Growth and Rupture Mechanism of Partially Thrombosed Aneurysms

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Key Words: intracranial partially thrombosed aneurysm, treatment, hemorrhage, mass effect

Summary

Within the group of giant and large aneurysms the subgroup of the so-called "partially thrombosed" aneurysms can be differentiated according to clinical and neuroimaging findings. The present study was carried out to determine the site of bleeding of these aneurysms and what implications concerning their pathomechanism can be drawn from these findings.

Twenty patients aged two to 77 (mean 44) years who exhibited a partially thrombosed aneurysm that had recently bled were included. Images (MRI including T1 pre- and postcontrast and T2 weighted images in multiple planes, CT and digital subtraction angiography) and patients' charts were reviewed.

MRI showed an onion-skin appearance of the thrombus in 19 patients, rim enhancement of the aneurysm wall (either partial or complete) in 17, and a perifocal edema in 16 patients. The acute hemorrhage was typically crescent-shaped and located at the periphery of the aneurysm, distant from the perfused lumen of the aneurysm within the thrombosed part of the aneurysm.

The current denomination "partially thrombosed" intracranial arterial aneurysms leads to the presumption that thrombus is present endoluminal whereas in fact the site of hemorrhage is within the vessel wall. A more accurate nomination would, therefore, be "aneurysms with intra-

mural hemorrhage". The enhancing wall and the edematous reaction of the adjacent brain parenchyma might be a sign for an inflammatory pathomechanism which is reinforced by histological and pathophysiological studies. This disease should be regarded as a clinical entity separate from saccular or non-thrombosed giant or large aneurysms.

Introduction

On cross-sectional imaging studies large or giant intracranial arterial aneurysms can mimic mass lesions. Their symptomatology is typically related to their size producing mass effect with subsequent neurological deficits. There has been a debate about the rate of subarachnoid hemorrhage of these aneurysms. While in some studies the opinion prevails that giant aneurysms seldom rupture¹, the ISUIA study observed that aneurysms with a diameter of more than 24mm have a 50% chance of presenting with a subarachnoid hemorrhage in the posterior circulation within a period of five years².

This contradiction might be in part be due to the fact that the term "large" or "giant aneurysm" is only related to a specific size of the aneurysm but fails to convey further information concerning the presence or absence of thrombosis or intramural hematoma, the underlying vessel wall disease and the thus ex-

Figure 1 MRI (Proton Density in Frame A, T1 post contrast enhancement in Frame B) in a patient with a giant partially thrombosed aneurysm demonstrates onion-skin appearance of the thrombus and dense rim enhancement of the aneurysm wall.

pected clinical course and the response of the surrounding tissues³. Moreover, the term “giant” aneurysm is often used in a clinical context to describe a specific subgroup of aneurysms, i.e. the partially thrombosed aneurysms. Thus, different clinical and pathological entities might be subsumed under the same term. Therefore, it is unknown whether the high risk of subarachnoid hemorrhage observed in ISUIA is less in partially thrombosed aneurysms, since this subcategory was not reported out in this trial.

Using neuroimaging criteria, one can differentiate within the groups of large and giant aneurysms those that are completely perfused from the subgroup of the so-called “partially thrombosed” aneurysms, in which the diameter of the aneurysm as detected by cross-sectional studies is larger than the diameter of the perfused aneurysm detected by digital subtraction angiography. These partially thrombosed aneurysms exhibit particular features and must therefore be categorized as a separate entity, regardless of their size: they often continue to grow⁴, sometimes even after parent vessel occlusion⁵, they typically present with mass effect⁶ and show classical features of thrombus of different ages in an onion-skin type fashion with a smaller patent lumen⁷.

