

Cerebral pathology in subarachnoid haemorrhage

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Subarachnoid haemorrhage due to ruptured intracranial aneurysm is very common but there have been few reports of the pathology in brains of fatal cases. The work which has been done has largely been concerned with the distribution of clots and macroscopic infarcts (Robertson, 1949; Wilson, Riggs, and Rupp, 1954; Crompton, 1962). Tomlinson (1959) comments on ischaemic lesions observed macroscopically and histologically but only in the territory of the aneurysm-bearing vessel. Robertson (1949) and Birse and Tom (1960) mention cases in which ischaemic changes were found outside that territory.

The present study is confined to the brains of patients dying from the consequence of subarachnoid haemorrhage without significant cerebral disruption or intracerebral clot. Of 30 brains examined macroscopically, only eight fulfilled these criteria, three from patients who were not operated on and five from patients who had undergone various surgical procedures. The brains were investigated by embedding large blocks in low-viscosity nitrocellulose, nine blocks being taken from each brain.

CLINICAL SUMMARIES AND BRIEF MACROSCOPIC DESCRIPTIONS OF BRAINS

CASE 1 I.A., a woman aged 55, on 6 September 1960 collapsed with headache and vomiting. On admission to hospital she was unconscious with stertorous respiration. There was early papilloedema and a spastic tetraparesis. Her blood pressure was 110/80 mm. Hg and the cerebrospinal fluid was uniformly blood-stained. Bilateral carotid angiography showed a right anterior cerebral aneurysm. She remained mute and tetraplegic until she died 16 days later.

At necropsy the brain showed no macroscopic abnormality apart from subarachnoid haemorrhage.

CASE 2 O.B., a woman aged 68, on 2 March 1961 developed a sudden headache and fell unconscious. She regained consciousness after about half-an-hour and vomited repeatedly. Her blood pressure was 150/80 mm. Hg and the cerebrospinal fluid was uniformly blood-stained. The only abnormal neurological signs were bilateral extensor plantar responses. Bilateral carotid angiograms showed an aneurysm at the origin of the left

posterior communicating artery, and there was good cross flow on carotid compression. Two hours after the angiogram the patient became confused and dysphasic with a right hemiparesis. The following day a clamp was applied to the left internal carotid artery, which was occluded over the next 48 hours. Three hours after it was tightened the dysphasia and hemiparesis worsened. The clamp was immediately unscrewed but there was no clinical improvement and she died four days later, eight days after the bleed.

At necropsy the left temporal lobe and basal ganglia were palpably soft and the left hemisphere was more swollen than the right. There was blood in the interpeduncular fossa and over the left hemisphere.

CASE 3 R.H., a woman aged 54, on 4 June 1961 suddenly vomited and lost consciousness. She remained unconscious for about two hours and then steadily improved. On admission to hospital six days later, she was noted to have a stiff neck, papilloedema, and a motor and sensory deficit in the left leg. The blood pressure was 120/60 mm. Hg and the cerebrospinal fluid was uniformly blood-stained. Bilateral carotid angiography showed an anterior communicating aneurysm. Eleven days after the first bleed she bled again three times in 24 hours and died.

At necropsy there was subarachnoid blood in the basal cisterns and at the anterior end of the longitudinal fissure. A small clot, 3 cm. in diameter, extended through the cortex into the right frontal lobe. There was no white matter softening.

CASE 4 J.J., a woman aged 32, gave a history of migrainous right-sided headaches since childhood. On 4 June 1959 she was found unconscious and vomiting. She recovered consciousness within an hour but the vomiting persisted through the next day. On admission to hospital two days later the blood pressure was 120/60 mm. Hg and the cerebrospinal fluid uniformly blood-stained. Five days later she was noted to have a slight right hemiparesis and bilateral extensor plantar responses. There was a further bleed under the anaesthetic given for angiography and she did not recover consciousness afterwards. Bilateral carotid angiograms showed an aneurysm of the left anterior cerebral artery. Three days later a craniotomy was done and a screw clamp applied to the anterior cerebral artery proximal to the aneurysm. This was never tightened as the patient died 36 hours later, 17 days after her first ictus.

