Lipohyalinosis and Miliary Microaneurysms Causing Cerebral Hemorrhage in a Patient with Moyamoya

A Clinicopathological Study

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SUMMARY Moyamoya is an intriguing and controversial syndrome. This patient study serves to align the pathophysiology of intracranial hemorrhage in moyamoya with the cerebral vascular disease seen with hypertension, or aging. The historical evidence linking lipohyalinosis and microaneurysms to cerebral hemorrhage is reviewed, the pathogenesis of this angiopathy is discussed, and explanations considered for its association with the vascular pattern of moyamoya. We propose that hemodynamics, genetics or both are among the primary operant etiologic factors.

MOYAMOYA DISEASE was first recognized in 1961 by Nomura1 and Takeuchi2 as a clinical and radiological syndrome associating bilateral internal carotid artery narrowing or occlusion at the siphons with an unusual basal vascular network or rete. The nature and etiology of the basal rete or vascular mesh remain speculative.3-7 Nishimoto and Takeuchi8 proposed that acquired stenosis of the internal carotid arteries causes the development of basal collaterals to bypass the obstruction. Smith9 proposed a similar mechanism and observed that several mammalian species are known to possess a well-developed carotid retia in association with non-persistence or degeneration of the internal carotid artery.10 Since moyamoya in children usually presents as multiple cerebral ischemic events10,11 we speculate that the carotid stenosis must occur at an early age, or a genetic predisposition must be operant to produce the rete, thereby excluding the majority of later-life atherosclerotic lesions.

The frequent presentation of moyamoya in adults as subarachnoid hemorrhage or, less commonly, intracerebral hemorrhage is unexplained. Some authors suspect that acquired stenosis of the internal carotid arteries causes the development of basal collaterals to bypass the obstruction. However, other investigators6,10 have identified saccular aneurysms with an unusual frequency in the vertebral-basilar system.

We report a non-hypertensive Japanese male with moyamoya who suffered recurrent subarachnoid and intracerebral hemorrhages. Histopathological study of a final, massive, diencephalic hemorrhage revealed marked lipohyalinosis with fresh bleeding sites in multiple diseased vessels, including several ruptured microaneurysms.

Patient Report

S.S., a Japanese male, was well until age 43 years, when he was hospitalized following the abrupt onset of severe right occipital headache, nausea and vomiting. The past medical and family history were non-contributory. Examination revealed blood pressure of 110/72 mm Hg, drowsiness, mild nuchal rigidity and mild paressis of conjugate upward gaze. Lumbar puncture revealed grossly bloody cerebrospinal fluid (CSF). Bilateral carotid angiograms showed occlusion of the right internal carotid artery (ICA), 70% narrowing of the left ICA at the siphon, and occlusion of the left anterior cerebral artery. There was no evidence of aneurysm, space-expanding lesion or abnormal basal vascularity.

The patient recovered and was asymptomatic until 2½ years later, when he developed sudden weakness of the left leg, severe occipital headache, photophobia, nausea and vomiting. Examination revealed a blood pressure of 120/80 mm Hg, lethargy, marked nuchal rigidity and a left hemiparesis. The complete blood count, electrolytes, fasting blood sugar, blood urea nitrogen, urinalysis, VDRL, and quantitative immunoglobulins were within normal limits. The erythrocyte sedimentation rate was 3 mm/h, and the serum cholesterol was 227 mg/dl. A chest x-ray and an electrocardiogram were normal. Lumbar puncture revealed grossly bloody CSF. An isotopic cerebral flow study showed an abnormal accumulation of radioactivity in the left basilar region suggestive of extensive collateral vascularity between either the carotid and vertebral-basilar systems or between the external carotid and internal carotid arborizations. There was marked delay in the visualization of the right middle cerebral artery (MCA) system. The isotopic brain scan revealed patchy increased uptake deep in the right parietal region. The patient refused to have cerebral angiography and recovered with a mild left hemiparesis. A follow-up isotopic brain scan at 8 weeks was normal.

Six years later (age 51, eight and one-half years following the initial subarachnoid hemorrhage), the patient abruptly developed a severe right retro-orbital headache, increased left body weakness and a new left-sided numbness. The blood pressure was 155/90 mm Hg. Drowsiness, two millimeter anisocoria (right pupil greater than left), inability to adduct his right eye beyond the midline and a left homonymous
FIGURE 1. Right internal carotid angiogram, early arterial phase, showing narrowing of the distal internal carotid artery with total occlusion just beyond the origin of the ophthalmic artery. Collateral is provided by the meningohypophyseal trunk of the internal carotid artery and multiple branches of the ophthalmic artery.