Given these peculiarities of large and giant partially thrombosed aneurysms, it may be a too simplistic approach to think that their pathogenesis resembles those of the classical

saccular aneurysms that are supposed to be related (at least in part) to shear stresses (flow, turbulences, jet effects). If a different pathomechanism was present, the treatment strategies would also be likely to differ between the partially thrombosed aneurysms and the non-thrombosed aneurysms or the classical saccular aneurysms. Although it has been proposed, that partially thrombosed aneurysms grow due to recurrence of intramural hemorrhages in the aneurysmal wall⁸⁻¹⁰, their exact pathogenesis is not known, and the aforementioned hypothesis has not been tested yet in a larger series of patients.

The present study was carried out to determine where so-called “partially thrombosed” aneurysms bleed, to understand their growth mechanism and what implications concerning the patho-etiology of this subgroup of arterial intracranial aneurysms can be drawn from these findings.

Methods

Patients were selected after a retrospective search through the databanks of our hospitals from 1989 to 2005. From all patients with cerebral arterial aneurysms those patients in who the search term “partially thrombosed aneurysm” was found were further evaluated, patients with transmural dissecting aneurysms without partial thrombosis, patients with non-thrombosed giant or large aneurysms and pa-

Figure 2 This patient became symptomatic due to brain stem compression, MRI (T1 pre contrast enhancement in frames A and D, post-contrast in frames B and E and T2-weighted images in frame C) shows the typical findings of a partially thrombosed aneurysm of the V4 segment. Methemoglobin (T1 hyperintense on pre-contrast images) as a sign for an acute bleeding is present at the rim of the aneurysm far from the perfused part that is in this case located medially. T2-weighted images show perifocal edema and the onion-skin layer of mural thrombus of different ages.

tients with fusiform or serpentine aneurysms without signs of thrombosis were not included in the following analysis. Using this method, a total of 41 patients were found whose files and images were subsequently reviewed. Inclusion criteria based on patients' charts were history of an acute hemorrhagic event or a progress of pre-existing symptoms prior to imaging, in six patients, no imaging data in this acute context were present (as deduced from the clinical history and as visible on non-enhanced CT and T1 weighted sequences). In 12 patients, MR or CT imaging data were not complete to allow for the retrospective confirmation of the diagnosis of a partially thrombosed aneurysm, and in two patients the imaging quality was too bad to be retrospectively interpreted. To evaluate the site of bleeding in partially thrombosed giant aneurysms, the aforemen-

tioned 20 patients were excluded from any further analysis. These strict inclusion parameters were chosen to make sure, that only those partially thrombosed aneurysms were included that had recently bled, i.e. where recent acute symptoms suggesting acute enlargement and image evidence of recent thrombus (methemoglobin signal – hyperintensity on T1, crescent shaped hyperdensity on non-enhanced CT), were present.

Twenty-one patients were thus included whose age ranged from two to 77 with a mean age of 47 years. There was a slight male preponderance (13/8). Eight patients had a history of smoking, and 11 patients had a history of hypertension (which was sufficiently treated in four). The images (MRI including T1 pre- and postcontrast and T2 weighted images in multiple planes, CT and digital subtraction angiogra-

phy) were reviewed according to the following criteria: number and location of the aneurysm, size (width by height) of the perfused part of the aneurysm and total size, presence of associated anatomical variations of the circle of willis, presence of rim enhancement, perifocal edema, or onion-skin shaped layers of thrombus of different ages. Charts of the patients were subsequently reviewed for age and gender, clinical presentation (subarachnoid hemorrhage, intracerebral hemorrhage, neurological deficits due to mass effect, seizure, or headaches) associated diseases (hypertension, vessel wall disease such as fibromuscular dysplasia, Ehlers Danlos IVb disease, etc.)