At necropsy the subarachnoid blood was mainly confined to the anterior half of the brain, particularly the median fissure. The white matter was slightly swollen

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and soft. The anterior part of the corpus callosum had been ploughed up by the clot and was necrotic.

CASE 5 G.N., a woman aged 58, on 24 April 1961 had a severe bout of coughing followed by vomiting and occipital headache. On admission to hospital she was found to be disorientated and the plantar responses were extensor. The blood pressure was 180/100 mm. Hg and the cerebrospinal fluid uniformly blood-stained. On 29 April she bled again and became confused with a left hemiparesis, a left homonymous hemianopia, and papilloedema. A right carotid angiogram showed a saccular aneurysm at the Sylvian point with associated spasm of the carotid, middle, and anterior cerebral arteries. A craniotomy was done the following day and the sac ligatured. She deteriorated and died the day after operation seven days after the first ictus.

At necropsy the subarachnoid clot was more extensive over the right than the left hemisphere. The right temporal lobe showed superficial necrosis where it had been ploughed up by the clot in the Sylvian fissure. The underlying white matter was very soft.

CASE 6 K.P., a woman aged 57, suddenly lost consciousness on 13 January 1961, recovering about two hours later. She was observed to have a right hemiparesis and bilateral extensor plantar responses. On admission to hospital six days later the blood pressure was 150/85 mm. Hg and the cerebrospinal fluid uniformly blood-stained. Bilateral carotid angiograms were normal. Six days later a left vertebral angiogram showed a large bilobular aneurysm arising from the basilar bifurcation. On 29 January she bled again and did not recover consciousness. She died 25 days after the first ictus.

At necropsy there was clot in the interpeduncular fossa and in the third and lateral ventricles. There was an infarct in the corpus callosum at the level of the optic chiasma. Softening of the white matter was extensive, being particularly severe posteriorly.

CASE 7 F.R., a man aged 57, had a sudden severe headache while in bed on 8 December 1960 and became semiconscious with a left hemiparesis. On admission to hospital four days later he was stuporose with a left hemiparesis and bilateral extensor plantar responses. The blood pressure was 170/130 mm. Hg and the cerebrospinal fluid uniformly blood-stained. Bilateral carotid angiography showed a saccular aneurysm at the origin of the right posterior communicating artery and there was good cross-circulation on carotid compression. A clamp was applied to the right internal carotid and tightened over a period of five days. Two days later he developed a left hemiplegia and lost consciousness. The clamp was removed. He improved and became alert until on 3 January 1961 he had a further bleed and died on 14 January, 36 days after his first attack, without recovering consciousness.

At necropsy the subarachnoid blood was mainly over the right side of the brain. There was some laminated clot in the right temporal lobe and some generalized white matter softening, particularly around the lateral ventricles which contained fresh blood clot.

CASE 8 A man aged 62 had a sudden headache on 30 April 1959 and during the night he vomited, had a right-sided Jacksonian attack, and lost consciousness. The blood pressure was 260/130 mm. Hg and the cerebrospinal fluid uniformly blood-stained. He was found to have a right hemiparesis and bilateral extensor plantar responses. Bilateral carotid angiography showed a saccular aneurysm arising from the anterior communicating artery filling from either side, but more readily from the left. On 8 May a craniotomy was done and the left anterior cerebral artery was clipped proximal to the aneurysm. On 13 May he bled again and died on 19 May, 19 days after his first ictus.

At necropsy the subarachnoid blood was mainly over the left hemisphere. There was a tantalum clip on the left anterior cerebral proximal to the anterior communicating artery. The medial frontal cortex showed superficial damage on both sides.

In all cases the ruptured aneurysm was demonstrated at the site shown on the angiogram. The volume of brain involved by these macroscopic lesions, apart from the white matter softening, was small in all cases and it was felt that in themselves they would not have caused death.

HISTOLOGICAL FINDINGS

Histological examination showed that damage was widespread and sometimes severe. The lesions of both grey and white matter were maximal in the territory supplied by the aneurysm-bearing vessel, but there were lesions to be found in all six supratentorial vascular territories, except in case 3 in which the posterior cerebral territories were spared.

