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Intracerebral Hemorrhage Caused by Cerebral Amyloid Angiopathy: Radiographic- Pathologic Correlation

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Seven cases of nontraumatic intracerebral hemorrhage due to histologically confirmed cerebral amyloid angiopathy were observed over a period of 2½ years. Initial computed tomographic (CT) scans demonstrated lobar hemorrhages in all but one patient, who had presented with corpus callosum hemorrhage. Superficial location, irregular borders, and surrounding edema were characteristic features. Angiography was performed in three cases. Findings included mass effect (three cases), opercular branch occlusion (one case), and pericallosal irregularity (one case), all in the areas of the hemorrhage. Clinically, none of the patients had a history of prior cerebrovascular disease. Mild hypertension had been present in three patients and dementia in two. These findings suggest that cerebral amyloid angiopathy is not a rare cause of atraumatic lobar hemorrhage, particularly in a normotensive, elderly population.

Several recent clinicopathologic studies [1–4] and case reports [5–10] have described intracerebral hemorrhage as a consequence of cerebral amyloid angiopathy. Most nontraumatic hemorrhages occur in the basal ganglia and thalamus. Those in other locations are usually caused by aneurysms, vascular malformations, neoplasms, and bleeding diatheses [11]. To these may be added cerebral amyloid angiopathy. We report our experience with seven cases of intracerebral hemorrhage associated with histologically proven amyloid angiopathy, illustrating pertinent radiologic and clinical findings.

Materials and Methods

Clinical histories were obtained retrospectively from the medical records and are outlined in table 1. All patients were seen between May 1980 and February 1983. Except for case 1, all presented with the typical clinical features of an acute, massive intracerebral event. None of the patients had a prior stroke or transient ischemic event.

Initial CT scans were obtained with an Ohio-Nuclear Delta 50. Only cases 1, 2, and 7 received contrast enhancement, a 300 ml Renodip infusion. Cerebral angiograms were obtained in cases 1, 6, and 7.

Five of the patients died (cases 1–5), and four had complete postmortem examinations; in case 5, examination was restricted to the brain. Cases 6 and 7 had surgical specimens. The brains were fixed in 15% formalin for at least 2 weeks before sectioning. Microscopic examination was performed in all cases using hematoxylin-eosin, Bodian, Congo red, and thioflavin-T stains.

Results

Computed Tomography

In all cases the initial CT scans demonstrated a large mass lesion with homogeneously high absorption values (about 60–65 H), consistent with a recent hemorrhage (figs. 1–4). All of the hemorrhages were located in the cerebral hemispheres

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TABLE 1: Cerebral Amyloid Angiopathy: Clinical, Radiologic, and Pathologic Findings

