Cerebral artery spasm

A histological study at necropsy of the blood vessels in cases of subarachnoid hemorrhage

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From a larger series of autopsies with subarachnoid hemorrhage (SAH), 20 cases were selected for the known complication of cerebral vasospasm. Evidence for vasospasm was radiological and pathological in 17 cases and pathological alone in three. A systematic histological examination of the large arteries in places known formerly to have been in spasm showed that, in the 12 early cases (death before 3 weeks), there were relevant changes in all the layers of the arterial wall, the most significant being evidence of necrosis in the tunica media. In the eight late cases (death after 3 weeks), in addition to the sequelae of the earlier acute changes, there was marked concentric intimal thickening by subendothelial fibrosis, again located in the segments of arteries formerly in spasm. Changes were also found in the small arteries, capillaries, and veins, both in the early and late cases but these changes, although striking, were thought to be caused by the ischemia due to the vasospasm; similar changes were also seen in the control cases with ischemia from arterial occlusion.

KEY WORDS : cerebral vasospasm • subarachnoid hemorrhage • ruptured congenital berry aneurysm • cerebral artery pathology

Cerebral artery spasm is a phenomenon frequently present in human cases of subarachnoid hemorrhage (SAH), a condition that most often ensues from the rupture of a congenital “berry” aneurysm situated on one of the major intracranial arteries. In the management of a case, the state of spasm may be suspected when there is an otherwise unexplained progressive and severe lowering of consciousness with or without focal neurological signs. Angiography is diagnostic by demonstrating extensive narrowing of the lumen of one or more major cerebral arteries. The condition can be recognized at autopsy by the finding of evidence of severe ischemia localized to the territories of one or more major cerebral arteries in which no occlusive pathology can be found. The present study surveys the histological changes specifically associated with cerebral vasospasm in a series of 20 autopsies of cases with this complication of SAH with varying periods of survival.

Materials and Methods

Cases of Vasospasm

From a large autopsy series of cases of SAH examined by the Department of Neuropathology at the Radcliffe Infirmary
over a 20-year period, 20 necropsies were chosen in which there was clear evidence of cerebral vasospasm (Table 1). In 17 cases, one or more cerebral angiograms during life had demonstrated vasospasm (Fig. 1). Frequently the vasospasm was demonstrated on a second or third angiogram, obtained commonly after a major intracranial operation, and usually to investigate a deterioration in the condition of the patient. Sometimes, as in Case 6, slight vasospasm was seen on the preoperative angiograms, and the spasm was seen to have increased on subsequent postoperative angiograms. In the three cases without radiological diagnosis, vasospasm was incriminated because necropsy showed severe ischemia in one or more major cerebral artery territories, without histological evidence, despite a careful search, of occlusion in the appropriate arteries. In these three cases (Cases 1, 4, and 20), the early angiograms taken soon after hospital admission did not demonstrate vasospasm, and no further angiograms were obtained at the relevant time of the deterioration of the patient’s condition when the vasospasm was thought to have developed.

**Control Cases**

Because of the nature of the blood vessel changes looked for, we thought it important to compare histologically the parts of the arteries known to have been in spasm with adequate control material. Several other autopsy series were examined to discover the vessel changes existing in incidental cerebrovascular disease, cerebrovascular disease sufficiently serious to cause death, hypertensive encephalopathy, and prolonged recurrent SAH. Control cerebral arteries were examined from a series of 10 cases of cerebral glioma. A large autopsy series of cerebral stroke cases forming part of a previous study was examined, these cases being frequently also cases of hypertension. One case of severe hypertensive encephalopathy was also studied. The changes found in the SAH series were also compared with a series of necropsies of hemispherectomy cases, reported some years ago from our laboratory, in which extensive recurrent bleeding over many years had caused hemosiderosis.

