Cerebral Amyloid Angiopathy: Incidence and Complications in the Aging Brain

I. Cerebral Hemorrhage

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SUMMARY The clinical and pathologic findings in eleven patients with fatal cerebral hemorrhages related to cerebral amyloid angiopathy (CAA) are described. The hemorrhages were bihemispheric, though not necessarily of simultaneous onset in four patients, and favoured the fronto-parietal cortex and white matter in ten patients. Dissection into the subarachnoid space was common. Cerebrovascular lesions or cardiomegaly related to hypertension coexisted with those of CAA in three cases. Seven patients were not demented prior to the ictus. Ten of eleven brains contained abundant senile plaques and/or neurofibrillary tangles, whether or not the patient had been clinically demented. In the elderly, CAA is an important etiologic consideration for cerebral hemorrhage, especially if the hemorrhage occurs in a peripheral location in the brain and is superimposed on a history of dementia.

Although the pathogenesis of cerebral amyloid angiopathy (CAA) is obscure, it is associated with recognized clinicopathological states — dementia of the Alzheimer type, nontraumatic nonhypertensive intracerebral hemorrhage in older patients, a familial Icelandic syndrome of intracerebral hemorrhage at an early age, a variety of unusual degenerative and demyelinating diseases, and late post-irradiation necrosis of the brain. The first two associations, dementia and hemorrhage, are clinically the most important. Jellinger, in a large series, found CAA as a cause of cerebral hemorrhage in 2% of patients, while Lee and Stemmerman found CAA in 9.3% of cases of intracerebral hemorrhage.

Eleven patients over 60 years of age, in whom massive fatal cerebral hemorrhage was associated with severe CAA are reported. In eight patients, there was neither clinical nor autopsy documentation of hypertensive cardiovascular disease, and no other structural or systemic finding could explain the hemorrhage. Three showed evidence of hypertensive cardiovascular disease or arteriosclerotic angiopathy in the brain in addition to CAA.

Results

Report of Cases (see table I)

Case 1

A 67-year-old man presented with a 2-day history of vomiting and mental confusion of sudden onset. Examination showed an elderly, alert man in mild distress, unable to give a history. The blood pressure was 130/80, pulse rate 60/minute and regular respirations. He was disoriented to time, recognized he was in hos-
Table 1  CAA-Related Cerebral Hemorrhages

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Sex</th>
<th>Dementia at onset</th>
<th>Clinical presentation</th>
<th>Location of hemorrhage(s)</th>
<th>Associated pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67 M</td>
<td>no</td>
<td>acute confusional state</td>
<td>r frontal-parietal, l frontal (old, evacuated)</td>
<td>arteriosclerosis (minimal), old and recent cerebral infarcts with small vessel occlusions, SP’s, NFT’s</td>
</tr>
<tr>
<td>2</td>
<td>84 F</td>
<td>no</td>
<td>unconscious and right hemiparesis</td>
<td>l frontal-parietal</td>
<td>generalized and coronary atherosclerosis, SP’s</td>
</tr>
<tr>
<td>3</td>
<td>79 F</td>
<td>mild</td>
<td>acute confusional state</td>
<td>bilateral fronto-parietal</td>
<td>recent L frontal infarct, SP’s, NFT’s, old myocardial infarct, cardiomegaly, severe generalized and coronary atherosclerosis, small old cerebral infarcts, plaque jaune, SP’s, NFT’s</td>
</tr>
<tr>
<td>4</td>
<td>87 F</td>
<td>yes</td>
<td>head injury; seizures</td>
<td>r occipital</td>
<td>anoxic encephalopathy, no SP’s, no NFT’s</td>
</tr>
<tr>
<td>5</td>
<td>61 F</td>
<td>no</td>
<td>headache, left homonymous hemianopsia</td>
<td>r occipital</td>
<td>cardiomegaly, athero- and arteriosclerosis, SP’s, NFT’s</td>
</tr>
<tr>
<td>6</td>
<td>73 M</td>
<td>no</td>
<td>confusion</td>
<td>l frontal-parietal</td>
<td>old subarachnoid hemorrhage, SP’s, old cerebral infarcts, SP’s, NFT’s</td>
</tr>
<tr>
<td>7</td>
<td>79 M</td>
<td>no</td>
<td>left hemiparesis</td>
<td>r frontal</td>
<td>SP’s, NFT’s, small old cerebral infarcts, SP’s, NFT’s, few, old rheumatic mitral valvulitis</td>
</tr>
<tr>
<td>8</td>
<td>69 F</td>
<td>no</td>
<td>coma</td>
<td>r frontal-parietal</td>
<td>SP’s, NFT’s, few</td>
</tr>
<tr>
<td>9</td>
<td>80 F</td>
<td>yes</td>
<td>left hemiparesis</td>
<td>r frontal-parietal</td>
<td>NFT’s few</td>
</tr>
<tr>
<td>10</td>
<td>78 F</td>
<td>no</td>
<td>coma</td>
<td>r frontal-lobe</td>
<td>NFT’s few</td>
</tr>
<tr>
<td>11</td>
<td>70 F</td>
<td>no</td>
<td>coma</td>
<td>r frontal-parietal (acute), l parietal (recent), r frontal (old), l occipital (old), r occipital (old)</td>
<td>NFT’s few</td>
</tr>
</tbody>
</table>

