Autopsy Study of Incidence and Distribution of Cerebral Amyloid Angiopathy in Hisayama, Japan

Junichi Masuda, MD, Kenzo Tanaka, MD, Kazuo Ueda, MD, and Teruo Omae, MD

The incidence of cerebral amyloid angiopathy (CAA) in the general population was evaluated in brains of 400 consecutive autopsies of residents of Hisayama, Japan (November 1971–October 1983). Six samples taken from frontal lobe, parietal lobe, temporal lobe, occipital lobe, hippocampus, and basal ganglia of the same side of each brain were stained with both hematoxylin and eosin and Congo red. The specimens were surveyed microscopically with polarized light for deposition of amyloid in the vascular wall. In 26 cases with brain hemorrhage, the region surrounding the hemorrhagic sites was further examined to study the probable causal relation between cerebral amyloid angiopathy and brain hemorrhage. Cerebral amyloid angiopathy was found in 40 of 218 men (18.3%) and 51 of 182 women (28.0%). The incidence increased with age in both sexes. The frontal lobe was most frequently affected (66 cases), followed by parietal lobe (65), occipital lobe (49), temporal lobe (44), and hippocampus (32); the putamen was never affected. The incidence of cerebral amyloid angiopathy did not correlate with blood pressure or with the severity of cerebral atherosclerosis. Among the 26 cases in which there was brain hemorrhage, only one cerebellar hemorrhage, in an 85-year-old man, was attributed to cerebral amyloid angiopathy. This case showed four microaneurysms in vessels, with cerebral amyloid angiopathy surrounding the hemorrhagic site. Thirty similar lesions were observed in eight cases without brain hemorrhage. Cerebral amyloid angiopathy may play an etiologic role in the development of brain hemorrhage through formation of angionecrosis and microaneurysm. (Stroke 1988;19:205-210)

Cerebral amyloid angiopathy (CAA) is characterized by the deposition of amyloid material in the wall of blood vessels in the brain and leptomeninges. It usually is not associated with deposits of amyloid elsewhere in the body. CAA is being increasingly recognized as an associated vascular lesion in cases of senile dementia of the Alzheimer type, a cause of nontraumatic, nonhypertensive brain hemorrhage in elderly patients, a variant of unusual degenerative and demyelinating diseases, and a late consequence of postirradiation necrosis of the brain.

There are, however, no reports concerning the age-related incidence and brain topography of CAA in the general population, although a few recent papers describe them in autopsy cases of hospitalized patients. A prospective population survey has been conducted since 1961 in the town of Hisayama, Japan, aimed at investigating the frequency and predisposing factors of cerebrovascular diseases in a general population sample. This survey provided a unique opportunity to elucidate some features of CAA, including the age-related incidence and brain topography of observed CAA and the relation of CAA to the underlying vascular lesion of cerebral hemorrhage in the elderly.

Subjects and Methods

A prospective study of cerebrovascular diseases was begun in November 1961 in the town of Hisayama, a farming community adjoining Fukuoka City on Kyushu Island, Japan. According to the 1960 census, the number of residents aged 40 years or older was 1,851, or 27.6% of the population; this ratio is identical to the Japanese national statistics (28%). Details of the epidemiologic methods have been published elsewhere. Causes of death were verified by autopsy in >80% of the deceased.

Our study comprised 400 consecutive autopsy cases of Hisayama residents aged 40 years or older (218 men, 182 women) during the period November 1971 to October 1983 and included >80% of the persons deceased during this period. The age and sex distribution of the examined cases is shown in Table 1. Six tissue blocks of identical size were taken from the frontal lobe, parietal lobe, temporal lobe, occipital lobe, hippocampus, and basal ganglia in the same side of each brain. Sections of leptomeninges, cortex, and subcortical white matter were also examined in most cases. Serial sections were stained with hematoxylin and eosin and Congo red.

All Congo-red-stained sections were examined with polarizing lenses to look for deposition of amyloid. The frequency of CAA observed in each section was recorded according to a semiquantitative grading scheme, number of CAA-involved vessels in the total number of vessels examined: 0 (-), 1–9% (1+), 10–49% (2+), 50–79% (3+), and >80% (4+). Only Congo-red-positive vessels in the brain parenchyma were counted as significant lesions because some
sections did not contain sufficient meningeal vessels for examination.

