Medical Journal of the
Islamic Republic of Iran

Volume 12
Number 1
Spring 1377
May 1998

ANATOMIC CORRELATION BETWEEN INTIMAL PATHOLOGY AND CEREBRAL VASOSPASM FOLLOWING SUBARACHNOID HEMORRHAGE

M.A. KHALILI*, B.R. CLOWER, AND K. IWASA**

*From the Departments of *Anatomy and **Neurosurgery, University of Mississippi Medical Center, Mississippi, U.S.A.*

ABSTRACT

Subarachnoid hemorrhage (SAH) resulting from a ruptured intracranial aneurysm can induce cerebral vasospasm with subsequent reduction in cerebral blood flow (CBF). The present study examines the pathological alterations in the wall of human cerebral arteries at autopsy, especially with regard to intimal pathology, following aneurysmal SAH. Arterial segments from the circle of Willis were fixed in 10% formalin, embedded in paraffin, sectioned at 4μ and stained with hematoxylin-eosin or toluidine blue. Similar numbers of sectioned vessels were also examined in control material. The areas of intima, lumen and the length of internal elastic lamina were compared with those from control sections. Pathological changes such as myonecrosis and fibrosis in muscular layers associated with a possible loss of compliance and elasticity of the vessel wall were also noted. The average luminal area decreased to 56.8% ± 12.5% compared to comparable controls ($p<0.005$). The tunica intima was the most abnormal component of the arterial wall with cellular proliferation which was made up predominantly of collagen fibers and loose fibroblasts. These pathological findings are mainly due to myonecrotic changes and intimal proliferation with the resultant luminal constriction and CBF impairment which might explain the high incidence of cerebral infarction in cases of SAH.

Keywords: Subarachnoid Hemorrhage, Cerebral Vasospasm, Intimal Pathology.

MJIRI, Vol. 12, No. 1, 25-29, 1998.

INTRODUCTION

Subarachnoid hemorrhage (SAH) usually occurs when an intracranial berry aneurysm ruptures and bleeds into the subarachnoid space.[6,8,11,14,19] It is a serious disease with high morbidity (20% to 30%) and mortality (40% to 50%) rates. Despite the progress that has occurred in medical and surgical treatment, the incidence of SAH remains unchanged.[5,16,17]

The most complicated and disastrous outcome of aneurysmal SAH is mainly due to the development of long-term cerebral arterial narrowing known as "cerebral vasospasm".[1,9,15] This can lead to decreased cerebral blood flow, resulting in neurological deficits, cerebral ischemia or infarction, and death. Cerebral arterial spasm is time-dependent, rarely occurs before the 3rd day and reaches its peak around 7-10 days after the bleed.[1,11,15,23]

The pathoanatomical changes that appear in the major

Correspondence: Dr. M.A. Khalili, Department of Morphoanatomy, S. Sadoughi University of Medical Sciences, Yazd, I.R. Iran, Tel: 0351-45444.

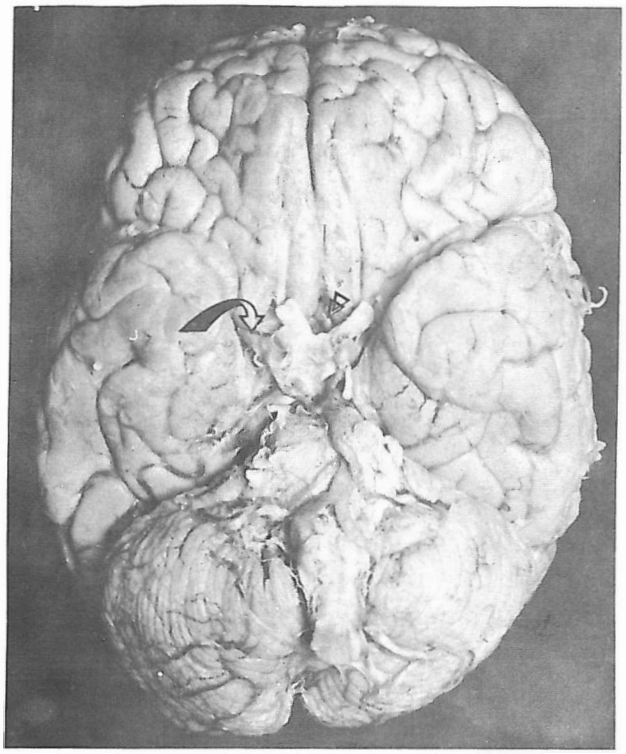

Fig. 1. Ventral view of the brain from autopsied cases of control showing the arterial patterns. Note the anterior cerebral (arrowhead) and middle cerebral (curved arrow) arteries.