1 = left; r = right; SP = senile plaque; NFT = neurofibrillary tangle; F = female; M = male.

Likely to the occipital pole of the lateral ventricle. The hemorrhage extended to the cortical surface but had not broken through the pia. Medially, it went as far as the sagittal sulcus and into the right side of the corpus callosum. In the right frontal pole, there were two small separate cystic areas margined by yellow discoloured tissue. The site of previous surgery in the left frontal pole was identified as a parasagittal softening with yellow discolouration. There were multiple old and recent small bland infarcts (fig. 2) on virtually every slice of cerebrum examined. The brain stem, cerebellum and spinal cord were normal.

Histologic sections revealed that numerous small arteries in the leptomeninges and cortex were thickened with an acellular hyaline material that stained positively with the periodic acid-Schiff (PAS) stain.

![Figure 1](http://stroke.ahajournals.org/)

**Figure 1.** Case 1. Coronal section of the brain at the level of the subthalamic nucleus. Large intracerebral hematoma in right centrum semiovale extends to pia and corpus callosum. A small old cortical infarct is present in the left superior parietal cortex (arrow).
and showed apple-green birefringence with the polarized Congo red stain, characteristic features of CAA (fig. 2). CAA was present throughout all areas of cortex, including regions around the recent hemorrhage. Around some of the vessels were small hemorrhagic and bland infarcts of various ages, a few showing hemosiderin-laden macrophages, others with cystic change with reactive gliosis (fig. 2). Many vessels had undergone thrombosis and recanalization.

Numerous senile plaques were noted in the neocortex. The hippocampi contained abundant senile plaques and neurofibrillary tangles, diagnostic of Alzheimer’s disease. A single Charcot-Bouchard aneurysm was seen in white matter in the right medial parieto-occipital region.

Case 2

An 84-year-old woman was well until she was found unconscious. She had been a mild maturity-onset diabetic, with no history of hypertension or heart disease. The blood pressure was 180/70, pulse 64/minute, she was obtunded but responsive to pain. A right homonymous hemianopsia was found, and eyes and head were deviated to the left. Right hemiparesis was present, greater in the leg than arm and the right toe was upgoing. Skull x-ray and ultrasound confirmed significant shift of midline structures to the right.

On the second hospital day the left pupil was dilated and the left toe was upgoing. Supportive care was given, but the patient developed respiratory distress and died 11 days after the onset of symptoms.

Pathology. Autopsy findings included multiple pulmonary abscesses and bronchopneumonia, moderate generalized and coronary atherosclerosis, right hydronephrosis and hydroureter, and a nodular goiter. The heart weight was 315 g, and the weight of each kidney 125 g.