Atherosclerosis of the excised cerebral arteries, including the basilar artery and the circle of Willis with its main branches, was graded and the atherosclerotic index (AI) was calculated according to the method described by Gore and Tejada. Patients were divided into six age groups for each sex, and AI of cerebral arteries was compared between cases with and without CAA in each sex-age group using Student's t test.

To study the relation of CAA to high blood pressure, patients were divided into five groups of 20-mm Hg intervals of systolic blood pressure and five groups of 10-mm Hg intervals of diastolic blood pressure for each sex, and the incidence of CAA was thus examined as a function of systolic and diastolic blood pressure. The blood pressure measured at entry (in 1961) was used as antemortem blood pressure, and if there were no readings at entry, blood pressure at the following examination was used. In addition, heart weight at postmortem examination as an indicator of long-standing hypertension was compared between cases with and without CAA. To ensure adequate numbers of cases, the analysis of heart weight was limited to those >70 years of age.

In our series, brain hemorrhage was found in 26 cases (6.5%). Several additional tissue blocks were taken from the area surrounding the hemorrhagic site to clarify the relation of CAA to brain hemorrhage.

**TABLE 1. Age-Sex Distribution of Examined Autopsy Cases; Higashiya, Japan; November 1971–October 1983**

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>40–49</td>
<td>22</td>
</tr>
<tr>
<td>50–59</td>
<td>25</td>
</tr>
<tr>
<td>60–69</td>
<td>43</td>
</tr>
<tr>
<td>70–79</td>
<td>71</td>
</tr>
<tr>
<td>80–89</td>
<td>50</td>
</tr>
<tr>
<td>90+</td>
<td>7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>218</td>
</tr>
</tbody>
</table>

**TABLE 2. Distribution of Cerebral Amyloid Angiopathy in 91 CAA-Positive Cases by Brain Area**

<table>
<thead>
<tr>
<th>Degree of CAA</th>
<th>Frontal</th>
<th>Parietal</th>
<th>Temporal</th>
<th>Occipital</th>
<th>Hippocampus</th>
<th>Putamen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1+–4+</td>
<td>66</td>
<td>65</td>
<td>47</td>
<td>49</td>
<td>32</td>
<td>0</td>
</tr>
<tr>
<td>4+</td>
<td>7</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>1</td>
<td>0</td>
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<tr>
<td>3+</td>
<td>7</td>
<td>11</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>2+</td>
<td>18</td>
<td>8</td>
<td>11</td>
<td>15</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>1+</td>
<td>34</td>
<td>42</td>
<td>26</td>
<td>25</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>-</td>
<td>25</td>
<td>26</td>
<td>44</td>
<td>42</td>
<td>59</td>
<td>91</td>
</tr>
</tbody>
</table>

CAA, cerebral amyloid angiopathy. Degree of CAA: 4+, >80%; 3+, 79–50%; 2+, 49–10%; 1+, 9–1%; -, 0% of vessels examined were CAA-positive.

**Results**

CAA of any grade (1+ to 4+) was found in at least one section in the 91 cases with CAA of the total 400 autopsies (22.8%), and included 40 of the 218 men (18.3%) and 51 of the 182 women (28.0%). The incidence of CAA increased with age (Figure 1). The incidence was 0% in men 40–49 years old, 4.0% in those 50–59, 9.3% in those 60–69, 18.3% in those 70–79, 38.0% in those 80–89, and 42.8% in those 90 or older. The incidence was 0% in women 40–49 years old, 10.0% in those 50–59, 13.6% in those 60–69, 23.3% in those 70–79, 36.1% in those 80–89, and 45.8% in those 90 or older. The incidence of CAA tended to be slightly higher in women than in men.

