THE CLINICAL AND PATHOLOGIC FEATURES of cerebral hemorrhages related to cerebral amyloid angiopathy (CAA) in eleven patients are reported.

To try and understand the pathogenetic mechanism in these cases we have asked: How common is CAA in the aging human population, and what is the cerebral cortical topography of amyloid vascular change?

Previous studies addressed but incompletely answered these questions. A survey of the cerebral cortical distribution of CAA as a function of age in a large unselected autopsy population has not previously been available.

Material and Methods

The survey was carried out on 84 post-mortem brain examinations in patients over 60 years of age, irrespective of the clinical diagnosis, taken from consecutive complete necropsies carried out in a large general hospital. However, none of the 11 patients described previously were included in this topographic survey. The age of the patients at death ranged from 61 to 97 years. The total number of brains examined in each age category was as follows: 60–69 years — 21, 70–79 years — 28, 80–89 years — 28, and over 90 years — 7. The average age of the patients at death ranged from 61 to 97 years.

The relative severity of CAA in a given section was assessed as follows. If one or two vessels were positive, the involvement was scored as 1+; if three to five vessels were positive, a score of 2+ was given; if six or more vessels were positive, a score of 3+ was assigned (fig. 2). A score of 3+ was arbitrarily taken to represent a severe degree of CAA. The numbers refer only to Congo positive vessels within the brain parenchyma. CAA was also assessed in the adjacent leptomeninges but the meninges were not present in their entirety over the cortex in every section.

Results

Except in 3 cases, one in each of the eighth, ninth, and tenth decade, whenever there were Congo red positive vessels in brain parenchyma there were positive vessels in the adjacent leptomeningeal vessels. In addition, in 4 cases, ages 76 to 82, in which no CAA was noted in the brain parenchyma there was the occasional (1+) positive vessel in the leptomeninges.

Incidence

The incidence of CAA as a function of age is summarized in figure 3. Of the 21 brains in the 60–69 year age category, only one showed CAA. However, it was seen in 12 of 28 brains (42.8%) in the eighth decade, and in 13 of 28 brains (46.4%) in the ninth decade. Over the age of 90 years, it was present in four of seven patients (57%). There was no significant difference between males and females in either the CAA positive or the CAA negative cases (table 1).

Topographic Distribution

Table 2 summarizes the data on the location of CAA within the brain. The table indicates all areas of the brain with one or more Congo positive vessels present, irrespective of the total number involved, i.e. it does
Congophilic Angiopathy

N=84

FIGURE 1. Diagram of coronal slices of cerebral hemispheres to show areas sampled histologically. Both hippocampi at level of lateral geniculate nuclei were also sampled.

not take into account the severity of involvement in a given section. Though the change was frequently present in the frontal, temporal and parietal lobes, it was most often encountered in the occipital poles. The table also emphasizes that it was least often noted in sections of the hippocampi. Within sections of the involved hippocampi, the dentate fascia itself was almost always spared.

If only severe involvement by CAA (i.e. 3+ by the scoring system) is considered then 14 brains showed severe CAA in at least one of the 10 sections examined (table 3). Of these severe CAA brains, one was from a patient in the seventh decade, six each from patients in the eighth and ninth decades, and one from a patient over 90 years of age. A severe degree of vascular involvement was noted most often, though not exclusively, in the parietal and occipital cortex. The relative sparing of the hippocampi by severe CAA is striking, only one case of 14 demonstrated a severe degree of angiopathy in this location.

There is an overall greater likelihood of finding CAA in the occipital cortex, but in any given brain, it may be a very focal, patchy and asymmetric process. It was not uncommon to find relatively severe CAA in only three or four of the 10 sections examined microscopically, with sparing of all other areas of cortex (table 3). The subcortical white matter was virtually never seen to contain Congo positive vessels. Some senile plaques, often with amyloid cores, were seen in almost every brain that had CAA, no matter how minimal the degree of CAA. Often there was close physical association of the plaque with a Congo positive vessel, a proximity that has been emphasized by others. In the group of brains that was negative for CAA, senile plaques were identified less frequently and in smaller numbers, though they were on the whole more common in older patients.