Results

Ten partially thrombosed aneurysms were located in the posterior circulation (six intradural vertebral artery, two lateral basilar artery, one basilar tip and one posterior communicating artery aneurysm), 11 aneurysms were in the anterior circulation including four supraophthalmic ICA, three MCA bifurcation, two ICA bifurcation, one cavernous ICA aneurysm and one aneurysm of the petrous portion of the ICA. Width of the aneurysms ranged from 11 to 44mm with a mean of 22 mm while the height of the aneurysms ranged from 14 to 36 mm with a mean of 27 mm. The perfused part of the aneurysms ranged in width from 3 to 21 mm with a mean of 10 mm, and demonstrated a height of 4-28 mm with a mean of 14 mm. In 19 patients no second aneurysm was found, two patients with ICA aneurysm showed a second, unruptured aneurysm (interestingly both were of the "mirror" or "twin"-type)³, that was not thrombosed and therefore not included in the further evaluation. In two patients angiographic criteria pointed to an underlying vessel wall disease (fibromuscular dysplasia). Anatomical variations of the circle of Willis were encountered in only two patients (hypoplasia of the A1 segment and an AICA-PICA, respectively). A history of hypertension was obtained in seven patients.

Neurological presentation was due to mass effect with neurological deficits in the majority of patients (14 of 21). These deficits were either due to brain stem compression, or direct compression of the cranial nerves depending on the localization of the aneurysm. Four patients pre-

sented with neurological deficits related to intraparenchymal hemorrhage. In four patients, headaches were present, only two patients presented with subarachnoid hemorrhage (Hunt and Hess grade 2 and 3, respectively) and two patients had seizures. Diffusion weighted images (available in four patients) and FLAIR images (available in 16 patients) did not show signs of recent embolic events in the territory distal to the aneurysm.

MRI showed an onion-skin appearance of the thrombus in 20 patients, rim enhancement of the aneurysm wall (either partial or complete) in 18, and a perifocal edema in 17 patients. A signal void (which was best discerned on T2 weighted images) matched the configuration of the radiographically demonstrated patent lumen. The acute hemorrhage was typically crescent-shaped and located at the periphery of the aneurysm. In all cases, the hemorrhage was distant from the perfused lumen of the aneurysm within the thrombosed part of the aneurysm (figures 1 to 4).

Discussion

The salient points of this retrospective review of partially thrombosed aneurysms are: hemorrhage occurring at the periphery of the aneurysm, within the "thrombosed part" of the aneurysm, far from the patent lumen and in a high percentage of aneurysms, a strongly enhancing rim and an edematous reaction (or ab-luminal inflammatory activity) of the adjacent brain parenchyma were visible. In the following we will discuss our results in the light of clinical and neuroimaging characteristics reviewed by other groups, surgical, histological and pathophysiological findings that might shed light on the mechanism of growth and rupture of this particular subgroup of aneurysms and, which, therefore, might alter current treatment strategies.

Clinical Features

Unlike classical saccular aneurysms, partially thrombosed aneurysms presented typically with progressive symptoms due to mass effect and only seldom presented with subarachnoid hemorrhage (SAH). Mizutani et Al. explained the subacute and chronic changes leading to this symptomatology by a dissecting process¹¹. Whereas in "classic" dissecting aneurysms a

Figure 3 This patient became symptomatic with an intraparenchymal bleeding that was observed posterior and superior to a mass lesion in the left basalganglia. The mass lesion extended to the basal cisterns and could be identified as a partially thrombosed carotid bifurcation aneurysm. T1-weighted images pre-contrast (A,C) and post contrast (B,D,E) demonstrate that the site of the bleeding is distant from the perfused part of the aneurysm that is located more anterior and inferior. There is partial rim enhancement, and T2-weighted images (F,G) demonstrate an extensive perifocal edema.

Figure 4 Non-enhanced CT (frame A) shows a hyperdense mass lesion in the MCA cistern with perifocal edema. On T1-weighted non-enhanced images (frame B, G and H) a crescent shaped hyperintensity on the lateral wall of the lesion suiting intramural hemorrhage can be seen. The source of the bleeding is not close but distant to the perfused aneurysm (that is demonstrated on T1 weighted images post contrast (frames I-L). There is clot/intramural hematoma inbetween the site of the bleeding and the aneurysm lumen. After contrast administration, a contrast enhancing ring surrounding the aneurysm can be perceived.

transmural dissection leads to an acute SAH, partially thrombosed aneurysms were characterized by recurrent subacute and non-transmural dissections that resulted in repeated subadventitial bleeding and progressive enlargement of the aneurysm. If SAH in these types of aneurysms was present, the neck of the aneurysm is most often involved, presumably due to a transmural dissection at this site. Arterial dissection might therefore generate a wide range of intracranial arterial aneurysms depending on the impact of extrinsic factors (inflammation, hemodynamic forces, etc.), the vessel wall integrity and the intrinsic repair systems as depicted in figure 5.