Case No. (age, gender)	Clinical Features	CT Findings (date performed after event)	Angiography	Gross Pathology
1 (66, F)	Normotensive; no h/o dementia; 20 kg weight loss over previous year; 3 mo before death had acute confusional state with generalized weakness and nonfocal neurologic exam; thought to have hemorrhage in glioblastoma of CC and treated with 6000 rad (60 Gy); progression to demise	(4 d) High-density lesion in genu and ant part of CC; mild enhancement with contrast infusion but no vascular malformation noted; separate area of low density in ant L frontal lobe; SAH (-), IVH (+)	4 wk after initial event and before radiation therapy, selective R and L common carotid art injections; pericallosal branch of R ant cer art showed marked irregularity; no tumor blush or vascular malformation	Large organizing hemorrhage in genu and ant part of CC with small focal rupture into R lat ventricle and SAS; smaller old hemorrhages in left frontal lobe and left insular cortex; no tumor present
2 (67, F)	Normotensive; 4 mo h/o dementia	(same day) Large hemorrhage within R frontoparietal centrum semiovale with surrounding low density and mass effect; SAH (-), IVH (+)	No angiography	Recent large hemorrhage within R post frontal and ant parietal centrum semiovale with extension into vent and SAS above post frontal cortex
3 (74, M)	Hypertensive; no h/o dementia; myocardial infarction 2 wk before event for which he was placed on Coumadin; prothrombin time reversed before clot evacuation; no excessive bleeding during surgery	(same day) L temporooccipital hemorrhage with surrounding area of low density and mass effect; small L temporal subdural; SAH (+), IVH (-)	No angiography	Recent large hemorrhage destroying entire L inf temporal and occipital lobes; extension into SAS but no IVH
4 (73, M)	Normotensive; 8 year h/o dementia	(2 d) L parietal lobe hemorrhage with mass effect and surrounding low density; SAH (+), IVH (+)	No angiography	Large wedge-shaped hemorrhage in L parietal lobe extending from cortical surface medially into lat vent; second hemorrhage in white matter of R middle temporal gyrus
5 (84, F)	Mild hypertension; no h/o dementia	(same day) Massive hemorrhage in R parietal lobe with mass effect and surrounding ring of low density; SAH (+), IVH (+)	No angiography	Recent massive hemorrhage into R sup parietal lobe with extension into adjacent SAS and rupture into post body of R vent with diffuse IVH
6 (62, F)	Mildly hypertensive; no h/o dementia; taken to neurosurgery same day for evacuation of hemorrhage	(same day) Large R parietooccipital hemorrhage extending from cortex to edge of vent, marked mass effect and surrounding band of low density; SAH (-), IVH (-)	1 wk after event selective R and L common carotid injections showing post-surgical effect and mild residual mass effect; no specific vascular irregularity	Surgical specimen
7 (74, F)	Normotensive; no h/o dementia; transferred from outlying hospital 5 wk after initial event; second event prompted neurosurgical evacuation of clot	(5 wk) Large R frontal hemorrhage extending from cortex to lat vent; surrounding low density; SAH (-), IVH (-)	1 day after CT, selective R and L common carotid injections showing mass effect and occlusion of frontoopercular branch of R middle cer art	Surgical specimen; large organizing hematoma; adjacent parenchyma shows organizing infarction

Note—wk = week; h/o = history of; CC = corpus callosum; d = day; R = right; L = left; mo = month; ant = anterior; cer = cerebral; art = artery; lat = lateral; SAS = subarachnoid space; sup = superior; post = posterior; inf = inferior; vent = ventricle; SAH = subarachnoid hemorrhage; IVH = intraventricular hemorrhage; + = present; - = absent.

outside the deep gray-matter structures; six were classified as lobar, and one was located in the corpus callosum. Extension of the hemorrhage through the superficial cortex was noted in three cases. Although some degree of subarachnoid extension of hemorrhage was noted pathologically in all cases, it could not be detected reliably by CT in four cases.

Ventricular extension was observed at postmortem examination in four cases and was evident on CT in the same four cases. Except for the corpus callosum hemorrhage (case 1), all of the lobar hemorrhages had irregular borders and were surrounded by a variable band of low density (20 H). Contrast infusion was performed in three patients (cases 1, 2, and 7),

