Clinico-Radiological Characteristics and Pathological Diagnosis of Cerebral Amyloid Angiopathy-Related Intracerebral Hemorrhage

Tadashi Doden, MD,*†‡ Hiromasa Sato, MD,* Etsuko Sasahara, MD, PhD,* Takahiro Murata, MD, PhD,§ Takehiro Yako, MD,§ Kazuo Kitazawa, MD, PhD,§ Kayoko Higuchi, MD, PhD,‖ Shigeaki Kobayashi, MD, PhD,§ and Takao Hashimoto, MD, PhD*†

Objective: We aim to clarify the clinico-radiological characteristics of cerebral amyloid angiopathy-related intracerebral hemorrhage and to investigate the efficacy of pathological diagnosis using biopsy specimens. *Method:* We retrospectively reviewed 253 consecutive patients with cortico-subcortical hemorrhage who had been admitted to Aizawa Hospital between January 2006 and July 2013. We had performed craniotomy and hematoma evacuation in 48 patients, as well as biopsy of the evacuated hematoma, cerebral parenchyma adjacent to the hematoma, or both, and they were classified according to the histological results (positive or negative for vascular amyloid deposition) and to the Boston criteria. We compared the clinico-radiological characteristics of cerebral amyloid angiopathy-related intracerebral hemorrhage. We also investigated the detection rate of cerebral amyloid angiopathy with respect to the origins of the specimens. *Results:* Pathological examination revealed that 22 subjects were positive for vascular amyloid. The number of the cerebral microbleeds located in the deep or infratentorial region was significantly larger in the negative group than in the positive group ($P < .05$). There was no significant difference in the distribution of lobar cerebral microbleeds and in the prevalence of hypertension. In the probable cerebral amyloid angiopathy-related intracerebral hemorrhage patients, the probability of having vascular amyloid detected by biopsy of both hematoma and parenchyma was 100%. Rebleeding in the postoperative periods was observed in 2 cases (9.1%) of the positive group. *Conclusions:* Our results demonstrate the importance and safety of biopsy simultaneously performed with hematoma evacuation. Deep or infratentorial microbleeds are less correlated with cerebral amyloid angiopathy-related intracerebral hemorrhage than with noncerebral amyloid angiopathy-related intracerebral hemorrhage.

From the *Department of Neurology, Aizawa Hospital, Matsumoto, Japan; †Brain Imaging Research Center, Aizawa Hospital, Matsumoto, Japan; ‡Department of Medicine (Neurology and Rheumatology), Shinshu University School of Medicine, Matsumoto, Japan; §Department of Neurosurgery, Aizawa Hospital, Matsumoto, Japan; and ‖Department of Anatomic Pathology, Aizawa Hospital, Matsumoto, Japan.

Received February 9, 2016; revision received March 15, 2016; accepted March 20, 2016.

Authors' roles: Tadashi Doden—patient evaluation, pathological evaluation, statistical analysis; wrote all drafts of manuscript. Hiromasa Sato—patient evaluation, interpretation of data. Etsuko Sasahara—interpretation of data. Takahiro Murata—patient evaluation, surgical intervention. Takehiro Yako—patient evaluation, surgical intervention. Kazuo Kitazawa—patient evaluation, surgical intervention. Kayoko Higuchi—pathological evaluation. Shigeaki Kobayashi—study design. Takao Hashimoto—study design, patient evaluation; edited drafts of manuscript.

Address correspondence to Tadashi Doden, MD, Department of Neurology, Aizawa Hospital, 2-5-1 Honjo, Matsumoto 390-8510, Japan. E-mail: aidr214@ai-hosp.or.jp.

1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2016.03.041

Key Words: Cerebral amyloid angiopathy—intracerebral hemorrhage—cerebral microbleeds—biopsy—diagnosis.