Figure 2. Left internal carotid angiogram, early arterial phase, showing total occlusion of the internal carotid artery in the supraclinoid portion with occlusion of the origin of the ophthalmic artery as well. Reflux into the external carotid artery shows collateral arising from the distal maxillary artery. Branches of the cavernous portion of the internal carotid artery also provide collaterals.

Hemianopsia were noted in addition to a marked left hemiparesis. Thirty minutes after hospitalization, the patient vomited and became semicomatose, with skewed ocular deviation and bilateral loss of pupillary light reflex. The fundi were normal. A computerized tomographic scan revealed a hemorrhage involving the right diencephalon and upper brainstem and extending into the third, fourth and portions of the lateral ventricles. Cerebral angiography revealed a pattern consistent with moyamoya. Both internal carotid arteries were occluded in the supraclinoid segment (figs. 1–2). The vertebro-basilar system was not stenotic and provided multiple routes of collateral flow including small telangiectatic vessels in the region of the thalamus which contained multiple microaneurysms (figs. 3–4). Small arterial branches from the external carotid arteries, the ophthalmic arteries, and the cavernous portion of the internal carotid arteries also contributed to this abnormal basilar rete.

The hospital course was progressively downhill, culminating in gastrointestinal bleeding, aspiration pneumonia, and cardiopulmonary arrest and death on the ninth hospital day.

Pathological Findings

The general postmortem examination revealed mild atherosclerosis of the aorta and medium and large arteries, bilateral necrotizing bronchopneumonia, multiple acute and chronic duodenal ulcers, and very mild subcapsular renal scarring. The heart, adrenals, and small systemic arteries were normal.

Histopathologic examination of the extracranial internal carotid arteries revealed hypoplasia on the right, with a maximum diameter of 3 millimeters and occasional focal eccentric atherosclerotic narrowing of up to 70% of the lumen. On the left the caliber was normal, but marked concentric atherosclerotic...
narrowing was present. Intracranially the right ICA was hypoplastic with absence of stainable elastica interna. The left ICA was occluded by an organized thrombus which extended 0.3 cm into the anterior cerebral branch.

The vertebral and basilar arteries were of normal caliber with mild atherosclerosis. Coronal sections of the cerebral hemispheres revealed a recent hematoma with destruction of the right thalamus, the hypothalamus, the posterior limb of the internal capsule and the globus pallidus. A tear through the wall of the third ventricle marked the site of intraventricular extension of the hemorrhage. Within the right internal capsule were two rubbery, firm, yellow discolored regions indicative of past hemorrhage, including a resorbing 1.2 × 0.3 cm slit hemorrhage.

Horizontal sections of the brainstem and cerebellum revealed that the diencephalic hemorrhage extended into the midbrain tectum and tegmentum and the rostral pontine tegmentum.

Histopathological examination of the right internal capsule, basal ganglia, and diencephalon was performed on multiple specimens of the hematoma and surrounding parenchyma. The tissue blocks were embedded in paraffin and serially sectioned every 10 microns. Gomori’s trichrome and Verhoeff’s elastin combined with van Gieson’s collagen stains were employed. The dorsal thalamus and the internal capsule were gliotic with plentiful reactive astrocytes, gitter cells, hemosiderin-laden macrophages and areas of cystic necrosis. An old lacunar infarct was identified in the inferomedial putamen.

Of particular interest was a transmural arteriolar disease process predominantly affecting vessels 50–1500 microns in diameter and consistent with lipohyalinosis. The intima of these vessels was often thickened and generally studded with foam cells (fig. 5). The elastica interna was reduplicated, frayed, and at times discontinuous (fig. 6). The media was thickened with hyalinized connective tissue (fig. 7). Smooth muscle was generally sparse and occasionally appeared necrotic. Unidentified cellular debris and
foam cells were scattered diffusely through the medial lamellae which were often separated by focal aggregations of red blood cells. Hemosiderin-laden macrophages were frequently abundant through the media, adventitia and beyond, indicating previous minor hemorrhage. In a few instances diseased vessels of 100–400 microns in diameter were also completely occluded by a hyalin fibrotic process extending from the media and intima.