cerebral arteries of patients who died at different time intervals following SAH, specifically associated with cerebral vasospasm, have been studied for many years.[3,4,19,20] However, the purpose of this study was two-fold: 1) to examine the histopathological changes of the cerebral arterial wall from the autopsied cases of patients dying after two weeks post-SAH; and 2) to determine the morphometric correlation between the intimal pathology and arterial narrowing which usually occurs following aneurysmal rupture. To our knowledge, this is the first morphometric study of cerebral arterial segments from autopsied cases.

MATERIALS AND METHODS

For light microscopy and morphometry, arterial segments from the circle of Willis of 2 control and 4 autopsied cases of patients who died after two weeks following SAH were fixed in 10% formalin. After several days, they were dehydrated in graded ethanol dehydration prior to embedding in paraffin. Then, the blocks were cut transversely into 4 micron sections, and stained with 1% toluidine blue or hematoxylin-eosin. The light microscopic slides were finally coverslipped and examined by a conventional light microscope. Five sections were taken proximal and distal to the site of aneurysmal rupture from

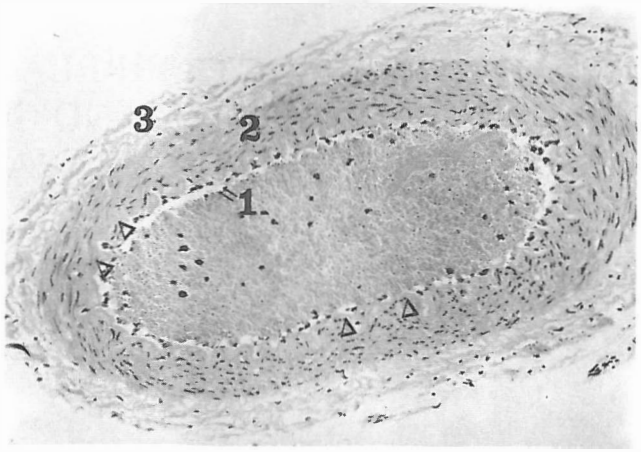

Fig. 2. Cross section of middle cerebral artery from control case. Note single layer of endothelial cells along intimal layer (1). The internal elastic lamina (arrowheads) lies between the endothelium and the smooth muscle of the tunica media (2). Note the thin adventitial layer (3) with no sign of inflammation. (× 47).

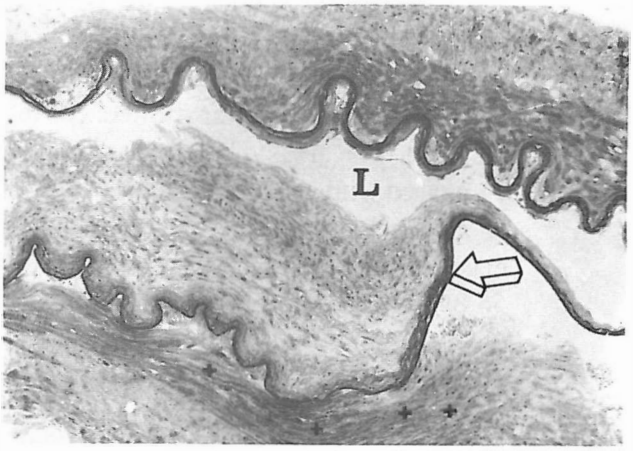

Fig. 3. Anterior cerebral artery from SAH case showing fibrosis of tunica media (+) and severely narrowed lumen (L) from abnormal intimal proliferation/thickening. Internal elastic lamina (arrow).(× 150).

both right and left middle cerebral arteries (M1 portions) and the anterior cerebral arteries (A1 portions) (Fig. 1). The length of the circumference of the internal elastic lamina, and the area of the intima and of the lumen of each human arterial section were measured using a Calcomp 2000 (Anaheim, CA) digitizer interfaced to a BBC computer.