Introduction

Cerebral amyloid angiopathy (CAA) is caused by the accumulation of amyloid fibril on the cortical and leptomeningeal vessel walls, and it is an important cause of cerebral cortico-subcortical hemorrhage, cerebral infarction, leukoencephalopathy, cerebral vasculitis, and dementia in the elderly.[1-4] The incidence of CAA increases with age. Approximately half of elderly people (aged 60 years and older) and 74% of the individuals aged 90 years and older are affected with CAA.[4] CAA is closely related to the etiology of Alzheimer's disease (AD) and vascular dementia. CAA is commonly found with an incidence of about 80%-100% in AD.[4-6] CAA leads to multiple cortico-subcortical or lobar hemorrhages in the elderly, and it is then referred to as CAA-related intracerebral hemorrhage (CAA-ICH).[3,7] Boston criteria were established for CAA-ICH by the Boston Cerebral Amyloid Angiopathy Group, and a definite diagnosis of CAA-ICH can be formulated only by demonstrating lobar or cortico-subcortical hemorrhage and severe CAA with vasculopathy after whole histological investigation of affected brain tissue is obtained at autopsy.[8,9] Biopsy of the evacuated hematoma or cerebral cortex contributes to premortem diagnosis of probable CAA-ICH with supporting pathology; however, the positive ratio of amyloid deposition in the specimens obtained from brain biopsy or hematoma evacuation has not been investigated enough.[9-12] We retrospectively searched the patients with clinically diagnosed CAA-ICH who underwent biopsy of evacuated hematoma, cerebral parenchyma, or both, and classified them into CAA-pathology positive and negative groups, depending on the pathological results. As a prerequisite, the CAA-pathology positive group could be estimated to have a higher ratio of definite CAA-ICH and a lower ratio of hypertensive ICH than the CAA-pathology negative group. We investigated the differences of clinico-radiological characteristics in these 2 groups. We also investigated the differences of positive ratios of amyloid deposition, depending on the site of biopsy.

Methods

We retrospectively reviewed 253 consecutive patients with cortico-subcortical hemorrhage who had been admitted to Aizawa Hospital Stroke Center between January 2006 and July 2013 (Fig 1, A). We had performed craniotomy and hematoma evacuation in 48 patients, and biopsy of evacuated hematoma, cerebral parenchyma adjacent to the hematoma, or both in 44 of these 48 patients. We divided 22 CAA-pathology positive patients and 22 CAA-pathology negative patients into 3 groups, "probable CAA," "possible CAA," and "excluded," respectively, according to the Boston criteria. The origins of the biopsy specimens in probable or possible CAA patients were evacuated hematoma in 6 patients, cerebral parenchyma in 13 patients, and both in 12 patients. This study was approved by the institutional ethical committee, and written informed consents for surgical treatment and biopsy were obtained from either the patients or their families.

In clinical and radiological evaluation, the age at onset, the clinical diagnosis of CAA-ICH (possible or probable), hypertension (blood pressure ≧140/90 mmHg) before onset, antithrombotic drugs, dementia (Mini-Mental State Examination ≦23) before onset, estimated volume in hematoma, rebleeding, cerebral microbleeds (MBs), intraventricular hemorrhage (IVH), focal subarachnoid hemorrhage (SAH), cortical superficial siderosis (SS), and white matter lesions were compared between the CAA-pathology positive group and the CAA-pathology negative group. Brain computed tomography (CT) was performed in all patients, and volume in hematoma was estimated by the ABC/2 formula.[13] Brain magnetic resonance imaging (MRI) was performed in 17 of the 22 CAA-pathology positive patients and in 7 of the 9 CAA-pathology negative patients. The ratio of rebleeding was calculated for all patients except for 2 CAA-pathology positive patients with whom contact had been lost. We checked for a history of antithrombotic drugs, hypertension, and dementia based on the information from patients' families and medical records.

The MRI techniques were as follows. Standardized T2-weighted image (WI), fluid-attenuated inversion recovery, and T2* gradient-echo sequence (T2*WI) were acquired from 24 subjects using the 1.5 T MRI scanner (MAGNETOM Avanto, syngo MR VB17; Siemens, München, Germany). T2*WI was obtained using the following parameters: axial slice thickness = 5.0 mm, interslice thickness = 1.5 mm, repetition time = 737 ms, echo time = 26 ms, flip angle = 20°, and matrix size = 512 × 512 pixels.

MBs and cortical SS were evaluated in T2*WI. MBs are defined as focal areas of very low signal intensity, homogeneous round lesions with a diameter of 2-5 mm; superficial vessels and small calcification in basal ganglia or dentate nucleus were excluded.[14] Cortical SS is defined based on rims of hypointensity enveloping the surface of the cortical fissures. White matter lesions in the periventricular areas and deep or subcortical areas were graded into 4 stages, according to the method of the previous reports.[15,16] Imaging analysis was done by an