The fresh brain weighed 1,450 g. Externally, there was subarachnoid hemorrhage, concentrated over the left frontal cortex, and posterior to this the brain was flattened and very soft. The basal arteries were patent but showed marked atherosclerosis. There was left uncal herniation. Coronal slices revealed a large left fronto-parietal hematoma (fig. 3). This had caused compression of the left lateral ventricle, with subfalcial herniation of the cingulate gyrus and a pronounced shift of all midline structure to the right. The hemorrhage itself occupied the centrum semiovale and communicated with the subarachnoid space. It extended from the frontal pole to behind the level of the lateral
geniculate nucleus. There was a recent bland infarct in the adjacent left lateral parieto-occipital cortex and white matter. In the left superior and mesial frontoparietal cortex and white matter, there was an older bland infarct. There was a hemorrhagic infarct in the left posterior cerebral artery distribution. The right cerebral hemisphere was unremarkable but the right lateral ventricle was dilated. The midbrain, pons, medulla, and cerebellum were normal.

Small cortical arteries adjacent to the left frontal hematoma and elsewhere showed changes of pronounced CAA. Sections of the left basal ganglia and thalamus showed the edge of the large left hemisphere infarct associated with the hemorrhage but no evidence of arteriosclerotic change or Charcot-Bouchard aneurysms. Throughout all areas of neocortex and hippocampi, there were many senile plaques indicative of Alzheimer’s disease.

**Case 3**

A 79-year-old woman, who had been living by herself, had the abrupt onset of confusion and urinary incontinence. She was somewhat forgetful over the previous year. She had been briefly treated for mild hypertension years earlier.

Blood pressure was 140/62 and pulse 94/minute with a normal general physical examination. She was alert, had poor recent memory, mild confusion, a short attention span, and no insight. A slight resting tremor of the hands was noted, and cogwheeling was present in the upper extremities. The remainder of the neurologic examination was normal. After 24 hours she was better oriented and walked without assistance. An isotope brain scan was normal. Chest x-ray showed a normal cardiac silhouette, but the electrocardiogram showed changes suggestive of left ventricular hypertrophy.

On HD-3, she complained of headache and became totally disoriented. A lumbar puncture demonstrated xanthochromic cerebrospinal fluid, with 71 white blood cells/mm$^3$, 800 erythrocytes/mm$^3$, a protein of 88 mg/dl and glucose of 62 mg/dl. Nuchal rigidity was present on HD-4. Penicillin therapy was started. There was no definite weakness or reflex asymmetry. She had word-finding difficulty, inappropriate responses and perseverative speech. On HD-9 a repeat isotope brain scan demonstrated a ring-like lesion in the left frontal pole. A CT scan showed increased density in the left frontal lobe and displacement of the frontal horn of the left lateral ventricle. On HD-10, she was confused and aphasic, with slight right facial flattening. She experienced increasing headache and her level of consciousness deteriorated. A left hemiparesis was noted and the eyes came to be deviated to the right. The right pupil became dilated and fixed. A strong suspicion of brain tumor resulted in a burr hole biopsy from the left frontal lobe. There was necrotic, hemorrhagic brain and senile plaques and Congo-red positive vessels. Postoperatively, she was unresponsive with midposition, fixed pupils and she died the next day.

**Pathology.** Autopsy was restricted to the brain. External examination and coronal slices revealed massive swelling and distension of the right frontal lobe, with abundant overlying subarachnoid blood. A large intracerebral hemorrhage in the right hemisphere with dissection into the subarachnoid space produced cingulate and uncal herniation and midline shift. The hemorrhage extended to the level of the lateral geniculate body. The left frontal biopsy site was identified 1.5 cm behind the frontal pole with an area of infarction lateral to the putamen. There was marked bilateral cerebellar tonsillar herniation. Basal arteries showed patchy atherosclerosis only.

The midbrain demonstrated a secondary brain stem hemorrhage on the left side (separate from the cerebral hemorrhages) with destruction of the upper aqueduct, posterior thalamus, and upper pontine tegmentum. This hemorrhage had dissected into the left cerebellar hemisphere, the basis pontis and the fourth ventricle. Histologic sections of the left inferior frontal lobe showed a recent infarct in the white matter, containing abundant macrophages, some with hemosiderin, surrounded by a few reactive astrocytes and neovascularization. Adjacent to this infarct was fresh hemorrhage surrounded by a few polymorphonuclear leukocytes (biopsy site). The subarachnoid space of the right frontal lobe showed evidence of older hemorrhage, with hemosiderin-laden macrophages, hematoxidin, and associated fibroblast proliferation. There were no hypertensive vascular changes in the basal ganglia or elsewhere.