Table 2 summarizes the degree, frequency, and distribution of CAA in the brain parenchyma of the 91 cases with CAA. The frontal lobe was most frequently affected (66 cases), followed by parietal lobe (65), occipital lobe (49), and temporal lobe (44); these differences in the frequency of CAA among the different cerebral lobes were not significant. The hippocampus was relatively spared (32 cases), and the putamen was never affected. The amyloid deposition was almost always noted in the leptomeningeal and cortical vessels in affected cases but was somewhat less frequently noted in the capillaries of the cortical parenchyma (Figure 2). Congo-red-positive vessels, however, were never seen in the subcortical white matter.

There was no significant difference in the severity of atherosclerosis of major cerebral arteries, indicated by AI, between cases with and without CAA.

No definite correlation was observed between blood pressure and the incidence of CAA, and there was no difference in heart weight at postmortem examination between cases with and without CAA by Student's t test.

Brain hemorrhage was found in 19 men and 7 women in our autopsy series. Hemorrhagic sites were located in the basal ganglia and thalamus (23 cases), frontoparietal lobe (1 case), frontoparieto-occipital lobe (1 case), and cerebellum (1 case). CAA was noted in three men (aged 82, 84, and 85). Bleeding was considered to be caused by rupture of CAA-involved vessels in only one case, that of an 85-year-old man with a cerebellar hemorrhage. This case showed widespread
amyloid deposition in cerebral vessels of the frontal (2+), temporal (2+), parietal (2+), and occipital lobes (2+); there was marked involvement of the cerebellar cortical vessels (4+). In the cerebellum, four angionecrotic vessels with aneurysmal dilatation were observed surrounding the hemorrhagic site, and the findings of amyloid deposition on the vascular wall suggested that these lesions could be secondary to CAA (Figure 3). Antemortem blood pressure of this case was in the nonhypertensive range at four periodic examinations. The remaining two cases with CAA and brain hemorrhage had Congo-red-positive vessels in the cerebral cortex, but direct evidence that hemorrhage was due to CAA could not be obtained. The two cases of lobar cerebral hemorrhage had no CAA in any section sampled from the brain surrounding the hemorrhagic sites.

Angionecrosis in vessels with CAA was found in 30 vessels of eight cases without brain hemorrhage; four of these eight cases had no history of hypertension.

Five cases of systemic amyloidosis were included in this series, but amyloid deposition in the cerebral blood vessels was noted in only one case, a 93-year-old woman, in the blood vessels of the frontal (2+) and
parietal lobes (1+). The remaining four cases of systemic amyloidosis showed no amyloid deposition in any vessel of the brain.

Discussion

The type of vascular amyloidosis that primarily affects cortical parenchymal capillaries (microangiopathy) is generally known as “plaque-like degeneration (drusige Entartung)” of Scholz, and it shows frequent involvement of the adjacent cerebral tissue by amyloid. The other type, which affects larger leptomeningeal or superficial cortical perforating arteries, is sometimes referred to as “congophilic angiopathy” of Pantelakis; in this form, amyloid is largely confined to the vascular wall. These two types are, however, not mutually exclusive, and they probably designate different manifestations of CAA rather than different disease processes.

The exact nature of the mechanism leading to amyloid deposition within cerebral blood vessels is still unknown. Several studies have demonstrated γ-globulins or prealbumin in senile plaques and amyloid angiopathic lesions. Such deposition, however, might also be due to nonspecific exudation of
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serum protein through disrupted endothelial layers. Recently Glenner and Wong purified a cerebrovascular amyloid protein and analyzed its amino acid sequence. According to their results, this protein has no homology with any protein sequenced thus far, including a human gamma-trace serum protein.

The incidence and topographic distribution of CAA in elderly persons have been previously described. These studies, however, were of hospitalized persons, and thus the observed incidence may not accurately reflect the incidence in the general population. Our study included >80% of the deceased among the defined general population of a Japanese community. They were not necessarily admitted to a hospital for medical care before death, and no medical attention had been given to some of them. Senility was frequently listed on the death certificates; however, bronchopneumonia, unrecognized malignant neoplasms, or latent congenital heart failure were the most frequent causes of death at autopsy. This study population is considered to be more representative of a general Japanese population than hospitalized cases, even though the autopsy rate was not 100%.