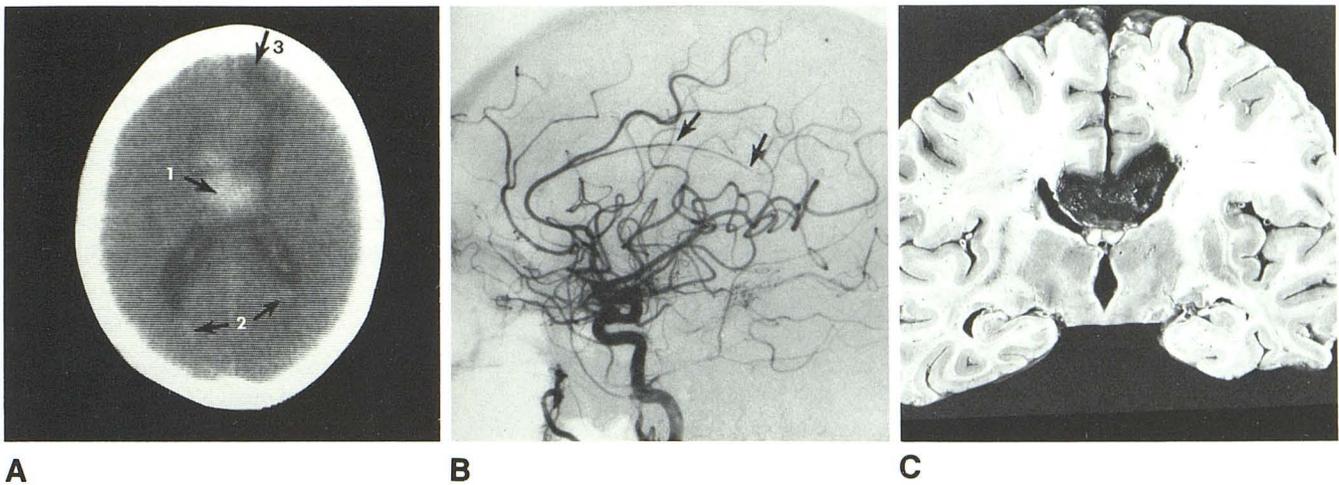


Fig. 1.—Case 1. Corpus callosum hemorrhage. **A**, Unenhanced CT scan. Acute hemorrhage in corpus callosum (arrow 1) with small amount of blood in occipital horns of lateral ventricles (arrows 2). Small separate region of low attenuation in left frontal lobe (arrow 3), possibly due to old hemorrhage or infarct. **B**, Right carotid angiogram. Narrowing of right pericallosal artery (arrows). **C**, Large hemorrhage in corpus callosum.

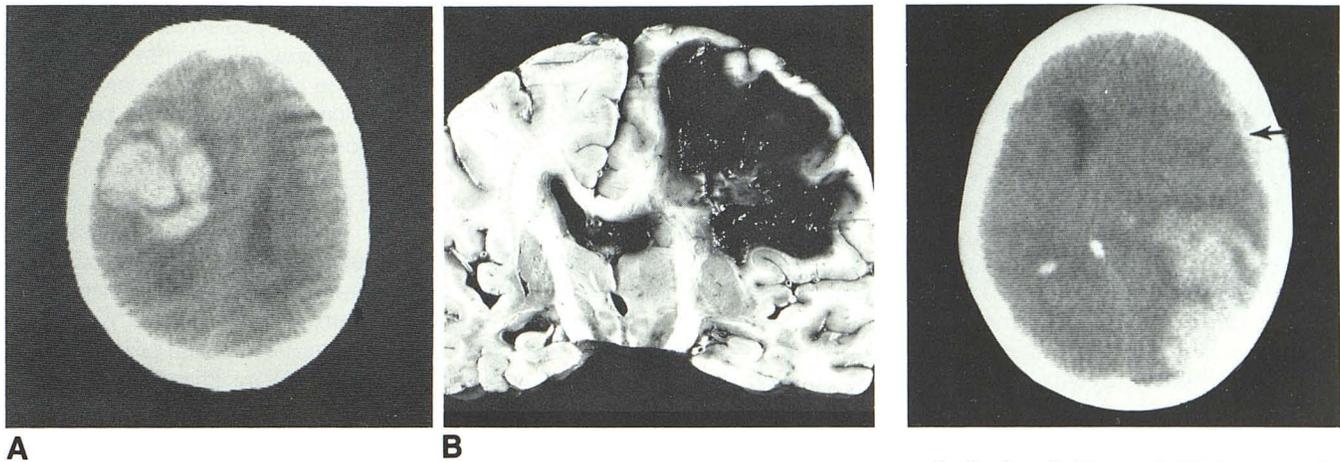


Fig. 2.—Case 2. Frontoparietal hemorrhage. **A**, Unenhanced CT scan. Irregular hemorrhage in right frontoparietal centrum semiovale with surrounding edema. **B**, Corresponding macroscopic section. Note blood in right lateral ventricle.

Fig. 3.—Case 3. Temporal and occipital lobe hemorrhage. Unenhanced CT scan. Hemorrhage in left temporal and occipital lobes with surrounding edema. Small separate temporal subdural hematoma (arrow).

which showed slight irregular enhancement at the periphery of the hemorrhage in cases 1 and 7 (fig. 4A).