In all areas of neocortex and overlying leptomeninges, there was severe CAA. Some of the affected vessels showed stenosis or occlusion. Sections of cerebellum showed CAA both in the molecular layer and adjacent leptomeninges. Numerous senile plaques were present, together with an occasional neurofibrillary tangle. The hippocampi showed changes of Alzheimer’s disease with neuron loss, abundant senile

**FIGURE 3.** Coronal sections of the brain from 4 cm behind frontal pole (A) to level of the mammillary bodies (D). Large left fronto-parietal hematoma with shift to right of midline structures. Blood extends into subarachnoid space.
plaques, neurons with granulovacular degeneration or neurofibrillary tangles and Hirano bodies.

Case 4
An 87-year-old woman, a nursing home resident because of dementia was admitted to hospital after a fall. She was unresponsive with conjugate eye deviation to the right, and had shifting focal seizures. Pupils were equally reactive, respirations were spontaneous and regular. Tendon reflexes were brisk, moe so on the right, and both toes were upgoing. Blood pressure was 120/70, pulse 60/minute and regular. She had an occipital hematoma. Anticonvulsants were administered. Over 24 hours, she deteriorated, with frequent decerebrate posturing and little response to pain. An electrocardiogram was suggestive of an acute subendocardial infarct. She developed a urinary tract infection, and died seven days after admission.

Pathology. General autopsy findings included atherosclerosis, complete occlusion of the right coronary artery with an old infarct of the posterior wall of the left ventricle, cardiomegaly (650 g) with left ventricular hypertrophy, arteriolonephrosclerosis (left kidney weighed 95 g, right 160 g), and pulmonary thromboembolism (with infarction) to the right lower lobe.

The brain weighed 1,390 g, there was bilateral uncalgrooving and cerebellar tonsillar herniation. An old hemorrhagic contusion (plaque jaune) was present on the undersurface of the right temporal lobe. Both frontal and parietal lobes were softened and hemorrhagic, with blood in the subarachnoid space. There was severe patchy atherosclerosis of the basal vessels but all were patent.

Coronal cerebral slices disclosed large intraparenchymal hemorrhages in both anterior superior frontal lobes, extending from the plane of the genu of corpus callosum posterior so far as the pulvinar. The hematoma were in the centrum semi-ovale on each side, and extended into the subarachnoid space at several places. Small adjacent satellite hemorrhages were seen in the cortex and white matter. The left lateral ventricle was compressed and distorted. Sections of brain stem and cerebellum were normal.

Both superior frontal lobes disclosed thickening and fibrosis of the leptomeninges with focal old subarachnoid hemorrhage, and prominent thickening of leptomeningeal blood vessels (Congo-red positive). Around the intraparenchymal hematomas were many Congo positive vessels. An occasional vessel showed the appearance of a lumen within a lumen. CAA was found in most other areas of neocortex, which furthermore showed narrowing of the cortical ribbon, patchy loss of neurons, and many scattered micro-infarcts. In the right anterior frontal region, an older infarct affecting the cortex and white matter of several gyri was seen. An old cystic infarct in the left anterior thalamus extended into the massa intermedia and mammiolithalamic tracts and shrinkage of the left mammillary body was seen. Numerous senile plaques and neurofibrillary tangles were seen in the cortex and in both hippocampi.

Case 5
A 61-year-old woman was in good health until she experienced a sudden severe frontal headache. She was blind for a few minutes and that evening experienced neck stiffness, nausea, and vomiting. The symptoms persisted and she was brought to the emergency department the following day. Blood pressure was 160/90 and physical examination was normal. She was drowsy, oriented, had a left homonymous hemianopsia, left arm drift, mild left-sided hyperreflexia inattention to the left, and the left toe was upgoing. Meningismus was present. Chest x-ray and electrocardiogram were normal.