Four diseased arterioles were demonstrated to give rise to microaneurysms which were all sites of hemorrhagic rupture. The parent vessels ranged from 100–1500 microns in diameter, the aneurysms ranged from 100–2500 microns in greatest dimension and in three instances arose in continuity with a vascular branch point. Elastica interna and tunica media extended from the parent vessels into the proximal walls of the aneurysms (fig. 8), before discontinuing. Foam cells were frequently identified within the subintima of the aneurysms. In 3 aneurysms necrotic smooth muscle continued for short distances from the parent vessel before thinning and finally disappearing. In the fourth instance, prominent subendothelial cushions identified the neck of the aneurysm beyond which smooth muscle was not identified (fig. 9). All 4 aneurysms were ruptured in regions of the fundus where the elastica interna was absent and the media reduced to a thin hyalin layer. At the sites of rupture recent hemorrhages with masses of red blood cells transected by fibrin bands were seen to extend well beyond the well-demarcated walls of the aneurysms proper.

Four additional instances of vascular rupture with hemorrhage were found in diseased arterioles at sites of focal thinning and fibrinoid necrosis but without aneurysm formation (fig. 10). The involved vessels ranged from 100–500 microns in diameter.

Larger arterioles of 1500–3000 microns in diameter, including several located within the subarachnoid space surrounding the diencephalon, were also oc-
casionally diseased, but to a lesser extent. These larger vessels were not found to be sites of microaneurysm formation or of hemorrhage.

Discussion

This report is the first documentation of lipohyalinosis and multiple hemorrhagic microaneurysms in moyamoya and serves to validate the proposed role of microaneurysms and multiple bleeding sites as the source of intracerebral hemorrhage in other conditions associated with lipohyalinosis, notably hypertension.23–28

The concept of intracerebral hemorrhage arising from rupture of miliary microaneurysms was first proposed by Charcot and Bouchard in 1868.29 Several
more recent studies have supported their viewpoint. Matsuoka18 concluded from microscopic studies of autopsy specimens that "angionecrosis" and true aneurysm were the causes of brain hemorrhage. "Angionecrosis" was described as a process affecting arteries of 50-200 microns in diameter and involving subendothelial, intimal and medial deposition of a "homogeneous plasma-like substance," attenuation of the elastica and, finally, arteriolar dilatation due to internal pressure into an aneurysm 150-600 microns in diameter. Matsuoka maintained that the severity of angionecrosis and the incidence of aneurysm formation correlated with the height of blood pressure during life, and he proposed that hypertensive cerebral hemorrhage arose from the simultaneous or consecutive rupture of many necrotic or aneurysmal arteries. Matsuoka identified cerebral angionecrosis, aneurysm formation and hemorrhages in rabbits with hypertension induced via the Goldblatt procedure. He speculated that changes in blood chemistry secondary to renal alterations might be etiologically related to angionecrosis. Santos-Buch et al.19, 20 have enriched this hypothesis by identifying necrotizing arterial lesions, microaneurysms and hemorrhage in the retinae of rabbits subjected to surgical renal alteration with or without subsequent hypertension. It is possible that alterations in the aldosterone-renin-angiotensin system are involved.18

Studies by Russell21 and Cole and Yates22 confirmed the occurrence of microaneurysms in an anatomical distribution closely correlated with that of hypertensive hemorrhages and further defined the epidemiology of microaneurysms. Russell21 identified a strong association between miliary aneurysms 300-900 microns in diameter and hypertension. A few aneurysms were observed in his control group of normotensive (diastolic BP less than 110 mm Hg), but 84% of this group were 60 years of age or older. Cole and Yates22 observed that microaneurysms of 50-2500 microns in diameter were uncommon below age 50 years even in hypertensive subjects. In normotensive subjects microaneurysms were infrequent and restricted to patients over 66 years of age with diastolic blood pressure over 100 mm Hg.20 Therefore, both hypertension and age appear to be major factors in the formation of microaneurysms. Russell21 and Cole and Yates22 found the aneurysms to be located most commonly at branch points of parent vessels 100-400 microns in diameter. The parent vessels in all cases were diseased, characteristically showing reduplication of the elastica interna, hyalin thickening of the intima and media, loss of medial muscle, and hemosiderin-staining of the adventitia. In two instances actual hemorrhages were reportedly traced to specific microaneurysms.