**Methods of Examination**

All the necropsies described here were performed by one of three neuropathologists (J. T. H., D. R. Oppenheimer, and Margaret M. Esiri). The necropsy included a macroscopic and microscopical examination of the internal organs. The fresh brain was inspected, and the amount and distribution of blood clot, the state of the major cerebral arteries, and the position of the aneurysm or aneurysms was noted. The brain was hardened by suspension in 10% formalin for 3 weeks, after which the hindbrain was removed by transversely cutting the midbrain. The cerebrum was then sliced, usually coronally. In addition to the customary macroscopical inspection and routine histological examination, the preserved fixed brains were re-examined for the present study and further sections taken as shown in Fig. 2. In the series of cases with vasospasm, both the large and small cerebral vessels were systematically examined histologically. The 11 specific blocks taken of the arteries of the circle of Willis and its main contributors and branches are shown in Fig. 2. The small cerebral arteries, capillaries, and veins were examined in large tissue blocks, always including the arterial territories of arteries known to have been in spasm. Similar numbers of sectioned vessels were examined in the control material. In addition to the routine use of hematoxylin and eosin stain,
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sections stained to show elastic with a Van Gieson counterstain and others stained by phosphotungstic acid hematoxylin were also examined.

Results

Summary of Cases

The sex, age, interval between the onset of hemorrhage and death, site of aneurysm or aneurysms, the cerebral arteries formerly in spasm, the arterial territories affected by ischemia, whether the case was operated on, and the side of the cerebral swelling are given in Table 1. The cases are listed according to the interval between hemorrhage and death. In 12 cases, the interval was less than 3 weeks, and in eight greater than 3 weeks, this dividing time being important in the transition between the early and late changes. Of the 20 patients, 11 were male and nine female. Ages ranged from 36 to 65 years. In six cases there were two aneurysms and the position of an aneurysm known not to have ruptured is given in Table 1 in parentheses. The two most frequent sites of aneurysm were the right internal carotid artery (six ruptured and one unruptured), and the anterior communicating artery (five ruptured and two unruptured). In these two situations the arteries in spasm were commonly the right anterior and middle cerebral arteries combined with the right internal carotid artery in the case of a ruptured aneurysm on the right internal carotid, and the right and left anterior cerebral arteries in the case of an aneurysm on the anterior communicating artery. The territories showing ischemia were those corresponding to these locations. In Cases 5, 9, and 18, one or more angiograms showed generalized arterial spasm. In these three cases, the distribution of the ischemic changes at necropsy was a better indication of which arteries were formerly in spasm. For further details see Table 1. In 15 cases, an operation on the aneurysm was performed in the acute phase. The patients in Cases 14 and 20 underwent a ventriculoatrial shunt operation at a late stage. Thus, in five of these 20 cases, cerebral artery spasm had developed without an intracranial operation. The cause of death in most cases was the effect of cerebral swelling and ischemia in causing recumbency and a lowered state of consciousness predisposing to either bronchopneumonia or pulmonary embolism.

Changes were observed in the large arteries, small arteries (including arterioles), capillaries, veins, and also in the parenchyma of the brain. The nature of the changes was related to the time interval between SAH and death. While there was a gradual transition of the observed pathological changes, there were important differences between the cases with a short interval (early), and those where the interval was long (late), the changeover being about 3 weeks.

Early Changes

Large Arteries. The changes to be described were observed in the major cerebral arteries known to have been in spasm (Figs. 3 and 4), and were absent from other sectioned parts of the circle of Willis and related major cerebral arteries, and from the control material. These changes, although always