Cerebral angiograms disclosed a right occipital mass. She was taken to surgery where a right occipital blood clot, amounting to approximately 20 ml, and situated 1 to 2 cm deep to the cortex, was excised. Blood vessels in the adjacent brain were prominent, suggesting the possibility of an arteriovenous malformation. The resected tissue included a small amount of neuraltissue with acute inflammation and many blood vessels with hyaline thickening of their walls, but no arteriovenous malformation. Postoperatively she was no better. Repeat craniotomy disclosed reaccumulated blood in the right occipital lobe. A portion of the occipital pole was resected. Again, subarachnoid arteries and veins were large and prominent, and many were thickened with hyalinized walls, but a definite arteriovenous malformation was not seen. Brain tissue was hemorrhagic and necrotic. Small arteries in the cortex had thickened Congo positive vessels.

Postoperatively she deteriorated and died 9 days after the onset of her illness.

Pathology. Autopsy restricted to the brain showed swelling especially the right hemisphere, with bilateral uncalgrooving and cerebellar tonsillar herniation. The right medial occipital lobe contained soft friable necrotic tissue and a small amount of clotted blood. The inferior and medial portions of both temporal and occipital lobes were soft and friable. Basal vessels were normal, as were the venous sinuses. Coronal cerebral slices showed right to left shift, and an extensive hemorrhagic infarct in the right posterior cerebral artery territory. There was a less extensive hemorrhagic infarct in the left posterior cerebral artery territory. Secondary midbrain and pontine hemorrhages were observed.

The frontal cortex showed recent cortical infarction in layers 3 to 6, and scattered microhemorrhages. Small cortical and leptomeningeal blood vessels showed CAA which was more prominent in the occipital lobes. The hippocampi showed extensive acute ischemic neurons. Scattered micro-abscesses were present in the temporal and occipital lobes.

The right occipital cortex and white matter revealed almost total infarction of varying ages, with foci of
macrophages infiltration and capillary proliferation. The number of small blood vessels was increased posteriorly, and many had Congo positive walls; an arteriovenous malformation was not demonstrated. Some vessels were occluded with thrombus. There were no arteriosclerotic vascular changes. Special stains failed to show senile plaques or neurofibrillary tangles in any area of the brain.

Case 6

A 73-year-old man who lived alone in a rooming house was admitted with abdominal pain and hematemesis of one to two weeks' duration. He was dishevelled and disoriented to time and place. He had normal blood pressure and tachycardia. He had no focal neurologic findings other than diminished perception of all sensory modalities below the knees, and absent ankle jerks. He was managed with supportive care, nasogastric suction, and librium for alcohol withdrawal. Eight days after admission he was "more oriented and communicative" though his speech was slurred and he was periodically more confused and restless thought to be hepatic encephalopathy. X-ray studies showed a large gastric ulcer. He became stuporous on HD-14 and had generalized rigidity. Pneumonia, a urinary tract infection, and thrombocytosis supervened. An isotope brain scan was normal on HD-20.

Two months later he complained of a severe headache, required periodic nasogastric suction. Three months after admission, a vagotomy and gastrectomy were performed. Four days postoperatively he had a convulsion. Seven days postoperatively, he eviscerated through the surgical incision and this was repaired. He developed jaundice and hepatic failure. After 3½ months in hospital, he suddenly lapsed into coma and died 24 hours later.

Pathology. General autopsy disclosed mild atherosclerosis, an acute left upper lobe bronchopneumonia with acute pulmonary edema, and a fatty liver with suppurative cholangitis. The heart weighed 458 g, with a normal left ventricular wall thickness. The left kidney weighed 232 g, the right 221 g.

The brain weighed 1,440 g, and the left hemisphere was severely edematous and necrotic. There was subarachnoid blood at the base. Branches of the circle of Willis showed patchy non-occlusive atheroma. Bi-lateral uncal and cerebellar tonsillar herniation were noted. Coronal sections showed a large hematoma in the left fronto-parietal regions extending from the level of the genu of corpus callosum to a level of the cerebral aqueduct. The hemorrhage communicated with the subarachnoid space at the level of the optic chiasm, and extended into the ventricular system, which was filled with blood. Brain tissue around the hematoma was necrotic, with satellite hemorrhages. The brain stem contained secondary hemorrhages, the cerebel-lum showed slight atrophy of the superior vermis.