Angiography

Selective right and left common carotid arteriograms were obtained in three patients (cases 1, 6, and 7) at intervals of 1–4 weeks after the initial CT scans. As expected, all confirmed the presence of an avascular mass. In addition, in case 1 the pericallosal branch of the right anterior cerebral artery adjacent to the corpus callosum hemorrhage showed marked irregularity in caliber (fig. 1B). In case 7, a frontoopercular branch of the right middle cerebral artery was occluded in the area of the hemorrhage (fig. 4B). No intrinsic vascular abnormalities were observed in case 6.

Pathology

The gross neuropathologic findings in cases 1–5 are summarized in table 1. The large hemorrhages observed on CT were documented in every case in which a postmortem examination was performed. Contiguous zones of organizing infarction were also observed with the hemorrhages seen in cases 2 and 7. Smaller hemorrhages, not seen on CT, were found in cases 1 and 4. Scattered cortical “ball” hemorrhages (1–3 mm) and multiple small infarcts were also present in cases 1 and 2.

Microscopic examination in all cases showed medium-sized and small arteries and arterioles within the leptomeninges and cerebral cortex which had irregularly thickened walls replaced by an amorphous pink material (fig. 5A). The amyloid nature

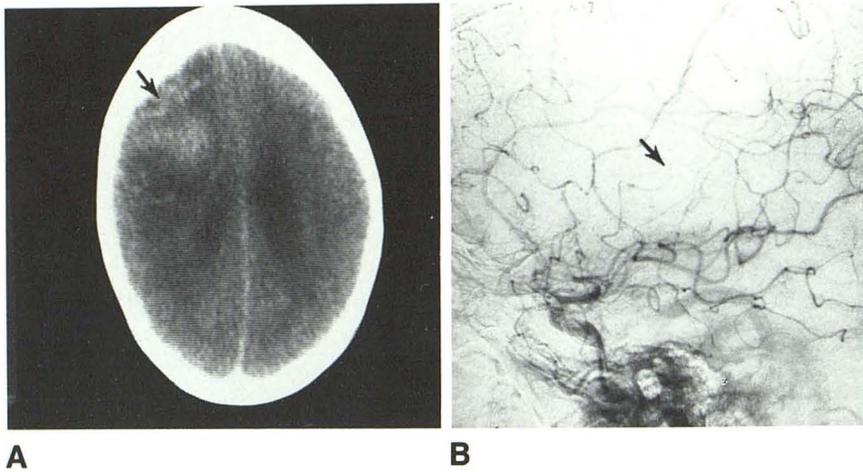


Fig. 4.—Case 7. Angiographic features. **A**, Enhanced CT scan. Faint linear areas of enhancement (*arrow*). **B**, Right carotid angiogram. Occluded frontal opercular branch of right middle cerebral artery (*arrow*).

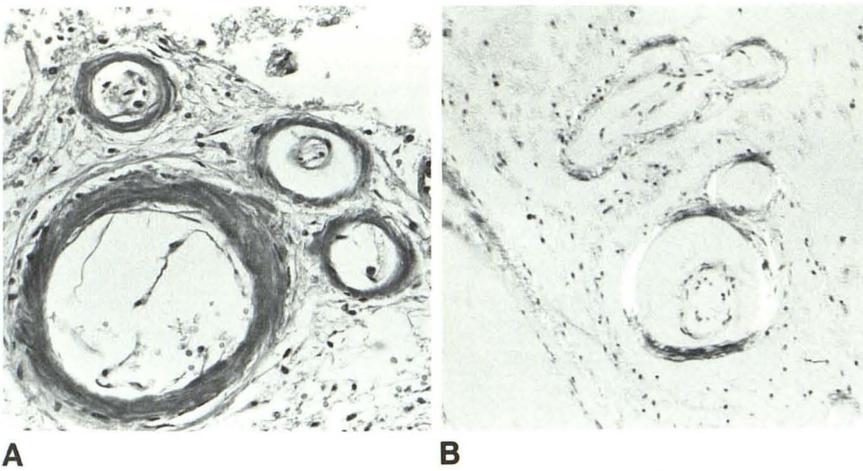


Fig. 5.—Case 5. Histology. **A**, Small meningeal arteries with irregularly thickened walls replaced by amyloid. H and E $\times 63$ (original magnification). **B**, Congo red-stained section viewed with polarized light showing characteristic yellow green birefringence of amyloid in vessel walls. Original magnification $\times 25$.