FIG. 2. Diagram of the circle of Willis with its tributaries and branches. The thick transverse lines indicate the 11 places where arteries were systematically examined. The interrupted transverse lines show where the posterior communicating and vertebral arteries were examined in large tissue blocks taken of the pons and medulla.
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*ICA = internal carotid artery; ACA = anterior cerebral artery; MCA = middle cerebral artery; PCA = posterior cerebral artery; ACoA = anterior communicating artery; PCoA = posterior communicating artery; VA = vertebral artery; GS = generalized spasm.
†Spasm seen on two or more angiograms.
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seen in areas of arteries formerly in spasm, were sometimes present in two cerebral arteries and also in areas both near and remote from the aneurysm. The tunica adventitia showed minor changes incidental to the surrounding hemorrhage being thickened by edema with a surrounding exudate of lymphocytes, plasma cells, and macrophages, the last-named of which sometimes containing hemosiderin. The tunica media showed a range of changes (Fig. 3) which were interpreted as necrosis of the smooth muscle. The muscle fibers were sometimes pale with indistinct nuclei or in other areas the nuclei were dark and pyknotic. Some muscle fibers were disrupted and others were more rounded than normal. The most striking and consistent change was the presence of abnormal cells, which we propose to call "plump" cells (Fig. 4). These cells were large, often with a rounded well defined cell outline, and had medium-sized round nuclei. Sometimes the cytoplasm had a foamy appearance. These cells were probably macrophages evoked by tissue damage. They appeared round in the sections, including those cutting the artery wall in the oblique and the longitudinal plane. They could be distinguished from damaged or regenerating smooth-muscle cells (also seen) by the cytoplasmic staining of the latter. The "plump" cells were also seen immediately beneath the intima and more rarely just beneath the adventitia. The tunica elastica was frequently abnormal, usually with minor irregularities (Fig. 3) but sometimes with a complete break of the elastic layer. Abnormally disposed elastic fibers were also seen in the tunica media in arteries formerly in spasm. Irregularities of elastic fiber were also seen in the control material, however, but here were related to distortion caused by the fibrosis and atheroma of arteriosclerosis. Atheroma and fibrosis were uncommon in the series of spasm cases, but were found in Cases 3, 6, and 14 in the proximal parts of the large arteries only. Atheroma when present could be distinguished by the asymmetrical enlargement of the endothelium by the atheromatous plaque. The tunica intima of the large arteries known to have been in spasm showed slight changes, chiefly those of swelling. Note however the intimal changes described below in the small arteries and capillaries and also the intimal changes seen in the large arteries of the late cases.

Small Arteries and Capillaries. The small branches arising immediately from the large cerebral arteries known to have been in spasm and also the remote territories of these large arteries showed marked intimal changes (Fig. 5). The intima was lifted by an exudate of either protein, red cells, macrophages, or polymorphs, the relative occurrence of these products probably indicating the severity of the process. This subintimal change, which was also seen in control material from territories of acute infarction, was interpreted as due to ischemia causing hypoxic endo-

FIG. 3. Case 9. Photomicrograph of transverse section of the right middle cerebral artery. The lumen of the artery is above. The tunica intima (i) is swollen and the tunica elastica (e) irregular and probably abnormal. The tunica media (m) is disorganized, with necrosis of smooth-muscle cells and the presence of "plump" cells. H & E, ×250.
FIG. 4. Case 8. Photomicrograph of transverse section of the right internal carotid artery (known to have been in spasm). The picture shows a typical "plump" cell, probably a phagocyte, within the damaged tunica media. H & E, × 1500.

FIG. 6. Case 8. Photomicrograph of transverse section of the cerebral vein. Note the edema and the red cells within the swollen wall of the vein. Some of the dark particles are hemosiderin. H & E, × 220.

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Late Changes

The early changes described above were observed in the 12 cases with an interval between SAH and death of 17 days or less. In the remaining eight cases, in which the interval between SAH and death was 26, 29, 31, 33, 38, 83, 105, and 164 days, the changes now to be described were found. Again the...
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Fig. 7. Case 19. Cerebrum sliced horizontally after fixation showing both anterior cerebral arteries (arrows) in relation to the corpus callosum (CC). Note the narrowing of the lumen (compare with Fig. 8) due to intimal thickening. See also the angiogram in Fig. 1.

Changes were confined to segments of arteries formerly in spasm.

Large Arteries. The most striking abnormality of the large arteries formerly in spasm was a gross mural thickening, which in several cases could be seen in the sliced brain with the naked eye (Fig. 7). In sections (Figs. 8–11), the tunica adventitia showed a slight increase in connective tissue often with an encrustation of hemosiderin, both free and within macrophages. The tunica media was markedly atrophied (Fig. 9) with fewer layers of smooth-muscle fibers than in control material. Moderate fibrosis of the media was evident. The tunica elastica was thinner than normal, often irregular, and sometimes ruptured (Fig. 9). The tunica intima was the most abnormal, and always showed a concentric subendothelial thickening by fibrosis (Fig. 9). In Case 19, this was present to a marked degree in both anterior cerebral arteries (Fig. 8) which had been in spasm as is shown in Fig. 1. The subendothelial thickening consisted of collagen fibers, fibroblasts, and foamy macrophages. Some “plump” cells as seen in the early cases were also present (Fig. 11). The whole series of changes described in these arteries could be summarized as an artery with an enlarged external diameter, a normal or narrowed lumen, and a wall which is thicker than normal but made up chiefly of an abnormal intimal thickening by subendothelial fibrosis, the tunica media being atrophied.