The changes in the white matter were those of oedema. There was pallor of the myelin which often ended abruptly at the edge of a vascular territory (Fig. 1). The axons were irregular, sometimes split, or ribbon-like, but ran from pale to normal staining areas without change. Cases 4 and 6 showed myelin breakdown at the anterior part of the corpus callosum and in the adjacent central white matter (Fig. 2). There was a general increase in the number of astrocytic nuclei present of the types described by Greenfield (1939) in cerebral oedema. Only in case 1 did they have any stainable cytoplasm with haematoxylin and eosin or P.T.A.H. techniques. Even in that case the number of gemistocytic forms was scanty.

The cortical lesions were those of ischaemia. The most severely damaged areas showed sharply circumscribed patches of neuronal necrosis with preservation of astrocytes and capillaries (Fig. 3). The individual lesions were usually quite small, although, particularly in the territory of the aneurysm-bearing vessel, they sometimes became confluent to involve large strips of cortex. In case 1 there was a generalized increase of microglia throughout the cortex but in the other seven cases an unusual patho-



FIG. 1. Case 5. The left frontal lobe of a patient with a right middle cerebral aneurysm. There is oedema of the white matter and neuronal necrosis in the left anterior cerebral territory. This lesion cannot be seen on the brain slice. Haematoxylin and van Gieson.

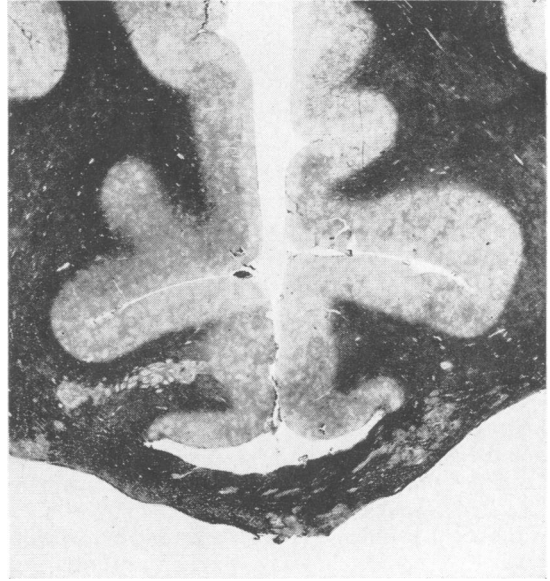


FIG. 2. Case 6. The anterior part of the corpus callosum and cingulate gyri of a patient with an aneurysm at the bifurcation of the basilar artery. There is patchy infarction of the corpus callosum and adjacent white matter. Davenport/luxol fast blue.

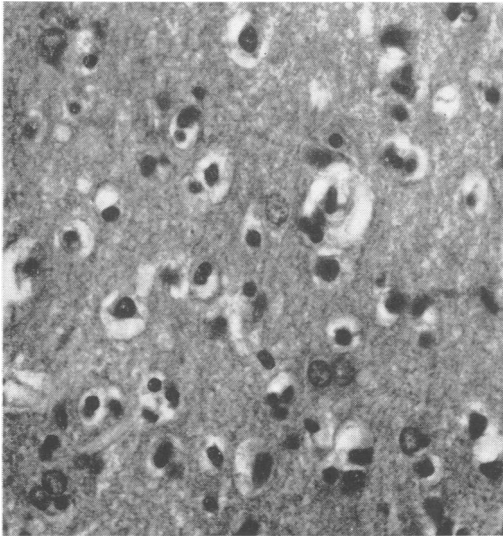


FIG. 3. Case 6. The right superior temporal gyrus of a patient with an aneurysm at the bifurcation of the basilar artery. The cytoplasm of the neurones is shrunken and 'twinned' astrocytes are present. Haematoxylin and eosin $\times 300$.

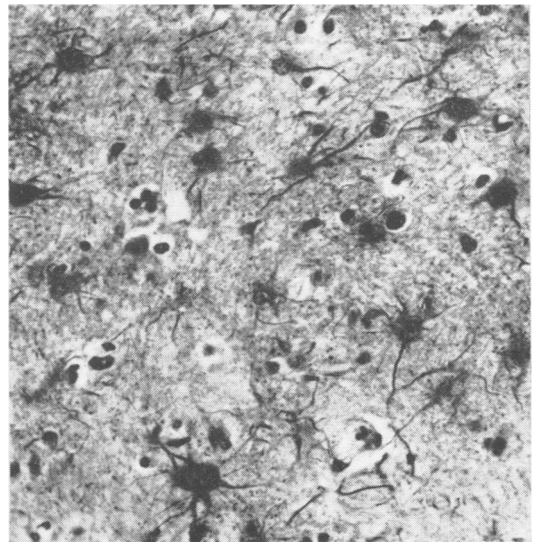


FIG. 4. Case 1. The right caudate nucleus of a patient with a right anterior cerebral aneurysm. There is marked astrocytic proliferation. P.T.A.H. $\times 250$.