Neuroimaging

Evidence for intramural hemorrhage of partially thrombosed aneurysms were first put forward in 1980 when Schubiger et Al suggested that the formation of intracranial giant artery aneurysms could be due to a subacute recurrent dissection process associated to repeated subadventitial hemorrhages from the vasa vasorum^{8,9}. They found fresh clot at the periphery of the thrombosed portion of the aneurysm that had no communication with the patent lumen. Typically a sickle-shaped zone or a complete ring of contrast enhancement was present in the periphery of the aneurysm. These authors argued that the aneurysm wall was vascularized by a dense network of vasa vasorum that behave like the membrane of a chronic subdural hematoma and that intramural hemorrhages are the main factor for the observed growth.

Further neuroimaging support of this hypothesis can be derived from a recent review of MR imaging characteristics of partially thrombosed aneurysms by Teng et Al⁷. In nine of ten patients with partially thrombosed aneurysms, a hyperintensity on non-enhanced T1-weighted images indicative of fresh hemorrhage was present within the thrombus along the aneurismal wall and away from the patent lumen. In three of five patients in whom contrast was given, an enhancing rim was perceived. The typical onion-skin appearance of a multilayered thrombus wall was present in eight of ten cases.

In their series of giant aneurysms, Vorkapic et Al performed MRI in four patients with partially thrombosed aneurysms and found perianeurysmal bleeding in one, rim enhancement in all four patients and an onion-skin appearance in all patients that demonstrated layers of

fresh thrombus within the periphery, whereas older thrombus as detected by MRI criteria was present in the central parts. Surrounding edema was present in nearly all cases¹².

Kaneko et Al report on a serial neuroimaging findings of a patient with a thrombosed giant anterior cerebral artery aneurysm that demonstrated a stable size regarding the aneurysm lumen but whose thrombosed portion grows due to hemorrhage into the thrombus and/or the aneurismal wall⁴. Whenever new hemorrhage was encountered it was distal to the patent lumen, close to the periphery of the aneurysm.

In a case report by Koyama et Al an intramural hemorrhage (that presented as a convex-shaped high-density lesion on CT) suggestive of dissection between the layers of the aneurysm wall or the periphery of the thrombus could be appreciated¹³.

Katayama et Al report on a case of growth of a completely thrombosed giant aneurysm, that demonstrated no patent lumen on angiography¹⁴. Despite this, the patient gradually deteriorated and imaging studies demonstrated an ever increasing mass with the typical onion skin appearance of intramural thrombus of different ages and a strong peripheral contrast enhancement that the authors attributed to the highly vascularized arterial wall. Although there is no mention of imaging signs of fresh intramural hemorrhage, the reported growth despite the lack of luminal filling points towards a different source of clotted blood that lead to subsequent aneurysm growth.

These studies are in line with our findings, both concerning the onion-skin appearance, the location of the fresh hemorrhage in the periphery of the aneurysm, the vessel wall enhancement and the perifocal edema that will be discussed in further detail later.

It is known, that following aneurismal wall rupture, a protective layer of collagen is formed and capillaries begin to proliferate to form a neomembrane³. A vicious circle might start, in which minimal trauma (or other triggering events such as inflammatory responses that will be discussed later) might induce bleeding into the neomembrane and this hemorrhage might then induce further proliferation of neomembranes^{15,16}. The more peripheral layers of the thrombus therefore represent the more recent clots leading to progressive growth of the aneurysm.