Small Arteries and Capillaries. The small arteries often showed subintimal fibrosis (Fig. 12), this being the late counterpart of the subintimal exudation described in the early cases.

Fig. 8. Case 19. Histological sections of same area as is seen in Fig. 7. Both anterior cerebral arteries (arrows) show thinning and fibrosis of the media but marked enlargement of the intima by a subintimal proliferation of connective tissue. Note the bilateral infarction (i) of the cingulate gyri. See also Fig. 1. Elastic and Van Gieson, × 12.
FIG. 9. Case 19. Photomicrograph of transverse section of the anterior cerebral artery seen in Fig. 8. The tunica media is atrophied and fibrotic. The tunica elastica is irregular and in one place broken. The tunica intima is elevated above a thick concentric layer of fibrosis. Elastic and Van Gieson, × 90.

FIG. 10. Case 19. Photomicrograph of transverse section of anterior cerebral artery. From above down can be seen the thickened intima (i), the irregular elastica (e) and the fibrotic media (m). H & E, × 220.

Sometimes subintimal changes similar to those seen in the early cases were present. The capillaries were proliferated, distended, and crowded with red and white cells, particularly in the brain and in the territory of the cerebral ischemia. The brain here showed partial liquefaction with many lipid phagocytes, the appropriate findings following cerebral ischemia some weeks before.

Veins. These were sometimes dilated and frequently the adventitia was thickened by fibrosis often accompanied by hemosiderin deposition.

Discussion

The data presented in this paper provide further evidence that cerebral artery spasm develops as a complication of SAH due to ruptured intracranial aneurysms. The pathological observations also show that
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Fig. 12. Case 14. Photomicrograph of small artery in subarachnoid space showing elevation of the intima with layers of subintimal acellular fibrosis. H & E, × 220.

cerebral artery spasm causes marked structural changes in the arterial wall. The changes we have described are confined to the segments of cerebral arteries known to have been in spasm, and are absent from other arteries in the same case and from the various control series. The structural changes are related to the time interval between the SAH (the nearest convenient point to the onset of spasm) and death. In the early cases we found only slight swelling of the tunica intima but there was a conspicuous necrosis of the smooth muscle of the tunica media, with the constant presence of cells we have called "plump" cells, which are probably macrophages. The tunica elastica was also abnormal in showing irregularities, and the tunica adventitia had changes that were probably caused by the surrounding blood. Over a period of time, with a changeover point at about 3 weeks these "acute" changes were replaced by the "late" changes of medial fibrosis and medial atrophy with an intimal thickening by subendothelial fibrosis, the latter causing a concentric narrowing of the arterial lumen. This concentric narrowing of the major arteries formerly in spasm can be seen at necropsy with the naked eye (Fig. 7).

Reports of the pathological findings in SAH at necropsy are numerous. In some of these reports, no changes were described in the major cerebral vessels, or only brief comments were made. Crompton, in two important papers, described his examination of SAH in a large autopsy series. From 172 consecutive necropsies of SAH, 159 were selected for detailed study and of these 119 had cerebral infarction. In these 119 patients, 109 had angiograms during life, and in 40 of these (37%) the angiograms were observed to demonstrate cerebral artery spasm. By contrast, in the 33 cases without evidence of cerebral infarction at necropsy, only four (12%) showed spasm on angiography during life. Crompton described changes in arteries, capillaries, and veins, but these changes, judging from his illustrations, were mainly the changes that we found in the small arteries, capillaries, and veins, and have, because of their presence in ischemic control material, attributed to the effects of ischemia.

Conway and McDonald examined 12 consecutive autopsies of patients who died at periods ranging from 1 day to 15 months after SAH. In the five cases with survival longer than 4 weeks, they found concentric subendothelial granulation tissue thickening the intima of major intracranial arteries, a finding identical to that which we have described under "late" changes. Angiograms were obtained in eight patients and sometimes vasospasm was observed. In their Case 3, vasospasm was seen in the left middle cerebral artery at 8 days and intimal thickening was found in this artery at necropsy 4 months after the SAH. These authors suggested that this structural change in the artery might be confused angiographically with vasospasm and hence be regarded as "delayed" or "prolonged" vasospasm.