In our study, the age-related incidence of CAA was almost identical to that reported by Tomonaga but was relatively lower than that described by Vinters and Gilbert. This difference might be due to racial factors or to the fact that one study was of a general population, the other of hospitalized persons; in addition, Vinters and Gilbert sampled both sides of the brain, whereas we performed only unilateral sampling.

CAA usually affects the leptomeningeal or cortical vessels of the brain and spares the vessels of the medullary white matter. Sites of predilection for CAA are reported to be the occipital and parietal lobes by Vinters and Gilbert and occipital and temporal lobes by Tomonaga. In our study, frontal and parietal lobes were most affected by CAA. However, all previous studies have revealed that CAA is widely distributed throughout the cerebral cortex, although small topographic differences have been described. From this point of view, brain hemorrhages due to CAA may occur at any site of the cerebral cortex.

Brain hemorrhage as a complication of CAA was first reported in 1960. The patient was a 46-year-old woman who had severe amyloid angiopathy and numerous senile plaques and who died of a lobar hemorrhage in the left parietal lobe. This case, however, was also complicated by the presence of a vascular malformation. The reported frequency of CAA as a cause of spontaneous brain hemorrhage varies. Jellinger reported an incidence of 2% in cases of cerebral hemorrhage; hemorrhagic sites were located in the frontal and temporal lobes (three cases each) and in the parieto-occipital lobe and basal ganglia (one case each). Lee and Stemmermann reported a higher incidence of brain hemorrhage due to CAA: seven cases in 75 cerebral hemorrhages (9.3%); the hematoma was usually found in the cerebrum, most commonly in the basal ganglia, except for one case of hemorrhage in the cerebellum and pons. Ishii et al reported seven cases in 60 cerebral hemorrhages (11.7%) among elderly demented patients. Recently Tomonaga described eight cases of cerebral cortical hemorrhage secondary to CAA in 230 spontaneous brain hemorrhages (3.5%). These variations in frequency seem to reflect differences in the populations studied. In our study, one case of cerebellar hemorrhage was considered to be secondary to CAA in 26 brain hemorrhages (3.8%), but the frequency of CAA in the cerebellar cortex, unfortunately, was not examined. The frequency of CAA in the cerebellum is reported to be less than in the rest of the brain. It is difficult to relate our findings to the true frequency of brain hemorrhage secondary to CAA in the general population because the number of cases with brain hemorrhage was small and because hemorrhage occurred at an unusual site. Nonetheless, it is probable that CAA causes <10% of all nontraumatic brain hemorrhages as judged from a review of the literature.

Okazaki et al and Mandybur described fibrinoid degeneration (angioneerosis) and microaneurysmal formation of the small arteries associated with amyloid deposition and suggested the possibility that rupture of these aneurysms leads to massive hemorrhage. An association between fibrinoid necrosis and CAA-affected vessels has been occasionally documented; fibrinoid necrosis has been followed rarely by microaneurysm formation. It has also been suggested that a history of head trauma or, less commonly, a prior neurosurgical procedure have preceded the onset of CAA-related cerebral hemorrhage. This raises the possibility that some of these hemorrhages may be related to trauma.

In our study, no definite correlation was found between the frequency of CAA and either the degree of atherosclerosis or blood pressure. The development of CAA is thought to be independent of cerebral atherosclerosis and its risk factors. It follows that brain hemorrhage secondary to CAA can occur in normotensive subjects. In our study, microaneurysms were found not only in the case of cerebellar hemorrhage, but also in 30 vessels with CAA in the cerebral cortex of eight cases without brain hemorrhage. This suggests that CAA may rarely lead to cerebral hemorrhage through angioneerosis and microaneurysmal formation and that this process is probably independent of hypertensive vascular changes.

Several reports describe an association between CAA and senile dementia of the Alzheimer type. Neuritic plaques and neurofibrillary tangles were not systematically looked for in the present study. In addition, scales to quantify dementia, such as DSM III or that of Hachinski et al, were not applied to all demented persons before death. It is difficult, therefore, to assess the relation between CAA and senile dementia in this group of patients. More detailed studies are now underway using the Hisayama subjects.

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References


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