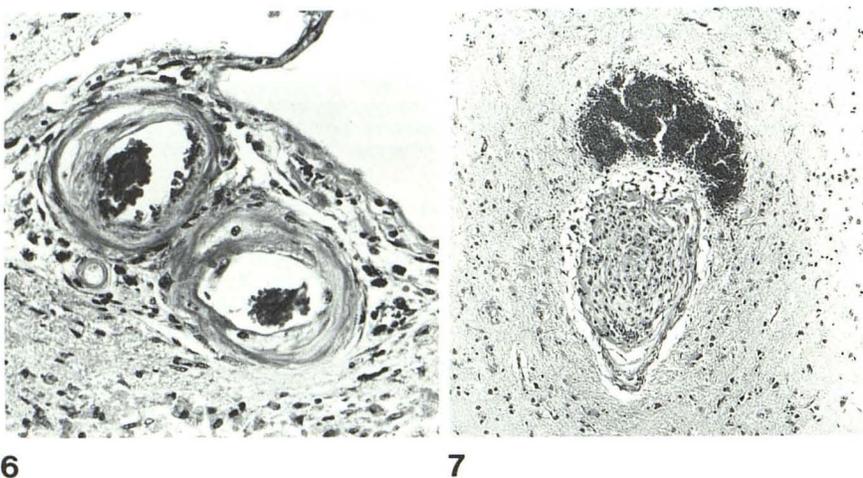


Fig. 6.—Case 1. Histology. Amyloid-containing vessels surrounded by hemosiderin-laden macrophages. H and E $\times 63$ (original magnification).

Fig. 7.—Case 2. Histology. Microaneurysm with recent hemorrhage in cerebral cortex. H and E $\times 25$ (original magnification).

of this material was confirmed by the observation of green yellow birefringence after Congo red staining and polarization (fig. 5B), and by fluorescence of thioflavin-T sections viewed with ultraviolet light. Evidence that the bleeding was in fact

due to the angiopathy was suggested by the observation of amyloid-containing vessels close to the hemorrhages. Isolated amyloid-containing vessels showing heme-staining of their walls, which were surrounded by hemosiderin-laden macro-

phages, were indicative of prior extravasation (fig. 6). Some of these vessels also showed severe degenerative changes, including marked intimal fibrosis with luminal narrowing or occlusion, fibrinoid change and microaneurysm formation, the latter sometimes associated with evidence of recent or old hemorrhage (fig. 7). Careful examination of the hemorrhages in every case disclosed no evidence of a neoplasm or vascular malformation. No amyloid was found in organs other than the brain in those cases that had complete autopsies.

Discussion

The major types of brain hemorrhage resulting from intrinsic vascular disease are deep hemorrhages due to hypertension-induced degenerative changes in small penetrating vessels, subarachnoid/intraparenchymal hemorrhages due to ruptured berry aneurysms, and hemorrhage from arteriovenous malformations. Secondary hemorrhages are most often due to trauma or bleeding diatheses, but may also occur with tumors, infarcts, and occasionally necrotizing lesions such as herpes simplex encephalitis.

Cerebral amyloid angiopathy has been considered an unusual and relatively infrequent cause of primary intracerebral hemorrhage. That we observed seven cases within a relatively short period of time (2½ years) suggests that this condition might be more common than generally appreciated. Jellinger [1] studied 400 consecutive nontraumatic cerebral hemorrhages and found only 15 cases associated with amyloid angiopathy; eight of these were massive hemorrhages (2% of series). Okazaki et al. [2] found only nine cases of massive intracerebral hemorrhage due to amyloid angiopathy in a review covering 10 years. Ropper and Davis [11], in their recent review of lobar cerebral hemorrhages, found that only half of their 26 cases had an identifiable cause, and amyloid angiopathy was not noted in any of their four autopsied cases.