Figure 5 Schematic representation of aneurysms resulting from dissecting processes

Surgical Findings

Macroscopic inspection during surgery further underlines the proposed pathomechanism: Yasargil reported that on surgical exploration of partially thrombosed intracranial aneurysms a tremendous network of fine vessels covering the aneurysm can be seen, most likely representing the vasa vasorum or angiogenesis induced by the hematoma¹⁷.

Iihara et Al noted growth of a giant partially thrombosed aneurysm after complete occlusion of the parent vessel in a patient. Although there was no angiographically demonstrated evidence of filling of a lumen, the aneurysm continued to enlarge, requiring surgery⁵. During the operation, the presence of markedly developed vasa vasorum was recognized on the parent artery and neck of the aneurysm. During surgery oozing of blood from the thrombus persisted even after the parent artery was clipped and only stopped after removing the clot and coagulating the aneurysm wall. This case report therefore demonstrated that the area of bleeding in fact were vasa vasorum of the aneurysm wall rather than the parent lumen.

Histological and Pathophysiological Studies

Histological examinations of a thrombosed giant aneurysm reported by Yasui demonstrated more recent hemorrhage between old thrombus and the aneurysm wall with clefts of fresh blood present, indicative of a dissection of the aneurysmal wall by blood flow¹⁸.

In the same line, Nagahiro et Al demonstrated on three histological specimen of partially thrombosed aneurysms intrathrombotic vascular channels some of which had endothelial lining and demonstrated proliferating smooth muscle cells¹⁹. They argued that not vasa vasorum but instead a proliferation of newly formed capillaries within the thrombus of the aneurysm might be the cause of the intramural hemorrhage that lead to subsequent aneurysm growth.

The study of Atlas et Al focussed on a second important observation in partially thrombosed aneurysms⁶. They found in two histological specimens that macrophages were present in the aneurysm wall, especially near the periphery of the thrombus. The role of inflammation in the formation of giant aneurysms has re-

cently been further underlined by a study of Zhao et Al²⁰. They found that macrophages positive for a key enzyme in the inflammatory pathway, i.e. the 5-lipoxygenase (5-LO), localized to the adventitia of diseased mouse and human arteries in areas of neoangiogenesis and that these cells constitute a main component of aneurysms. 5-LO generates different forms of leukotrienes that are potent mediators of inflammation by further activating macrophages and recruiting monocytes and T-cells²¹. One of the leukotrienes, LTD4 binds to endothelial cells of the newly formed vascular channels which leads to an increase of leukocyte extravasation. This adventitial inflammation leads to a weakening of the media by release of proinflammatory factors that invade the media and lead to a dilation that subsequently results in aneurysm formation¹⁰. Inflammation of the vessel wall by a chemokine intermediary route was thereby linked to weakening of the vessel wall due to degradation of the extracellular matrix and the elastic lamina with subsequent aneurysm formation²².

A possible inflammatory component in our series of patients might be deduced from the extensive rim enhancement of the aneurysm wall seen in some patients and from the concomitant edema that was present, although the role of vasa vasorum concerning the rim enhancement and mass effect with subsequent venous congestion might also account for these findings. MRI contrast agents marking macrophages could be used to further differentiate these findings¹⁰.

Therapeutic Implications

Given the considerations discussed above, we think that the term "partially thrombosed aneurysm" might be misleading since it might imply that thrombus is located within the aneurysm lumen. Since neuroimaging, surgery and histology point toward clots of different ages within the vessel wall we prefer the term of "aneurysms with intramural hematoma". In addition, the inflammatory component that is likely to be present in these pathologies and the role of growth factors as also pointed out by Nagahiro et Al should be kept in mind¹⁹.

