Amyloid angiopathy and lobar cerebral haemorrhage

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SUMMARY Seven cases of lobar cerebral haemorrhage due to amyloid angiopathy were found among 60 necropsy cases of intracerebral haemorrhage. Clinically five patients were demented and two had hypertension. Immediately after the onset of stroke there was a high incidence of headache and vomiting, followed by nuchal rigidity. Amyloid angiopathy was most prominent in the cerebral cortex and the leptomeninges. Senile plaques were noted in all cases. One should suspect that a haemorrhage may be due to amyloid angiopathy, when lobar cerebral haemorrhage occurs in an aged, normotensive patient with or without dementia. Surgical evacuation of the haematoma is inadvisable, because of the diffuse nature of amyloid angiopathy, high recurrence rate and less tendency to cause brain stem compression.

Haematoma located outside the basal ganglia and the thalamus (lobar cerebral haemorrhage) is relatively rare among cases of intracerebral haemorrhage. Various aetologies are known for this type of haemorrhage, such as cryptic angioma, arteriovenous malformation, moyamoya disease, brain tumours, diseases associated with haemorrhagic tendency and hypertensive vascular changes. Recently, amyloid angiopathy has attracted attention as a further cause. A retrospective study of 60 cases with intracerebral haemorrhage disclosed seven cases that were due to amyloid angiopathy. In all of these, the haematomas were located in the cerebral cortex and the subjacent white matter.

Cases and methods

Kurate Kyoritsu Hospital is a 300 bed chronic hospital with geriatric, psychiatric and medical wards. From 1965 to 1982, 4310 patients were admitted to the hospital. Of these, 1352 died and 1080 underwent complete postmortem examination (necropsy rate 80%). There were 60 cases of spontaneous intracerebral haemorrhage, excluding those cases with aneurysm and haemorrhagic infarct in the necropsy files. These haemorrhages were at least 3-0 cm in diameter in the cerebrum and cerebellum or 1-5 cm in the brain stem. Age and sex distribution of these 60 cases is shown in table 1. All the organs including the brain were kept in 10% formalin for two weeks and sections were taken from each organ. Recently, additional sections were prepared from the brains of the 60 cases, and stained with haematoxylin-eosin, Congo-red, periodic-acid-Schiff and Bodian methods. Sections examined were frontal lobe (areas 8, 9), parietal lobe (area 7), temporal lobe (area 20, 21), occipital lobe (area 17, 18), insula, Ammon's horn and parahippocampal gyrus, basal ganglia, thalamus, pons, medulla and cerebellum (cortex, dentate nucleus), as well as areas around the haematomas. In seven cases, the haemorrhage was considered to be due to amyloid angiopathy. A representative case is described below.

A 78-year-old man (case 1), a retired mining engineer who had been living alone since his retirement, was admitted to a local hospital because of burns on his hands and legs. He was found to be demented and was transferred to Kurate Kyoritsu Hospital. On admission, his general physical examination was not remarkable. He had no hypertension. Neurological examination was unremarkable, except for a slight hearing disturbance and a positive palmmomental reflex. He had marked disorientation as to time and place, memory disturbance, spatial disorientation and acalculia. Laboratory data were all within normal limits. Electroencephalogram showed slow, poorly organised alpha rhythm with diffuse theta and some delta activity. He was
Table 1 Age and sex distribution of 60 cases with cerebral haemorrhage. Numbers in parenthesis indicate amyloid angiopathy.

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;39</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>40–49</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>50–59</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>60–69</td>
<td>15 (2)</td>
<td>8 (1)</td>
</tr>
<tr>
<td>70–79</td>
<td>8 (1)</td>
<td>9</td>
</tr>
<tr>
<td>80–89</td>
<td>3 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>90–</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Total</td>
<td>36 (4)</td>
<td>24 (3)</td>
</tr>
</tbody>
</table>

euphoric, wandered around the ward and chattered incoherently to everyone in sight. He could not identify his niece and grandchildren, nor could he remember his own room and toilet in the ward. Five days prior to his demise, he suddenly vomited and complained of severe headache in the right temporal region. One hour later he again vomited and became drowsy. Next day left hemiparesis and nuchal rigidity were noted. He died of bronchopneumonia at age 79, approximately one year after admission.