Fisher23-25 has further defined the pathological process affecting small cerebral arteries in hypertension and coined the term lipohyalinosis to specify a destructive vascular process previously catalogued under a varied nomenclature including "fibrinoid necrosis," "angionecrosis," and "hyaline arterionecrosis." In Fisher's view, raised arterial pressure alters the walls of small cerebral arterioles of 80-300 microns in diameter and leads to focal subintimal fibrinoid deposition, associated with the presence of fat-filled macrophages. As the process advances, the integrity of the elastica and media is lost, and the artery dilates locally to form a microaneurysm 500-1500 microns in diameter. Extravasations of red blood cells take place through the damaged walls and hemosiderin-filled macrophages are seen through and beyond the adventitia. Fisher found lipohyalinosis to be, by virtue of occlusion of the vascular lumen, the cause of many lacunar infarcts.24, 31 He could not confirm that microaneurysms were the sources of massive intracerebral hemorrhages.

In the present report lipohyalinosis and miliary microaneurysms were identified as the source of a fatal thalamic hemorrhage and probably of preceding subarachnoid and intracerebral hemorrhages in a patient with moyamoya. The role of this angiopathy in producing massive intracerebral hemorrhages is con-
firmed and Matsuoka's contention that massive cerebral hemorrhage arises from simultaneous or consecutive rupture of many diseased regional vessels is corroborated. This is also in agreement with Fisher's observation of a relationship between lipohyalinosis and lacunar infarcts.

The absence of recorded hypertension during life (except minimally following a final devastating di-enecephalic hemorrhage) and the relatively young age of 51 years make lipohyalinosis and microaneurysms remarkable lesions in this patient.

Is there a relationship between the moyamoya pattern and the vascular histopathology? Fisher identified a possible relationship between occlusive carotid disease and subsequent ipsilateral intracerebral hemorrhage. He reported two instances of deep cerebral hemorrhage arising from "unusual anastomotic channels" in adults with ipsilateral internal carotid hypoplasia and occlusion from early life. The microvascular histopathology and angiographic appearance of these cases was not identified. In our patient, internal carotid artery hypoplasia (presumably long-standing) and occlusion were present ipsilateral to a massive thalamic hemorrhage. In addition, progressive stenosis and finally occlusion of the contralateral internal carotid artery due to atherosclerosis developed concomitantly with the radiologic appearance of a basal collateral vascular rete. The thalamic hemorrhage arose from the region of this rete. Serial sectioning of the hemorrhage and surrounding parenchyma revealed typical lipohyalinotic arterioles and miliary microaneurysms including multiple sites of rupture contributing to the thalamic hemorrhage. Such histopathology has been reported in certain areas of the brain in association with the hemodynamic stress of hypertension and/or the wear-and-tear of long life. In this instance, it is likely that the basal vascular rete was subjected to abnormal hemodynamic stress, or underwent a premature aging process, or both. The presence of abnormal hemodynamic stress in moyamoya may be due to shunting through the basal collateral rete, and such stress may induce lipohyalinosis and microaneurysm formation. The consequent predisposition to vascular rupture helps to explain the frequent adulthood presentation of moyamoya as an intracranial hemorrhage. (Adams et al. similarly suggested that hemodynamic factors played a role in the occasional appearance of saccular aneurysms of the posterior circulation in moyamoya.)

Alternatively, the basal rete of moyamoya may be composed of inherently abnormal vessels which undergo premature degeneration and hemorrhage. It is clear that the typical radiological appearance of moyamoya can be acquired as a non-specific manifestation of a number of disorders. However, there seems to be an unusually high frequency of the syndrome among otherwise healthy patients of Japanese heritage. In this group, as in our patient, hypoplasia of one or both internal carotid arteries is a frequent concomitant. Perhaps some individuals or genetic subpopulations share with certain mammalian genera the predisposition to develop a collateral basal rete in response to stenosis or degeneration of the carotid artery. Such a phylogenetically anachronistic process might produce an intrinsically abnormal vasculature subject to premature degeneration and hemorrhage.

References

24. Fisher CM: Pathological observations in hypertensive cerebral

Erratum
In Vol 10, No 6 (November-December, 1979) page 693 (Regional Glucose Utilization/Hawkins et al.) correct equations 5 and 6 to read as follows:

EQUATION 5

Read: \( \text{SpA brain} = \frac{E}{T} \int_{0}^{T} \text{SpA plasma} \, dt - \int_{0}^{T} \text{SpA brain} \, dt \)

EQUATION 6

Read: \( \text{SpA brain} = E \int_{0}^{T} \text{SpA plasma} \, e^{(1-T)E} \, dt \)
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Stroke. 1980;11:405-412
doi: 10.1161/01.STR.11.4.405

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