Ten of 14 cases of severe CAA had the pathologic diagnosis of Alzheimer's disease (table 4). Though quantitative morphometric methods are now important in defining the differences between 'normal' cerebral
TABLE 1 Age-Sex Incidence in CAA

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Number of cases</th>
<th>CAA positive cases</th>
<th>CAA negative cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>male</td>
<td>female</td>
<td>male</td>
</tr>
<tr>
<td>60-69</td>
<td>21</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>70-79</td>
<td>28</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>80-89</td>
<td>28</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>90+</td>
<td>7</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Totals</td>
<td>84</td>
<td>14</td>
<td>16</td>
</tr>
</tbody>
</table>

CAAs are common findings in the brains of individuals over 70 years of age. It was present in some degree in 30 out of 84 patients (or 36%) over 60 years old, and in 46% over 70 years old. CAA is a focal, patchy, often asymmetric process that is most likely to involve the parieto-occipital cortex and to spare the hippocampi, even with severe involvement elsewhere.

Discussion

Use of the Congo red stain and polarization microscopy to look for characteristic apple-green birefringence in vessel walls is of primary importance in a survey of this sort, as the lesion may be otherwise missed. Criticism of this staining procedure based on sections of muscle and nerve has been made, as false positives may be found in which birefringence is closely related to excess dye retained in the tissue. The fact that in some sections only one or two of many cortical vessels were definitely Congo positive also serves as an internal control for the staining procedure, so that criticisms which apply to its use in muscle and nerve may not necessarily be relevant to cerebral cortex. In a recent study the statement is made that “Of the stains employed only the alkaline Congo red reaction, followed by polarization microscopy to produce a green polarization colour (“Congo red birefringence”) detected amyloid unequivocally and with great sensitivity,” a claim that we feel validates our decision to use this as the method of choice among the several available.

CAA is a condition that involves small and medium-sized cortical vessels (whether they are arteries or veins) that are often difficult to tell as others have stressed but does not affect white matter or other portions of the central nervous system to a significant degree.

In a recent autopsy study of individuals over 60 years of age, Tomonaga found the frequency of CAA (by decade) to be 8% in the 60–69 decade, 23% in the 70–79 decade, 37% in the 80–89 decade, and 58% in patients older than 90 years. The number of sections per brain examined or the topography of CAA, except in seven cases of severe CAA were not commented on. In this latter group, temporal and occipital cortex were most commonly affected. These incidence figures agree closely with ours. Our higher incidence in the eighth and ninth decades may reflect more rigorous histologic sampling of cortex.

Another multiple organ study found amyloid (though not necessarily CAA) in 11 of 47 brains (23%) in the age group 60–79 years, and in 27 of 44 brains (61%) in the group 80–107 years old. The presence of cardiac, aortic or pancreatic amyloid was not correlated with that of cerebral amyloid. Again, the number and site of origin of sections of brain examined is not stated precisely, and the distinction between senile plaque amyloid and CAA was not made for purposes of the survey, although it is now known to be important.

Surbek described 79 cases of “dyshoric angio­pathy” diagnosed by pathologic examination over a period of ten years in a psychiatric clinic. Histologically, “dyshoric angio­pathy” represents a combination of amyloid in the vessel wall and perivascular space, with penetration of the surrounding nervous tissue. It is synonymous with the term “drusige Entartung.” The distinction between either of these entities and CAA is not meaningful, and we have therefore used only the designation CAA for the lesions described. Surbek’s very thorough study based on almost 600 autopsies disclosed the presence of angiopathy in 18% of patients over 69 years of age. There was an increasing incidence from age 55 years to 94 years of age, and a marked tendency for the vascular change to occur in the fourth layer of the striate cortex (line of Gennari). Angiopathy was always accompanied by senile plaques, though not necessarily in the same region of gray matter. Men were slightly more commonly affected than women.

Pantelakis noted CAA in 26 (31.7%) out of a total

TABLE 2 All Areas of Cerebral Cortex with CAA (Regardless of Severity)

<table>
<thead>
<tr>
<th>Ages (years)</th>
<th>Number of cases</th>
<th>Frontal lobes</th>
<th>Temporal lobes</th>
<th>Parietal lobes</th>
<th>Occipital lobes</th>
<th>Hippocampus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>L</td>
<td>R</td>
<td>L</td>
<td>R</td>
<td>L</td>
</tr>
<tr>
<td>60-69</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>70-79</td>
<td>12</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>80-89</td>
<td>13</td>
<td>4</td>
<td>7</td>
<td>5</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>90+</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Totals</td>
<td>30</td>
<td>12</td>
<td>17</td>
<td>12</td>
<td>13</td>
<td>13</td>
</tr>
</tbody>
</table>