Atherosclerosis and arteriolosclerosis of cerebral and basal ganglia vessels were seen. Other small and medium-sized arteries demonstrated CAA. Some vessels showed fibrinoid necrosis with small intraluminal thrombi. An occasional vessel showed combined changes of amyloid and fibrinoid degeneration.

Abundant senile plaques were seen in the cortex, and the hippocampi showed changes of Alzheimer's disease with severe neuron loss, many cells with granulovacular degeneration and neurofibrillary tangles, as well as multiple Hirano bodies.

Case 7

A 79-year-old retired man was admitted to hospital because of the sudden onset of left sided weakness, arm greater than leg. His blood pressure was 160/105 and he was oriented with normal mentation. He had left facial weakness, flaccid left hemiplegia and a left upgoing toe. On HD-4, he developed respiratory distress and fever, he was treated for pneumonia with antibiotics. His level of consciousness deteriorated, his eyes maintained deviation to the right. He improved after a few days but died suddenly on HD-9.

Pathology. Autopsy showed generalized and coronary atherosclerosis with a heart weight of 462 g, left ventricular wall thickness of 15 mm. The kidneys weighed 114 and 127 g. He had bronchopneumonia. The brain weighed 1,345 g and showed no atherosclerosis and only mild right uncal herniation. The right frontal lobe was swollen and there was overlying subarachnoid hemorrhage. Coronal sections of the cerebral hemispheres showed a large hematoma on the right, predominantly in white matter but extending, in places, to the subarachnoid space. The hematoma extended from anterior to the genu of corpus callosum, posteriorly to the level of the mammillary bodies. There was minimal subfalcine herniation of the right cingulate gyrus and blunting of the right lateral ventricle. Brain stem sections were normal.

From the vicinity of the hematoma there were many small cortical and meningeal blood vessels with CAA. Some vessels contained fibrin thrombi. The subarachnoid space contained hemosiderin-laden macrophages with fibroblast proliferation, suggestive of older hemorrhage.

Sections from other areas of cortex showed focal, though less severe CAA than around the hematoma. In the right frontal lobe away from the main area of hemorrhage, there was a focus of very severe CAA of leptomeningeal vessels, with some occluded and re-canalized vessels associated with underlying cerebral infarction. There was mild CAA of meningeal blood vessels overlying the cerebellum. Senile plaques were scattered throughout the cortex, but were numerous in the hippocampi.

Case 8

A 69-year-old woman who was well became suddenly stuporous while talking on the telephone. On admission to hospital, she had a hemiparesis and a right third nerve palsy. She lapsed into deep coma and a CT scan showed a right hemisphere intracerebral hemorrhage. She died within 24 hours.

Pathology. The general autopsy findings were normal. The heart weighed 370 g with a normal left ven-
tricular wall thickness. The kidneys weighed 155 g and 165 g.

There was a large hemorrhage in the right frontoparietal region of the brain. This extended into the lateral ventricle at the level of the lateral geniculate body. Blood also extended through cortex to the subarachnoid space in the right frontal region. There was right uncal herniation and right to left shift of all midline structures, with secondary brain stem hemorrhages.

Histologic sections of cortex around the hemorrhage demonstrated severe CAA, as did other sections of frontal, parietal and occipital lobes. There were no changes indicative of hypertension. The hippocampi showed the occasional senile plaque and neurofibrillary tangle.

Case 9
An 80-year-old woman was a resident in a nursing home for five years because of dementia. She was able to ambulate, was intermittently confused and aggressive. There was no hypertension. She was admitted to hospital with rapidly progressive left hemiparesis and a depressed level of consciousness. Her blood pressure was 160/100 mm Hg. She deteriorated with persisting signs of left sided paralysis, developed a dilated left pupil and ataxic breathing, and died about 36 hours after admission.