The brain weighed 1,170 grams. There was a recent haematoma, measuring $4 \times 5 \times 6$ cm, in the right temporal lobe. It extended to the overlying leptomeninges, as well as to the temporal horn and the body of the right lateral ventricle (fig 1). Microscopically, the most striking finding was severe deposition of amyloid in the wall of small arteries and arterioles in the cerebral cortex and the leptomeninges (fig 2). Also present was prominent drusige Entartung (plaque-like degeneration), namely amyloid deposit in the capillary wall with infiltration into the adjacent brain parenchyma (fig 3). These changes were observed throughout the cerebral cortex. Amyloid deposits were also noted in the Ammon's horn, the basal ganglia, the thalamus and the cerebellar cortex, but to a lesser extent than in the cerebral cortex. There was no amyloid in the

Fig 1 Right temporal lobe haematoma. Case 1.

Fig 2 Amyloid deposit in the small arteries and arterioles of the leptomeninges and the cerebral cortex. a; Congo-red stain, b; Same area as a, showing intense birefringence under the polarised light, $\times 67$, Case 1.

Fig 3 Amyloid deposit in the wall of the arterioles and the capillaries in the left temporal lobe cortex. Perivascular amyloid deposit (drusige Entartung) is also seen (arrow). a; Congo-red stain, b; Same area as a, under the polarised light, $\times 132$, Case 1.
Table 2  Clinical and pathological findings of 7 cases

<table>
<thead>
<tr>
<th>Case No (Autopsy No)</th>
<th>Age &amp; Sex</th>
<th>Blood pressure</th>
<th>Heart weight</th>
<th>Dementia</th>
<th>Signs &amp; symptoms</th>
<th>Vomiting</th>
<th>Nuchal rigidity</th>
<th>Focal sign</th>
<th>Brain weight</th>
<th>Hematoma</th>
<th>location &amp; size</th>
<th>Congophilic angiopathy</th>
<th>Senile plaque</th>
<th>Alzheimer's neurofibrillary tangle</th>
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</thead>
<tbody>
<tr>
<td>1 (678)</td>
<td>79, male</td>
<td>normal</td>
<td>250g</td>
<td>severe</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>lt. hemiparesis</td>
<td>1170g</td>
<td>rt. temporal (5 x 4 x 6 cm)</td>
<td>Severe; TC, FC, OC, PC</td>
<td>Severe; TC, FC, OC, PC</td>
<td>Severe; AmH</td>
<td></td>
</tr>
<tr>
<td>2 (654)</td>
<td>66, female</td>
<td>normal</td>
<td>200g</td>
<td>moderate dementia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>1100g</td>
<td>rt. parietal (5 x 4 x 5 cm)</td>
<td>Moderate; TC, OC, PC</td>
<td>Moderate; TC, OC, FC</td>
<td>Moderate; FC, AmH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 (574)</td>
<td>94, female</td>
<td>normal</td>
<td>250g</td>
<td>moderate dementia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>1100g</td>
<td>lt. frontal (3 x 4 x 2.5 cm)</td>
<td>Severe; FC, TC, OC</td>
<td>Severe; TC, Amyg</td>
<td>Moderate; FC, PC, AmH</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 4 (137)              | 85, male  | normal         | 340g         | no dementia | +               | +        | +              | +          | 1500g        | (4 x 6 x 7 cm) | Moderate; FC, InC | Moderate; TC, AmH, OC | Moderate; FC, TC, PC |
| 5 (478)              | 69, male  | normal         | 300g         | no dementia | -               | +        | +              | -          | 1100g        | rt. parietal (3 x 2 x 2 cm) | Severe; OC | Slight; PC, AmH, InC | Moderate; FC, TC, OC, PC |
| 6 (812)              | 77, male  | moderate hypertension | 200g         | moderate dementia | +     | +              | +          | 1100g        | lt. frontal (old hematoma) | Moderate; FC, TC, OC | None; BG, Th, Hth, BS, CeC, DN | None; BG, Th, Hth, BS, CeC, DN |
| 7 (755)              | 82, female| slight hypertension | 220g         | severe dementia | -               | -        | -              | -          | 980g         | lt. frontal (old hematoma) | Moderate; FC, TC, OC | Moderate; FC, TC, InC, AmH | Severe; AmH, HC |

**Summary of the clinical findings:** The seven patients were over 65 years old at the time of death, with a mean of 77.4 years. The average age of 53 cases of cerebral haemorrhage other than these seven cases was 65.2 years. Four patients were males and the other three females. Five patients were demented, two of them severely. Their clinical diagnoses were Alzheimer's disease and senile dementia. There was a history of hypertension in cases 6 and 7. Case 7 had been treated for several years. In case 4, hypertension was not noted, but the heart showed left ventricular hypertrophy at necropsy, suggestive of an unnoticed clinical hypertension in the past.