Mitzukami, et al., made a study of six necropsies of SAH, paying particular attention to the histology of those major cerebral arteries which by angiography had been shown to be narrowed. In their case with sur-
viral to 8 days, they found necrosis of the media and swelling of the intima, which, however, was asymmetrical and associated with thrombus. They were unsure in this case of the correlation with angiographic narrowing. In their cases with longer survival, they also described medial necrosis, medial thinning, and endothelial proliferation which was again focal and associated with thrombus. The asymmetry of their intimal changes contrasts with the concentric changes we have described in our late changes. Where we found focal or asymmetrical intimal change, in our main series and in control material, we preferred to disregard these changes as being due to degenerative arterial disease.

Our own findings, from their anatomical location in the individual cases, and by comparison with our extensive control material, prove an association between cerebral arterial spasm and a variety of histological changes in those parts of the arteries known to have been in spasm. The early changes are those of recent mural necrosis, while the late changes might be regarded as repair phenomena. This link between arterial spasm and arterial mural damage is the most important part of our findings, but we have also shown, by the negative evidence in the hemispherectomy control material, that SAH alone without vasospasm does not appear to cause these changes. Myonecrosis has been observed in experimental animals in which chronic cerebral vasospasm has been induced by the injection of blood or norepinephrine into the subarachnoid space. The link that we have demonstrated between vasospasm and mural damage presumably arises because cerebral vasospasm damages the arterial wall. In our view, it is unlikely that both the vasospasm and the histological changes are caused simultaneously by another mechanism, and it is also improbable that the arterial damage causes the vasospasm. Represented diagrammatically we have three explanations of the association, and of these we prefer the first:

1. SAH → vasospasm → arterial wall necrosis

2. SAH

3. SAH → arterial wall necrosis → vasospasm.

If our view is correct, why does vasospasm cause these histological changes? An artery subjected to prolonged contraction of its smooth-muscle coat may be physically damaged or there may be a pharmacological action due to the accumulation of excess metabolites in the vessel wall. Alternatively, the contraction of the tunica media may so alter the intima that diffusion between the lumen and the vessel wall in one direction of various nutrients and in the other direction of toxic metabolites may be impeded. We have considered an effect of SAH on the vasa vasorum but it appears from our findings and the anatomy of these nutrient vessels that this is unlikely. Vasa vasorum are very small or absent from even the large intracranial arteries and probably supply at most only the tunica adventitia and the outermost part of the tunica media. The damage we have described affects the intima, elastica, and the whole of the media, while the adventitia is much less affected. An explanation based on a failure of diffusion through the intima accords with our findings better than an effect on vasa vasorum.

The late change of concentric intimal thickening that we describe here, and which was also found by Conway and McDonald, is remarkably similar to that called Heubner's arteritis. This arteritis, also called endarteritis obliterans, was described by Johann Otto Heubner of Berlin in the chronic leptomeningitis of syphilis, but a similar condition occurs in chronic meningitis caused by Mycobacterium tuberculosis and by some pyogenic bacteria. An endarteritis obliterans is also present in a widespread arterial disease called Buerger's disease described by Leo Buerger of New York. Detailed discussion of these diseases is outside the scope of this paper, but we can suggest an explanation linking this type of arteritis with that found in association with SAH. Vasospasm has been postulated to occur in leptomeningitis and to be the explanation of the arterial infarctions found in these cases. The arterial pathology, which is so like our own findings, might thus be the sequel of vasospasm rather than being itself the primary cause of the focal cerebral ischemia. It is also of interest and relevance that Hugo Spatz described the concentric thickening of a retinal artery in a patient with Buerger's disease whose retinal arteries during life had been observed by ophthalmoscopy to be in spasm.

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Acknowledgments

We are grateful to the clinicians of the Oxford Hospitals for permission to use their notes and in particular to Mr. C. B. T. Adams and Mr. M. Briggs under whose care most of these patients were admitted. Dr. P. W. E. Sheldon allowed us the use of cerebral angiograms most of which had been obtained under his direction. Drs. D. R. Oppenheimer and M. M. Esiri gave us generous access to their autopsy reports and preserved fixed specimens.

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