Pathology. She had mild generalized atherosclerosis, heart weight of 300 grams with a normal left ventricle. The fresh brain weighed 1,232 grams with a swollen right hemisphere and subarachnoid blood over the right frontoparietal region. The vessels at the base were normal. There were right uncal herniation, brain stem compression and distortion, secondary brain stem hemorrhages and bilateral tonsillar herniation. Coronal sections of the hemispheres revealed a large frontoparietal hemorrhage which had extended to the subarachnoid space, destroyed white matter and extended to the lateral ventricle. There was a shift of structures from the right to the left with cingulate herniation. The ventricles were dilated.

Congophilic angiopathy was prominent in all areas of the neocortex and there were abundant Alzheimer plaques and neurofibrillary tangles. In the hippocampi, granulo-vacuolar change was prominent. The hemorrhage was acute with ischemic changes in all adjacent areas of cortex and white matter. Small old infarcts were noted in cortex of the left inferior frontal lobe and in the right lateral medulla.

Case 10
This 78-year-old woman in good health fell backwards striking her occiput while stepping over a large dog. She was well afterward but within one hour began to drop things from her left hand. Within minutes she lapsed into coma and had a dense left hemiparesis. A CT scan showed a large hemorrhage in the right hemisphere which had extended to the ventricular system. She died a few hours later.

Pathology. Autopsy revealed a vertex subgaleal hematoma but no skull fractures. The brain weighed 1,410 grams, with fresh subarachnoid blood over the right hemisphere and at the base. The vessels of the Circle of Willis and the basilar artery were normal. Coronal sections revealed two distinct large hemorrhages in the right hemisphere. The more rostral hemorrhage was present in the medial superior aspect of the frontal lobe where it had extended to the subarachnoid space. A separate more extensive hematoma was present in the centrum semiovale, extended through to the cortex to the subarachnoid space and was noted from the level of the optic chiasm to within 5 cm of the right occipital pole. This hematoma extended to the lateral ventricle and the lateral, third and fourth ventricles were filled with blood.

The heart weighed 360 grams with healed mitral valvulitis (probably rheumatic). There was moderate generalized atherosclerosis. Histologic sections disclosed widespread congophilic angiopathy. There were senile plaques and a few neurofibrillary tangles in both the hippocampi and occipital cortex.

Case 11
This 70-year-old woman developed a right homonymous hemianopsia, left occipital lobe hemorrhage six years prior to death. Two years later she had surgical evacuation of a right occipital lobe hematoma; congophilic angiopathy was noted on the cortical tissue removed with the hematoma. From this time on she was a resident in a chronic care center. Five months prior to death she became confused and drowsy but improved. She then experienced sudden right hemiplegia and confusion. Her blood pressure was 160/100 mm Hg and her pulse was regular. Her hemiplegia persisted and a CT scan showed a moderate sized left parietal hemorrhage. Despite pneumonia and septicemia, treated with antibiotics, she improved slightly to where she was awake and could communicate with the occasional word. She lapsed into coma suddenly and died the next day.

Pathology. The heart weight was 340 grams and there was a small mucinous cystadenoma of the right ovary. The brain weighed 1,120 grams, and there was fresh subarachnoid hemorrhage over the right hemisphere. There was extensive orange staining of the subarachnoid space in the posterior fossa. Coronal sections revealed resolving hematomas in the right frontal lobe (3 x 4 cm), the left parietal lobe (3 x 6 cm), the left occipital lobe (2 x 2 cm), and a cystic orange stained irregular cavity (2 x 3 cm) in the right occipital lobe. A large hemorrhage was present in the right posterior frontal and parietal lobes with destruction of white matter, displacement of tissue; cingulate and uncal herniation with secondary brain stem hemorrhages.

There was severe congophilic angiopathy throughout leptomeningeal vessels and the neocortex. Congophilic angiopathy was also present in the cerebellar cortex. Sections from the multiple hematomata showed decomposition of blood, macrophage invasion with surrounding gliosis. There was acute necrosis of tissue adjacent to the fresh hemorrhage in the right hemisphere.
hemisphere. A few Alzheimer plaques and neurofibrillary tangles were present. The subarachnoid space showed fibrosis and old hemorrhage.