RESULTS

Using light microscopy, the cerebral arteries from control autopsy cases were consistent in morphology with endothelium forming a continuous monolayer overlying a non-convoluted internal elastic lamina. No sign of smooth-

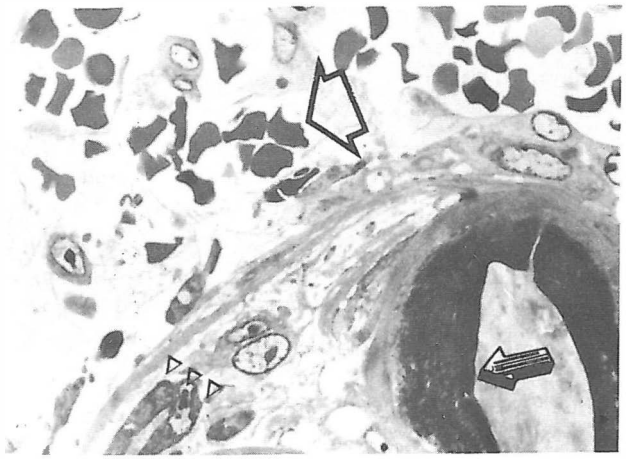

Fig. 4. High power magnification of intimal loose fibroblasts (arrowheads) from anterior cerebral artery. Open arrow points out to the red blood cells within the arterial lumen. Internal elastic lamina (arrow).(× 720).

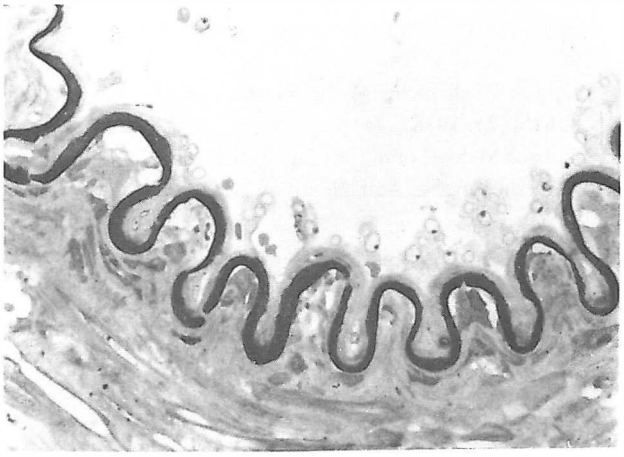

Fig. 5. Middle cerebral artery from SAH case showing fibrosis and patchy necrosis of smooth muscle fibers in the tunica media. (× 100).

muscle proliferation or necrosis, or of adventitial inflammatory infiltrate was apparent in the control specimens (Fig. 2). Table I shows the mean length of the circumference of the internal elastic membrane, and the areas of the intima and of the lumen of the control arterial sections.

In all of the autopsy cases of SAH studied, pathological changes were found in the anterior and middle cerebral arteries (Figs. 3-5). The intimal cellular proliferation was the most obvious change observed, made up predominantly by the loose fibroblasts and collagen between the corrugated internal elastic membrane and arterial lumen (Figs. 3, 4). This pathological reaction was associated with a corresponding reduction in the area of the arterial lumen (Figs. 2,6). The internal elastic lamina was frequently found to be abnormal, being markedly infolded and

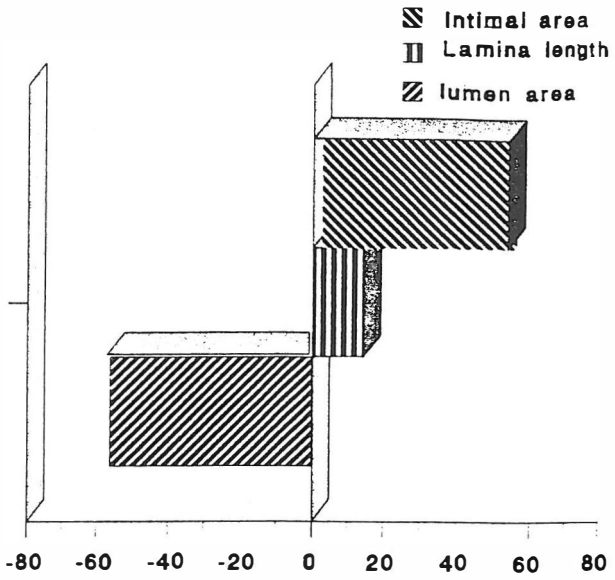

Fig. 6. Percent change in cross-sectional area of intima, lumen, and length of elastic lamina of human cerebral arteries after subarachnoid hemorrhage ($p<0.005$).