L = left; R = right.
of 82 patients with "varied psychiatric affections." All patients with CAA had been demented and old, with a mean age of 81.5 years. Multiple areas of cortex were examined and when CAA was minimal, it was always found in the occipital cortex or overlying leptomeninges. White matter was not involved. No correlation with a mean age of 81.5 years. Multiple areas of cortex were examined and when CAA was minimal, it was always found in the occipital cortex or overlying leptomeninges. White matter was not involved. No correlation between CAA and cerebral arteriosclerosis was noted.

Mandybur found CAA in 13 of 15 patients with Alzheimer's disease, and commented on the fact that CAA rarely or never involved the basal ganglia, cerebellum, and brain stem. Qualitatively, the temporal and occipital cortex seemed most involved, whereas Ammon's horn was spared by the vascular pathologic change, a finding that our study strongly re-emphasizes. The high incidence of CAA in Alzheimer's disease has been stressed by others and one recent study has suggested that specific psychiatric symptomatology may be associated with the presence of CAA, a premise we find difficult to accept. Some authors have considered CAA to be an atypical "vascular" form of Alzheimer's disease, but others feel CAA is a distinct entity entirely separate from the latter.

Mountjoy et al compared CAA in 15 patients with senile dementia of the Alzheimer type with 30 patients who had normal mentation and died with a variety of medical conditions. An "amyloid score" was developed in which assessment was made of plaques and CAA vessels in the cortex and vessels in adjacent meninges. The topographic distribution of CAA was not studied systematically yet they found CAA in all lobes of the brain in both demented and non-demented patients. The hippocampus per se was not commented upon. The authors conclude that there is "some relationship" between plaques and the presence of amyloid in cerebral vessels. However, patients with plaques were seen without CAA and some patients with CAA had no plaques, a finding which agrees with our own.

The hippocampal formation is a key structure in showing the cellular and parenchymal changes that underlie Alzheimer's disease. An exhaustive morphometric study of hippocampal microvasculature in young, old and demented old patients has found significant changes in capillary and arteriolar diameters and densities with aging, and regional changes in these parameters that may be important in the pathogenesis of senile dementia of the Alzheimer type. The study used techniques that did not take into account any potential thickening of vascular walls external to the endothelium, such as might result from CAA, and so did not concern itself with the possible relationship between CAA and Alzheimer's disease. Our findings indicate that the most severe cases of CAA are noted with Alzheimer's disease. However, CAA is found (albeit to a mild degree) in a large proportion of elderly brains and is least conspicuous in the hippocampi.

The role of CAA in the pathogenesis of Alzheimer's disease, if any, is unknown. Nevertheless, support is given for a close association of CAA and the amyloid (senile) plaque by the recent demonstration using immunoperoxidase techniques of the presence of components or fragments of immunoglobulin and the presence of neurofilament proteins in both structures.

CAA occurs independently of systemic amyloidosis with rare exceptions. These patients often show far more extensive central nervous system amyloid deposition than is the case in pure CAA. For example, deposits are frequently identified in the brain stem and spinal cord. Extensive nervous system amyloid deposition, often in the form of non-vascular globules, is also found in some familial degenerative neurologic syndromes associated with CAA.

This study shows an obvious and important discrepancy between the location of the most severe degree of CAA (parietal and occipital) and the location where CAA-related hemorrhage tends to occur, namely the frontal or fronto-parietal regions. Specific explanation for this phenomenon can be offered but one can speculate that factors other than the severity of angiopathy alone must play a part in causing the hemorrhages.

| \( \text{Age} \) & \( \text{Number of Cases CAA} \) & \( \text{Number of Cases CAA} 3+ \) & \( \text{Number of cases Alzheimer disease} \) & \( \text{No Alzheimer disease} \) |
|---|---|---|---|---|
| 60-69 | 1 & 1 & 1 & 0 |
| 70-79 | 12 & 6 & 4 & 2 |
| 80-89 | 13 & 6 & 4 & 2 |
| 90+ | 4 & 1 & 1 & 0 |
| Totals | 30 & 14 & 10 & 4 |
Acknowledgements

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