Discussion

Several common features characterize cerebral hemorrhages related to CAA — occurrence in elderly, sometimes demented people; localization to the cortex and subcortical white matter, with direct extension into the subarachnoid space; frequently, multiple occurrences in time and/or at several sites within the cerebral hemispheres. The changes of CAA may coexist with those of atherosclerotic or arteriosclerotic cerebrovascular disease, and with other evidence of hypertension in the affected patients, though hypertension is not believed to be important in the causation of CAA. Our patients 4, 6 and 7 would fall into such a ‘mixed vascular lesion’ group. The disease processes should not be considered mutually exclusive. Of the nine massive CAA-related hemorrhages described by Okazaki et al, three were in patients who had clinical evidence of hypertension, two in patients with cardiomegaly at necropsy, and three in patients who were on anticoagulant therapy for transient neurologic symptoms at the time of the fatal bleed. Eight of the 15 patients described by Jellinger, had autopsy evidence of hypertension. Both of these authors have illustrated that even individual blood vessels may be involved by hypertensive change (e.g. fibrinoid degeneration with Charcot-Bouchard microaneurysm formation) in one segment and CAA in an adjacent segment.

Torack has described three CAA-related hemorrhages after neurosurgical procedures. Perhaps such examples should suggest caution in the surgical approach to these hematomas. Case 3 may be an instance in which a second intracerebral bleed was precipitated by surgery. The frequent superficial location of the hemorrhages may invite surgical intervention, yet surgery may eventually prove fatal to the patient. By the same token, whenever an intracerebral clot is submitted for pathologic examination, the surgical pathologist must carefully examine the tissue for brain fragments that may contain thickened vessels. Congo red staining and polarization of the histologic sections is necessary to confirm this diagnosis. The diagnosis of CAA was made antemortem in our patients 3, 5, and 11 and has been similarly noted by others.

The vast majority of affected vessels in our cases were small and medium-sized arteries located in the cortex and subarachnoid space. Despite the associated vascular arteriosclerosis in 2 patients the severe degree of CAA likely explains the hemorrhage in each patient. The hemorrhages presumably result from weakness of the blood vessel walls related to amyloid replacement of the media. In cases 1, 4, 7, and 9 there were small old cerebral infarcts similar to those described by Okazaki et al and Tominaga. These may be associated, at least in our case 4, with atherosclerosis of the basilar arteries rather than CAA. Congo positive vessels in the subarachnoid space frequently showed the double-barrel lumen with subintimal proliferation also observed by Okazaki’s group.

Lee and Stemmermann showed a strong female preponderance (six of seven patients, eight of eleven in this series) and although the details are scant, there was a tendency for the location of the hemorrhages to be ganglionic rather than peripheral. As well, they observed a posterior fossa bleed thought to be due to CAA. With severe brain involvement by CAA, cerebellar vessels may be involved (our cases 3, 7, and 11), but we have not seen a hemotma in this location. A subsequent paper will deal with the cerebral topographic distribution of CAA in the aging brain.

The Icelandic variety of CAA-related cerebral hemorrhage is clearly different. It occurs at a much younger age and pathologic findings in the involved brains do not include senile plaques or other Alzheimer changes. A recent study found indicators of immune dysfunction in peripheral blood lymphocytes in this unique kindred.

CAA has been demonstrated in up to 89% of brains with Alzheimer’s disease. Ten of our eleven patients showed senile plaques and/or neurofibrillary tangles in abundance, so that the qualitative impression was that of Alzheimer’s disease in eight of eleven brains. As table 1 indicates, however, only 4 patients were demented at the time of admission to hospital. It is noteworthy that 3 non-demented patients presented with an acute confusional state, though the hemorrhage apparently did not occur until several days after hospitalization. Their premorbid mentation may thus have been borderline, though this point cannot be verified. Only one patient’s brain, the youngest in the series, showed no senile plaques or neurofibrillary tangles.

Further evidence for a direct link of CAA with Alzheimer’s disease is the finding that immunologic staining of the amyloid cores of classical or perivascular plaques and the vascular amyloid of CAA are remarkably similar. The pathogenesis of CAA is not understood and the intimate relationship to Alzheimer’s disease is still under investigation.

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