Amyloid angiopathy principally affects the elderly and tends to increase in incidence with advancing age. The reported incidence varies from 5% to 23% in individuals over age 60 [12, 13], and may range up to greater than 60% in patients over age 80 [13]. The amyloid infiltration predominantly involves medium-sized and small arteries and arterioles in the leptomeninges and cerebral cortex, although capillaries and veins can be affected also. Larger arterial branches are almost never involved. Early involvement tends to be segmental and principally involves the adventitia and outer media, but eventually the amyloid may replace the entire wall, which may then undergo secondary "degenerative" changes, including intimal fibrosis with luminal stenosis or occlusion, fibrinoid necrosis, and microaneurysm formation [2]. The amyloid within the vessel walls presumably leads to their increased fragility and susceptibility to rupture, which may occur spontaneously or possibly in conjunction with minor head trauma, transient blood pressure elevation, anticoagulation, or surgical manipulation. Amyloid angiopathy seems to have a slight predilection for the temporal, parietal, and occipital lobes, especially the calcarine region. In more severe cases, virtually the entire cerebral cortex and leptomeninges can be involved. We have also observed cerebellar involvement in most of our cases,

but the vessels in the white matter, deep gray nuclei, and brainstem tend to be spared. The predominantly lobar and superficial location of hemorrhages correlates well with the anatomic distribution of the amyloid-containing vessels in the brain.

Patients who present with massive hemorrhage related to amyloid angiopathy may have a history of progressive dementia or cerebrovascular disease, including both ischemic and hemorrhagic lesions [2]. In most of our own cases there was no history of prior neurologic disease. Hypertension is likewise not a consistent clinical finding [2]. There is usually no family history of cerebrovascular disease, although a hereditary form of amyloid angiopathy associated with cerebral hemorrhage has been described in several Icelandic families [14]. In these patients the disease usually manifests itself at an early age, as contrasted with the sporadic form occurring in the elderly.

Large, acute intracerebral hemorrhages due to amyloid angiopathy can be detected easily by standard unenhanced CT. Although their CT characteristics alone do not allow a specific histologic diagnosis to be made [15], several features should be considered. The hemorrhages tend to be lobar and superficial in location in contrast to typical hypertensive bleeds, which most often occur in the deep gray-matter structures. Because of their superficial location they frequently rupture outward through the cortex into the subarachnoid space. Although small amounts of subarachnoid hemorrhage may be difficult to detect by CT, subarachnoid extension may be surmised if the hematoma extends to the inner table of the skull [10]. In our series intraventricular extension occurred in four of the seven cases. The corpus callosum hemorrhage represents an unusual site of bleeding even for amyloid angiopathy, but it underscores the need to consider the disease in the differential diagnosis of any cerebral hemorrhage occurring in an atypical location. The presence of multiple hemorrhages of either the same or different ages [9], as well as the simultaneous presence of both superficial hemorrhages and small cortical infarcts, should also raise the suspicion of amyloid angiopathy.

The angiographic findings in intracerebral hemorrhage secondary to amyloid angiopathy have not been well described in the literature. In our series, nonspecific intrinsic vascular abnormalities were observed in two of the three cases in which arteriography was performed. In the corpus callosum hemorrhage (case 1), arteriography showed tapering of the pericallosal branch of the anterior cerebral artery dorsal to the hematoma. In case 7 an opercular branch was occluded in the area of hemorrhage. Since the disease affects the small vessels in the leptomeninges and cortex, arteriography may not show the actual site of vascular involvement by amyloid.

Amyloid angiopathy is becoming an increasingly recognized cause of intracerebral hemorrhage, especially when occurring in an atypical location in a normotensive, elderly individual. CT may demonstrate the presence of one or more hemorrhages, usually lobar and superficial in location and often associated with a variable amount of subarachnoid hemorrhage. At present amyloid angiopathy can only be diagnosed by histologic evaluation of tissue removed at surgery or

autopsy. Because of this, it is important for the neurosurgeon to be alerted to the possibility of the disease, so that when a hematoma is evacuated, a representative section of adjacent leptomeninges or cortex can be sampled for pathologic confirmation.

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