Aneurysms with intramural hematoma might therefore be regarded as a proliferative disease of the vessel wall with growth induced by extravascular activity³. Mural thrombosis might act as a chronic triggering factor for

perivascular growth factors which might stimulate the further proliferation both of vessels within the clot and of the vessel wall itself, thereby differing grossly from the presumed pathomechanism in non-thrombosed or saccular aneurysms even of a size larger than 2 cm, and should be regarded as a separate clinical and pathological entity. It seems obvious that, since different kinds of aneurysms do not share a common pathophysiology, their respective treatment strategies will also likely to differ.

Given the specific histological considerations discussed above, we do not think that endovascular repair of these aneurysms by coils is an apt treatment option. In fact, we have found in those patients treated with coils, that the aneurysm regrew over time, maybe due to compaction maybe due to the fact that the pathological process is likely to be maintained in the vessel wall employing a purely luminal therapeutic approach.

Parent vessel occlusion might be a treatment option, since especially in the ICA territory, the vasa vasorum which might be involved in the disease process arise from the ICA itself and are thus occluded. However, for these kinds of aneurysms, the results of parent vessel occlusion are not predictable and it has been shown that aneurysms might continue to grow even after their parent vessels have been sacrificed⁵. Again, we presume that this might be due to pertinence of vessel wall disease.

The ideal treatment should be complete surgical excision of the lesion, however, this procedure might only be possible after distal and proximal vessel wall occlusion (trapping) which might not be tolerated by the patient depending on the location of the aneurysm³. Moreover, these surgical procedures are technically highly demanding and might pose serious risks to the patient¹⁹.

Apart from medical, i.e. anti-inflammatory treatment (such as steroids), one might also consider, in the future, a treatment regimen that is able to cross the vessel wall to reach the newly formed vascular channels and the most peripheral parts of the aneurysm wall. Drug eluting stents could for example be a possible treatment option that has to be further evaluated in the future. Recently, it has been shown that by inhibiting an enzyme that is involved in the degradation of the extracellular matrix due to chronic inflammation, regression of aortic aneurysms could be achieved²³. It would be in-

teresting to determine whether the same mechanisms might act also in intracerebral aneurysms with intramural hematoma.

Conclusions

The current denomination "partially thrombosed" intracranial arterial aneurysms is misleading and might be changed to aneurysms "with intramural thrombus". This disease should be regarded as a clinical entity separate from saccular or non-thrombosed giant or large aneurysms. Neurological defect due to mass effect instead of subarachnoid hemorrhage is the

typical presenting symptom. If present, hemorrhage typically occurs at the periphery of the aneurysm wall within the clot but far from the patent lumen. The strongly enhancing rim and an edematous reaction of the adjacent brain parenchyma might be a sign for an inflammatory pathomechanism (either causative or reactional) which is reinforced by histological and pathophysiological studies. Treatment strategies should include complete exclusion of the aneurysm, surgery, and, if not possible, anti-inflammatory treatment; an isolated endovascular coiling approach, on the other hand, might not be sufficient.

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EDITORIAL COMMENT

In our quest to gain better understanding regarding the development and natural history and therefore management of intracranial aneurysms it is critical to identify more precisely subgroups of aneurysms that do appear to behave differently from the “usual” aneurysms. Similar to the improved analysis of the angioarchitecture of brain arteriovenous malformations which led to different therapeutic strategies, improved recognition of aneurysm subtypes will likely result in different management strategies.

The Bicêtre neurovascular team known for its consolidated experience in the management of neurovascular disorders both in children and adults points out in this manuscript the peculiar evolution of a particular type of intracranial aneurysm (the partially thrombosed ones) which they were able to image in detail and follow in time. Their conclusion is that the natural history of such aneurysm is apparently not dictated by the lumen of the aneurysm (or parent vessel) but rather determined by the aneurysm wall or even the abluminal space adjacent to the aneurysm. Awareness of such a concept should be helpful as current aneurysm management is mostly directed toward lumen exclusion, while different strategies will likely need to be thought of to “repair” the aneurysm wall dysfunction. This manuscript will add to the body of knowledge that provides the basis for novel aneurysm management specifically directed to identifiable subgroups of intracranial aneurysms.

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