Table I. Results are mean cross-sectional areas (mm^2) and circumference (mm) from human arterial specimens, ±SEM (n= 4). Anterior cerebral artery (ACA), middle cerebral artery (MCA).

	Intimal area		Luminal area		Lamina length	
	MCA	ACA	MCA	ACA	MCA	ACA
Control	0.130 ±0.05	0.109 ±0.01	0.752 ±0.97	0.690 ±1.80	1.990 ±1.0	1.687 ±3.2
SAH	0.668 ±0.08	0.607 ±0.08	0.293 ±0.30	0.289 ±0.65	4.636 ±5.10	3.730 ±3.85

corrugated, but in some areas fragmented and displaced into the lumen (Figs. 3,4). Patchy areas of necrosis in the tunica media with disrupted muscle fibers were the other important findings (Fig. 5). Blood cell infiltration in the adventitia was also seen in most arterial specimens.

Morphometric results are summarized in Table I and in Fig. 6. The results indicated a 53% increase in intimal area, 15% increase in internal lamina length, but a 51% decrease in the luminal area of the arterial sections from autopsied cases of SAH, when compared with control values.

DISCUSSION

Today, cerebral vasospasm is recognized as the most important cause of disability and death in patients with SAH. It is time-dependent, as it rarely occurs before the 3rd day following the initial SAH, reaches a peak around the

end of the first week, and continues for two to three weeks.[11,15,20,21,23]

In all of the SAH cases that we studied, pathological changes were found in the tunica adventitia, media, and intima. Myonecrosis with disrupted muscle fibers and blood cell infiltration in the adventitia was a common feature of this arteriopathy. However, the most prominent change was the severe intimal cellular proliferation causing eccentric narrowing of the lumen (approximately 55%). Obviously, none of these vasculopathy changes were observed in control arterial sections. Peerless et al. suggested that cellular proliferation and fibrosis in the intima following SAH indicates a fundamental arterial wall response to various noxious stimuli. The results agree with the findings of other investigators that significant intimal thickening is usually not seen in the first week after hemorrhage, and is still not prominent till a few weeks have passed.[7,10,16] As we have reported earlier, extensive ultrastructural studies revealed that endothelial cells were the first to undergo degeneration and necrosis following experimental SAH in rats.[12,13] However, in contrast to the findings in arterial sections from autopsied cases of SAH, only mild intimal thickening, mainly due to the increased amount of amorphous material within the internal elastic membrane, was noticed. This may indicate that the mode of pathoanatomical changes following SAH is different in rats compared to autopsied cases.

From their classic investigation, Hughes and Schianchi found that in patients surviving 17 days or less from aneurysm rupture, the tunica intima was only slightly swollen, whereas in those surviving longer the intima became the most abnormal component of the arterial wall with concentric thickening due to fibroblast cells, collagen fibers, and macrophages. The same cellular components, except macrophages, were also observed in the present study. Therefore, it seems that the delayed appearance of intimal proliferation (>2 weeks) does not correlate with the time-course of vasospasm in humans which begins a few days after the onset of hemorrhage. It is likely that pathological responses related to the severity of the vessel wall injury (e.g., endothelial and smooth muscle cell necrosis) are directly related to the severity of vasospasm. Whereas the intimal proliferative reaction which usually occurs later during the course of vasospasm is a non-specific reaction, it may alter the maintenance of vascular physiological homeostasis.[7,13,21]

In summary, the pathological changes that were observed in intracranial arteries two weeks after SAH are in agreement with previous studies.[7,8,10,16,21] In addition to this, our morphometrical analysis showed a severe reduction in the arterial lumen with hypertrophy of the intimal layer. This certainly would affect the rate of blood flow to the cerebral cortex.

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