Cerebral Amyloid Angiopathy as a Cause of Subarachnoid Hemorrhage

Toshio Ohshima, MD, Toyoshi Endo, MD, PhD, Hideaki Nukui, MD, PhD, Shu-ichi Ikeda, MD, PhD, David Allsop, PhD, and Toshimasa Onaya, MD, PhD

Cerebral amyloid angiopathy is a pathologic condition characterized by the deposition of amyloid in the walls of small vessels in the cerebral cortex and meninges. Intracerebral hemorrhage is common in persons with this condition, but pure subarachnoid or subdural hemorrhage is rarely seen. Recently, the existence of two types of amyloid proteins related to cerebral amyloid angiopathy, β protein and cystatin C, has been reported, and immunohistochemical methods using antisera to these proteins have become available. We describe a patient with fatal subarachnoid hemorrhage presumably caused by β protein–type cerebral amyloid angiopathy, which was demonstrated immunohistochemically by using a monoclonal antibody to a synthetic peptide corresponding to residues 8–17 of β protein. We suggest that β protein–type cerebral amyloid angiopathy is a possible etiologic factor in subarachnoid hemorrhage of unknown cause. (Stroke 1990;21:480–483)

Case Report

A 68-year-old man was admitted to our hospital because of the sudden onset of severe neck pain. He had a history of duodenal ulcer and impaired glucose tolerance, but no history of hypertension. His mother and elder brother had died of cerebrovascular disorders at the ages of >70 years. On admission, the patient had neither headache nor nausea. Brain computed tomography (CT) demonstrated a high-density region within the subarachnoid space (Figure 1), and he was diagnosed as having subarachnoid hemorrhage. Neurologic examination on admission revealed clouding of consciousness with normal orientation, moderate neck stiffness, normal pupillary light reflexes, and no paresis or sensory disturbances. Laboratory data showed no abnormalities of platelet counts and no coagulopathy.

At admission, angiography was performed by direct injection of contrast into both common carotid arteries and by the left retrograde brachial route. Since neither cerebral aneurysm nor any other abnormality (such as arteriovenous malformation) causing subarachnoid hemorrhage was shown on angiography, conservative treatment was instituted. However, early the next morning the patient's level of consciousness had deteriorated into coma and his pupillary light reflexes had become sluggish. Repeat brain CT revealed an increase in the high-density area, ventricular hematoma, and acute hydrocephalus. Recurrent hemorrhage and impending brain edema were also noted. Final diagnosis was cerebral amyloid angiopathy.
herniation due to acutely raised intracranial pressure were diagnosed, and emergency ventricular drainage was performed. The patient's level of consciousness improved approximately 1 hour later, but he remained in a confused state.

On day 6 of hospitalization, repeat right carotid angiography by direct injection was performed, but again no cerebral aneurysm was found. Subsequently, the patient developed a perforated duodenal ulcer and acute renal failure and died on day 13 of hospitalization.

At autopsy, his brain weighed 1,560 g. The entire brain was edematous, and the subarachnoid hematoma was located mainly around the anterior communicating artery. In spite of a rigorous search, we could find no aneurysm anywhere in the cerebral vasculature, including the anterior communicating artery. There was no intracerebral hematoma nor any evidence of arteriovenous malformation. Microscopic studies using routine pathologic staining methods showed no abnormality that could have caused the patient's subarachnoid hemorrhage. A slight thickening of the walls of the small and medium-sized arteries by cosinophilic material was apparent in the cerebral cortex and meninges. Cerebral amyloid angiopathy was suspected.