TABLE

Case No.	Aneurysmal Site	Grade of Cortical Lesion					
		Left Anterior Cerebral Territories	Left Middle Cerebral Territories	Left Posterior Cerebral Territories	Right Anterior Cerebral Territories	Right Middle Cerebral Territories	Right Posterior Cerebral Territories
1	Right anterior cerebral	3	1	2	3	1	2
2	Left posterior communicating	3	3	3	3	3	3
3	Anterior communicating	3	2	0	3	1	0
4	Left anterior cerebral	3	1	1	3	1	1
5	Right middle cerebral	3	3	3	3	3	3
6	Basilar bifurcation	2	3	3	2	3	3
7	Right posterior communicating	1	1	2	2	2	1
8	Anterior communicating	3	3	1	3	2	1

Grade 3 = neuronal necrosis

Grade 2 = neuronal ischaemia

Grade 1 = gliosis

Grade 0 = normal brain

logical feature was the relative absence of any microglial reaction to the dead neurones. In less severely affected areas the neurones, again in localized groups, showed eosinophilia, with or without cell shrinkage. All the cases, and in particular cases 1, 6, and 7, showed a marked astrocyte proliferation throughout large stretches of the cortex. This is presumably the result of ischaemia which is not severe enough to produce histological changes in the neurones (Fig. 4).

There was very little thickening of small blood vessels even in the patient with severe hypertension (case 8). No organic occlusion of vessels was seen.

In order to give some idea of the extent of the damage in each case the cortical lesions have been graded and the findings presented in a table. It must be emphasized that the grade indicates that there are lesions of that severity in that vascular territory but they are patchy and there are also areas of normal brain.

No particular layer or area of the cortex appeared to be preferentially involved and tops of gyri and bottoms of sulci were equally affected. The lesions showed no predilection for watershed areas being, on the whole, maximal in the cingulate cortex, the hippocampus, and the insula. These are near the centre of their field of supply. The hypothalamus, thalamus, and basal ganglia showed very little abnormality and that only when they lay in the territory supplied by the aneurysm-bearing vessel.

In summary, the histological findings were oedema of the white matter and patchy cortical ischaemia short of actual tissue breakdown. The lesions were present throughout the cortex but were maximal in the territory supplied by the aneurysm-bearing vessel. The cerebellum and brain-stem were spared and the central grey matter was affected very little.

DISCUSSION

The pathological findings in these brains suggest that there has been a general reduction of blood flow

through the cerebral cortex and supratentorial white matter. This reduction has not been sufficient to produce actual infarction but has seriously impaired the nutrition of the cells with the highest demands for oxygen and glucose, namely the neurones and possibly the oligodendrocytes of the white matter, and stimulated astrocyte proliferation in the cortex.

Vasospasm occurring after a vessel has ruptured is such a well-known phenomenon both in the brain and elsewhere that it seems likely that this is the cause of the lesions in the territory of the aneurysm-bearing vessel. The lesions in territories other than that supplied by the aneurysm-bearing vessel are more difficult to understand. Widespread vasospasm in the cerebral tree following rupture of an aneurysm is frequently observed radiographically. However, not all the published cases have had angiograms after the spasm has worn off which makes the results hard to assess. The commoner finding is a localized spasm in the neighbourhood of the bleeding vessel. In one patient (case 5) with a middle cerebral aneurysm, an angiogram done the day after the second bleed showed radiological evidence of spasm in the neighbouring right anterior cerebral artery and right internal carotid artery. This was the only case in this series which showed any radiological evidence of spasm. The lesions themselves would appear to relate to arteries too small to be demonstrable radiographically. The sparing of the central grey matter in the same vascular field as damaged cortex is surprising if the failure of blood flow is due to spasm at the origin of the vessel.