At the onset of cerebral haemorrhage, five patients complained of headache. Three patients vomited. Nuchal rigidity was observed in five cases. One patient had generalised seizure. Hemiparesis...
was noted in three cases. Case 2 had two episodes of cerebral haemorrhage. The first stroke, occurring 3 months prior to death, was diagnosed as subarachnoid haemorrhage, because the patient presented with sudden loss of consciousness, vomiting and bloody cerebro-spinal fluid, but without focal neurological signs. Case 5 died a day after his cerebral haemorrhage. Four patients expired of broncho-pneumonia 5 to 14 days after their stroke. Two patients survived 2 and 4 months respectively, and died of pneumonia.

**Summary of the necropsy findings** General examination disclosed lymphocytic thyroiditis in case 1, early gastric cancer in case 3 and chronic bronchitis in case 6. There were no chronic diseases causing secondary amyloidosis, such as tuberculosis, osteomyelitis, rheumatoid arthritis, lupus erythematosus, Hodgkin's disease or multiple myeloma. No amyloid deposit was noted in the sections of the liver, kidney, pancreas, spleen, adrenal, heart and gastrointestinal tract in these seven cases.

The weights of the seven brains ranged from 980 grams to 1500 grams, with an average of 1153 grams. These are the weights of the brains including the haematomas and the surrounding edematous tissue. Therefore, all the brains except case 5 were atrophic. Case 1 and 5 showed slight uncinate herniation on the side of the haematomas. Other cases had no uncinate or cerebellar tonsillar herniation. Secondary brain stem haemorrhage was not observed in any of the cases. The haematomas were located in the cerebral cortex and the white matter, and extended to the overlying leptomeninges in all cases. In cases 1 and 2, the haematomas ruptured into the lateral ventricles. Case 2 had two haematomas; a recent haematoma in the right parietal lobe and an old haematoma in the left frontal lobe (fig 4). Case 3 had two recent haematomas in the left frontal and the right temporal lobes. Case 6 had an old small haemorrhagic lesion in the left putamen, in addition to an old haematoma in the left frontal lobe (fig 5).

Histologically, the most significant feature was amyloid in the walls of small arteries and arterioles of the cerebral cortex and the overlying leptomeninges (congophilic angiopathy). Its intensity varied in the different parts of the nervous system. The cerebral cortex was affected most severely in all cases, with some predilection in the occipital and the temporal lobes. The cerebellar cortex, Ammon's horn, basal ganglia, amygdala and thalamus exhibited slight to moderate amyloid deposits. There was no congophilic angiopathy in the white matter, except for case 1, in which slight amyloid deposit was observed in a few vessels of the subcortical U-fibres. The brain stem and the dentate nucleus of the cerebellum showed no amyloid. **Drusige Ernahrung** was seen in the cerebral cortex of five cases. It was severe in case 1, moderate in case 3, slight in cases 2, 4 and 5. There was predilection for the temporal and occipital lobes, but it was seen diffusely in all parts of the cortex in case 1. Senile plaques with or without amyloid were noted in all cases. They were observed diffusely in the cortex, but most...
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Amyloid was abundant in the temporal and occipital lobes. There seemed to be a correlation between the presence of senile plaques and the amyloid deposit in the vessel wall. In case 1, the senile plaques were larger than usual and were mostly arranged around the capillaries.

Alzheimer's neurofibrillary tangles were present in all cases; in cases 4 and 5, they were limited to the Ammon's horn. Cases 3, 4 and 5 showed a few small arteries undergoing fibrinoid degeneration in the basal ganglia and the thalamus. There were no cryptic angiomas or arterio-venous malformations in and around the haematomas. The white matter generally was well preserved and in no cases were there any infarcts, suggestive of subcortical arteriosclerotic encephalopathy (Binswanger). However, in the cerebral cortex of cases 1, 2, 3, and 7, there were small perivascular scars with haemosiderin laden macrophages and astroglial reaction, and occasional petechial haemorrhages.

Among the 53 cases of cerebral haemorrhage other than the seven cases described, eight showed slight amyloid angiopathy which was limited to the cerebral cortex and the leptomeninges. The eight cases were over 59 years old, with a mean of 71.1 years. Five of the eight cases had senile plaques, but generally few in number. The sites of haematomas of the eight cases were different from the present seven cases, that is they were in the basal ganglia (3), thalamus (2), dentate nucleus of the cerebellum (2) and pons (1). All of them had a history of hypertension. Therefore, in these eight cases haemorrhages are not considered to be due to amyloid deposit in the vessel walls.