All slides were stained further with Congo red and modified Bielschowsky's silver stain. Immunohistochemical staining of paraffin-embedded sections was performed by the peroxidase-antiperoxidase method using either a monoclonal antibody against a synthetic peptide (AL1) consisting of residues 8–17 of β protein or a polyclonal antiserum against human cystatin C.15

Congo red stain demonstrated amyloid deposits within the leptomeningeal and parenchymal microvascular walls (Figure 2, inset). The anti–β protein antibody revealed immunoreactive deposits in these vascular walls (Figure 2), while staining with anti-cystatin C gave negative results. Control experiments demonstrated that this staining was abolished by preabsorption of the diluted antiserum with 1 mg/ml AL1 peptide. Arterioles and venules of the cerebral and cerebellar cortices were also affected. As reported previously, pretreatment with 99% formic acid for 10 minutes enhanced the immunoreaction with anti-β protein antibody. Senile plaques were also found in sections stained with either anti-β protein antibody or modified Bielschowsky's silver stain. These plaques were widespread throughout the gray matter of the cerebral cortex, the basal ganglia, the hippocampus, and the brainstem. Few neurofibrillary tangles were seen in any region of the brain.

**Discussion**

In this patient, subarachnoid hemorrhage was associated with cerebral amyloid angiopathy. Neither angiography nor autopsy revealed an aneurysm or any other lesion that might have resulted in subarachnoid hemorrhage. Histopathologic and immunohistochemical studies revealed cerebral amyloid angiopathy.

Biochemical and immunohistochemical studies have identified the presence of a 4-kDa protein (designated β protein) in the amyloid deposits of patients with HCHWA-D and Alzheimer's disease and adults with Down's syndrome. Immunohistochemical studies using antibodies to this protein have demonstrated that cerebral amyloid angiopathy and the amyloid cores of senile plaques share this common amyloid subunit. In some cases of sporadic cerebral amyloid angiopathy, the vascular amyloid is antigenically related to β protein. In patients with HCHWA-I the amyloid is instead formed from a variant of cystatin C.

Cerebral amyloid angiopathy is emphasized as a cause of multiple, recurrent intracerebral hemorrhages in normotensive elderly individuals. Cerebrovascular amyloid deposition usually affects not only the cortical but also the leptomeningeal vessels, but pure subarachnoid or subdural hemorrhage has been seen only rarely in patients with...
cerebral amyloid angiopathy. Recent studies have described several microscopic vascular changes in the brains of patients with cerebral amyloid angiopathy and termed them cerebral amyloid angiopathy–associated vasculopathies. These include “glomerular” formations, mural aneurysmal formation, and “double-barrel” formation of microvessels; the hemorrhages are presumed to result from such pathologic changes. As far as we could establish by examination of the sections, no vasculopathy was apparent in our patient. It has been reported that some cases (5–10%) of subarachnoid hemorrhage have no obvious cause, such as a cerebral aneurysm or an arteriovenous malformation. Although the occurrence of cerebral amyloid angiopathy in any elderly individual simply may be a coincidental finding, our case does suggest that cerebral amyloid angiopathy is one of the etiologic factors in subarachnoid hemorrhage without aneurysm.

To clarify the exact incidence of cerebral amyloid angiopathy among patients with subarachnoid hemorrhage of unknown etiology, we must further investigate many such patients, especially elderly ones. Immunohistochemical techniques using antibodies to either β protein or cystatin C are highly sensitive and specific, and by using these methods we can classify cerebral amyloid angiopathy into two etiologic groups, one related to β protein and the other to cystatin C.

Acknowledgments

Antiserum to cystatin C (AG8206) was kindly provided by Dr. Anders O. Grubb and obtained through Dr. G.G. Glenner.

References

5. Ghiso J, Jeusson O, Frangione B: Amyloid fibrils in hereditary cerebral hemorrhage with amyloidosis of Icelandic type is a variant of y-trace basic protein (cystatin C). Proc Natl Acad Sci USA 1986;83:2974–2978
plaque amyloid fibrils in Alzheimer’s disease with an anti-\( \beta \) protein monoclonal antibody. *Lab Invest* 1987;57:446–449

**KEY WORDS** • amyloid • subarachnoid hemorrhage
Cerebral amyloid angiopathy as a cause of subarachnoid hemorrhage.
T Ohshima, T Endo, H Nukui, S Ikeda, D Allsop and T Onaya

Stroke. 1990;21:480-483
doi: 10.1161/01.STR.21.3.480
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1990 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/21/3/480

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/