Next the patients should undergo MR imaging including a T2*-weighted gradient-echo sequence. This MR imaging can sensitively disclose deposits of hemosiderin ascribable to previous minor hemorrhages or microbleeds¹⁵⁾¹⁶⁾. Although microbleeds are associated with some neurological conditions such as Binswanger's disease, traumatic brain injury, or primary angiitis of the central nervous system, they are most frequently observed in patients with a long history of hypertension or those with CAA¹⁶⁾. It has been shown that cortico-subcortical distribution of microbleeds is different between hypertension and CAA, the latter being located mostly in the posterior half of the brain, with a predilection for the parietal lobes¹⁹⁾²⁰⁾. Recently, the direct *in vivo* demonstration of cerebral A β amyloid deposits has become possible using a PET combined with novel amyloid-specific tracers: a Pittsburgh Compound-B (PiB) tracer has been used worldwide^{21)–23)}, while our BF-227 tracer is domestic and has been applied for patients with mild cognitive impairment or Alzheimer's disease¹²⁾, producing very sensitive detection of A β -derived senile plaque amyloid deposition.

Among the present three cases 1 and 2 possessed many microbleeds on T2*-weighted MR images, the distribution of which was typical for CAA. Additionally, in these three cases, A β amyloid deposition on an extensive area of cerebral cortex was indirectly shown by a positive BF-227 PET scan. The experience of the use of a PiB PET scan, of course, has revealed that cortical PiB retention is a feature not only of Alzheimer's disease, but also of functionally normal aged brain with A β amyloid deposition, mild cognitive impairment, CAA and dementia with Lewy bodies associated with Alzheimer's pathology²¹⁾²²⁾. In considering the differential diagnosis of these five brain conditions the clinical histories of non-hypertensive subcortical hemorrhages in our three cases strongly suggested that amyloid deposited as CAA was the dominant source of this BF-227 PET signal, ensuring the clinical diagnosis of CAA.

The usefulness of corticosteroid therapy is well known for CAA-related inflammation²⁴⁾: this pathology coexists with CAA and isolated cerebral angiitis²⁵⁾ and is alternatively called A β -related angiitis and cerebral amyloid inflammatory vasculopathy²⁶⁾, causing diffuse deep white matter degeneration. However, this therapeutic strategy

was applied to a limited number of cases with CAA-derived hemorrhages⁶⁷⁾. In this study we evaluated the long-term preventive effect of corticosteroid therapy for CAA-related hemorrhages in 3 cases. In case 1 symptomatic hemorrhage occurred 6 months after the cessation of corticosteroid therapy, upon which corticosteroid therapy was restarted and has been maintained with a low dose of prednisolone, resulting in an absence of symptomatic cerebral hemorrhages for 33 months. Similarly in cases 2 and 3, freedom from symptomatic cerebral hemorrhages has been 17 to 22 months respectively with low dose corticosteroid therapy. After treatment, SUVR of amyloid plaque deposition showed slight changes: it was increased in case 1, but decreased in case 2, both being insignificant for estimating any alteration in cerebrovascular amyloid deposits. We quantitatively examined another CAA-related brain lesion, that is, the area of microbleeds on T2*-weighted MR imagery. Since visualization of this lesion is known to be changeable either in different machines or different imaging conditions, we did not use the same machine under similar conditions in the series in this study. Even when considering this methodological bias, the lesions involved by microbleeds apparently extended in cases 1 and 2, indicating that CAA-related subclinical hemorrhages worsened irrespective of the use of corticosteroid therapy. In fact cases 1 and 2 experienced one symptomatic attack with small cerebral hemorrhages in spite of taking a low dose of prednisolone. On the basis of all these findings it is likely that corticosteroid therapy is clinically effective for the long-term prevention of recurrence of CAA-related hemorrhages, while the MRI findings are not supportive of our tentative conclusion.

It has been shown that in patients with Alzheimer's

disease immunization therapy can significantly reduce the A β amyloid plaque burden in the brain²⁷⁾²⁸⁾, and we have recently reported that regression of cerebrovascular A β amyloid deposits occurred in a case after corticosteroid treatment⁹⁾ in which proteomic analysis of the crude amyloid fractions isolated from the leptomeningeal vessels in CAA cases disclosed that the quantity and molecular pattern of A β and its derivatives were clearly different between the CAA case with and the one without corticosteroid treatment¹⁰⁾. The latter finding suggests that corticosteroid influences the turn-over of constituent amyloid fibril protein²⁹⁾ on cerebrovascular walls with A β amyloid deposits. Other actions of corticosteroid are surmised to reduce brain edema around hemorrhages, secondarily decreasing mechanical stress for CAA affected vessels with vascular fragility or to suppress CAA-related perivascular inflammation³⁰⁾ leading to vascular rupture. However, the detailed molecular basis for the beneficial effects of corticosteroid on this cerebrovascular amyloid lesion remains unclear. To demonstrate the effectiveness of corticosteroid therapy for the prevention of recurrent CAA-related hemorrhages more precisely, further studies including a double-blind clinical trial on a large scale are required.

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