Electron microscopic examination was done on small portions of the cerebral cortex, taken from cases 1, 2, 3 and 7. The tissues were postfixed with 2% osmium tetroxide, dehydrated and embedded in Epon 812. Thick sections were stained with toluidine blue and thin sections, with uranyl acetate and lead citrate solution. The severely involved arterioles and small arteries showed the media and the adventitia to be completely replaced by amyloid fibrils of approximately 90 nm in diameter (fig 6a, b). The smooth muscle cells could not be identified, but electron dense material, probably derived from degenerated smooth muscle cells, was observed in the media. The basement membrane was intact and no amyloid fibrils were seen within the endothelial cells. Generally, arterioles were more affected than the small arteries, and their lumina were narrowed. In less involved vessels, amyloid fibrils were noted more in the adventitia and the outer layer of the media, among collagen fibres and the smooth muscle cells. At the capillary level, amyloid fibrils extended into the surrounding brain parenchyma, perpendicu-

Fig 6. a; An electron micrograph of an arteriole of the left temporal lobe cortex, showing marked thickening of the wall due to amyloid deposit and narrowing of the lumen. Electron dense material, probably degenerated smooth muscle cells (arrow heads), is noted. e; endothelial cell, b; basal lamina, m; media, × 2600, Case 1. b; Amyloid fibrils in the media of an arteriole of the left temporal lobe cortex. × 22 000, Case 2.
lar to the basement membrane.

**Discussion**

Three forms of amyloid deposit have been recognised in the central nervous system. They are the amyloid core of senile plaques, deposit in the arterial and arteriolar walls (congoophilic angiopathy of Pantelakis), and deposit in the capillary and arteriolar walls with extension into the surrounding brain parenchyma (drusige Entartung of Schötz or dyshoric angiopathy). The latter two conditions are not mutually exclusive and are together called “amyloid angiopathy”. More than 70 years ago Bielschowsky stated that the substance in senile plaques represented perhaps amyloid on the basis of iodine reaction and metachromasia with cresyl violet. Divry confirmed both substances in senile plaques and within blood vessel walls as amyloid by using Congo-red stain and birefringence under polarised light. Electron microscopic studies by Terry et al. and Schloë revealed that both amyloid in senile plaques and vessel walls were composed of extracellular fibrils identical to amyloid fibrils in other organs. However, in a majority of cases of cerebral amyloid angiopathy, there is no amyloid in the blood vessels or the interstitium of any other organs. Hence it is a localised form of amyloidosis.

Amyloid angiopathy is present not infrequently in the cerebral vessels of elderly patients and its incidence increases with age. Above all, it is associated with Alzheimer’s disease or senile dementia of Alzheimer type. In a review of 15 cases of Alzheimer’s disease, Mandybur found amyloid angiopathy in 13 cases and noticed a correlation between the presence of amyloid-rich plaques and amyloid angiopathy. The seven cases with intracerebral haemorrhage described in this report are aged patients and five of them were clinically demented. Neuropathologically, there were moderate to severe degrees of senile changes such as plaques and tangles. Two other cases were not demented but they also had moderate numbers of plaques in the cerebral cortex. The coincidence of amyloid angiopathy and senile plaques is an interesting subject in regard to the formation of amyloid fibrils and genesis of plaques. However, in this paper, we would like to discuss fatal cerebral haemorrhage due to amyloid angiopathy, which has received much attention recently.