Another possible explanation of the lesions is that they are produced by a vasospastic substance in the cerebrospinal fluid. The vessels would be affected as they ran in the subarachnoid space and this would account for the sparing of the central grey matter. The substance involved would presumably come from the subarachnoid clot and might be 5-hydroxytryptamine. Other conditions such as surgical operations, however, may release blood into the cerebrospinal fluid without producing un-

toward consequences. The histological objection to this theory is that a substance contained in the cerebrospinal fluid should also affect the cerebellum. It also would not account for the widespread oedema of the white matter. Attempts to find adequate quantities of a vasospastic agent in the cerebrospinal fluid have not so far been successful. Raynor, McMurtry, and Pool (1961) have applied 5-hydroxytryptamine to the exposed cortical vessels of cats and have shown that some spasm is produced. The physiologically amines are substances which vary enormously in their effects in different species. Little is known about the effect of 5-hydroxytryptamine on human cerebral vessels, and until more information is available and until it has been extracted in adequate quantities from the cerebrospinal fluid after subarachnoid haemorrhage, little more can be said.

Patients who have subarachnoid haemorrhage often have raised intracranial pressure for hours or days. The reason for this has not been specifically stated. It would appear to be due either to a failure in absorption of cerebrospinal fluid or to cerebral oedema. If the former were true, one would expect to see more trouble after surgical operations in cases in which blood is liberated into the subarachnoid space. Since ischaemia is known to cause cerebral oedema it would seem likely that this is the cause of the raised pressure. Greenfield (1939) has shown in a series of gliomas that cerebral oedema may be associated with ischaemic changes in the cortex similar to those seen in these brains. He does not discuss the pathogenesis of the ischaemia but it could be the effect of pressure against the skull reducing the flow in capillaries. Since cerebral oedema, once established, takes some time to subside, this factor may serve to perpetuate cortical ischaemia even though the vasospasm due to the bleed wears off quite rapidly.

Hypotension as a cause of the lesions in these cases is unlikely on clinical grounds. They were not under observation for the first few hours of their illness but experience suggests that the bleed is more often associated with hypertension than hypotension. Thereafter they were under constant supervision and did not have any significant hypotensive episode either during operation or at any other time.

It is difficult to assess the effect of the surgical procedures on the pathological changes. In cases 4 and 5 the interval between surgery and death was probably too short to affect the picture significantly. In case 8 the ligation of the anterior cerebral artery may have increased the severity of the changes in the anterior cerebral territories but it is unlikely to have had much effect elsewhere. It is probable that the carotid ligation in cases 4 and 7, particularly in the former, where the patient deteriorated following

operation, increased the severity of the ischaemic lesions. It is interesting that in these two patients there is very little to choose between the severity of the pathological damage in the two hemispheres. The circle of Willis has obviously redistributed the reduced flow almost equally.

The pathology in these eight cases suggests that following subarachnoid haemorrhage there is a generalized reduction in supratentorial blood flow. This is probably mainly associated with vasospasm but the effect of oedema of white matter on cortical blood flow may be quite important. This oedema might depress the state of consciousness, and as patients in this age group do not tolerate prolonged unconsciousness, the lesions are indirectly a cause of death.

The large number of damaged neurones which can be seen in this material suggests a possible cause of the dementia which is sometimes a distressing finding in patients who survive their bleeds. Clinical measures designed to reduce the oedema and raised intracranial pressure in the first few hours or days after the haemorrhage, whether surgery is contemplated or not, might help to mitigate this result.

SUMMARY

The brains from eight patients who died from ruptured intracranial aneurysm without significant macroscopic brain damage have been shown to have widespread histological damage.

The findings were patchy ischaemia of the cortex and oedema of the white matter, maximal in the territory supplied by the aneurysm-bearing vessel but present throughout the cerebral hemispheres.

It is suggested that spasm of the aneurysm-bearing vessel with possibly some propagated spasm of other branches of the circle of Willis is responsible for many of the lesions and that pressure from oedema of white matter may perpetuate the cortical ischaemia after the vasospasm has worn off.

The oedema may be responsible for the lowered state of consciousness in these patients and the neuronal fall-out for the dementia which sometimes occurs in those who survive.

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