Neumann in 1960 reported probably the first of such cases. The patient was a 46-year-old woman with severe amyloid angiopathy and numerous peculiar senile plaques, who died of a lobar cerebral haemorrhage in the left parietal lobe. Torack cited two necropsied cases of amyloid angiopathy with massive intracerebral haemorrhages. The first patient suffered from a haemorrhage after a ventriculo-atrial shunting procedure. In the second patient, the haemorrhage was spontaneous. There were senile plaques in both cases. Jellinger found eight cases of massive cerebral haemorrhage due to amyloid angiopathy among 400 cases of non-traumatic cerebral haemorrhage. Seven of them were lobar haemorrhages and one was a basal ganglia haemorrhage. All had senile plaques and were demented. Okazaki et al. reported nine cases of massive lobar haemorrhage due to amyloid angiopathy. All of them were associated with senile plaques, but only one was clinically demented. Similar cases were reported by Tomonaga et al. and Scully et al. All of these were lobar haematomas. Lee and Stemmermann reported seven cases of cerebral haemorrhage, which they claimed to be caused by amyloid angiopathy, among 75 cases of spontaneous cerebral haemorrhage in a general hospital. The usual location of haemorrhage in the seven cases was in the cerebrum, most commonly in the lateral ganglia, and in one case the haemorrhage was in the cerebellum and the pons. This is the only paper stating that the haematomas are not lobar type, although they mentioned that amyloid deposits were identified in the cerebral cortex and that there was a strong correlation between senile plaques and amyloid angiopathy. Amyloid angiopathy has a topographical predilection. Generally, the cerebral cortex is constantly affected. The basal ganglia and the thalamus are slightly affected in some cases. The brain stem, dentate nucleus and white matter are usually spared. Therefore, haemorrhage from amyloid angiopathy occurs mostly in the cerebral cortex and involves the underlying white matter, hence lobar haemorrhage. Cases of haemorrhage in the brain stem and the dentate nucleus of the cerebellum should not be included in this category. Haemorrhage in the basal ganglia and the thalamus may be due to amyloid angiopathy in those cases which show amyloid deposit in these parts. An old putaminal haemorrhage in our case 6 is probably a hypertensive lesion, because this case had a history of hypertension and no amyloid is identified in a section of the basal ganglia. The leptomeningeal arteries and arterioles are involved by amyloid deposit as severely as the cortical vessels. But until now there have been no case reports of primary subarachnoid haemorrhage due to amyloid angiopathy. Careful examination in search of amyloid is necessary for a subarachnoid haemorrhage of unknown cause in an aged patient. Cerebral haemorrhage is also known to occur at a relatively early age in hereditary amyloid angiopathy of Iceland families. There are no senile plaques, nor
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Amyloid deposit in other organs in these families. A case of multiple lobar haemorrhage due to amyloid angiopathy without plaques has been recently reported in Japan.17

Haemorrhage due to amyloid angiopathy is most commonly the lobar type and easily ruptures into the subarachnoid space. Therefore, clinically as is seen in table 2, there is a high incidence of meningeal signs and symptoms, such as headache, vomiting and nuchal rigidity at onset. In case 1, although the patient was demented, he complained of severe headache at the right temporal region, which was confirmed to be the site of the haemorrhage at necropsy. Ropper and Davis18 collected 26 cases of lobar cerebral haemorrhage by computed tomography and analysed clinical features. The initial symptoms were headache alone or predominating over other symptoms in 12 patients, neurological symptoms referable to the affected lobe in 10, and simultaneous headache and neurological symptoms in three. Eleven patients vomited within the first few hours of illness. Five patients had neck rigidity on admission. Clinical features of our cases are generally in agreement with their data.

Lobar cerebral haemorrhage is relatively rare in necropsy series, because of its low mortality rate. According to various authors, it accounts for 5%19, 10%20 and 17%21 among intracerebral haemorrhage other than cases with trauma and aneurysm. In our material 18 cases belong to this category, comprising 30% of the total (table 3). The main reason for this high incidence is the seven cases of amyloid angiopathy. Kurate Kyoritsu Hospital is primarily a chronic geriatric hospital with many old demented patients, who stand a good chance of having amyloid angiopathy. Lobar haematoma may be an indication for a neurosurgical procedure. However, we think that routine surgical evacuation of the clot is inadvisable in cases of suspected amyloid angiopathy for the following reasons. Amyloid angiopathy is a diffuse process and recurrent haemorrhages occur in different parts of the brain. A case is reported of repeated operative removal of haematomas.18 In this case the patient had the third lobar haemorrhage 13 days after the second operation and expired 2 months later. Great difficulty in establishing haemostasis was encountered because of diffuse oozing of blood from the wall of the haematoma. In Torack's case, as mentioned above, haemorrhage occurred after a shunting procedure. Another reason is that in our necropsy records no cases were found to have died of cerebral herniation. In elderly patients, particularly those cases with senile dementia of Alzheimer type, the brain is atrophic and large subarachnoid and ventricular space is present. Hence there is less tendency of herniation, even with the increased volume of haematoma and the surrounding oedematous tissue.

References


Table 3 Locations of the haematomas of 60 cases with cerebral haemorrhage

<table>
<thead>
<tr>
<th>Location of haematoma</th>
<th>Number</th>
</tr>
</thead>
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<tr>
<td>Lateral type</td>
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</tr>
<tr>
<td>Medial type</td>
<td>5</td>
</tr>
<tr>
<td>Combined type</td>
<td>7</td>
</tr>
<tr>
<td>Cerebellar haemorrhage</td>
<td>3</td>
</tr>
<tr>
<td>Pontine haemorrhage</td>
<td>3</td>
</tr>
<tr>
<td>Lobar cerebral haemorrhage</td>
<td>18</td>
</tr>
<tr>
<td>Amyloid angiopathy</td>
<td>7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4</td>
</tr>
<tr>
<td>Brain tumour</td>
<td>4</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>2</td>
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<td>Unknown</td>
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