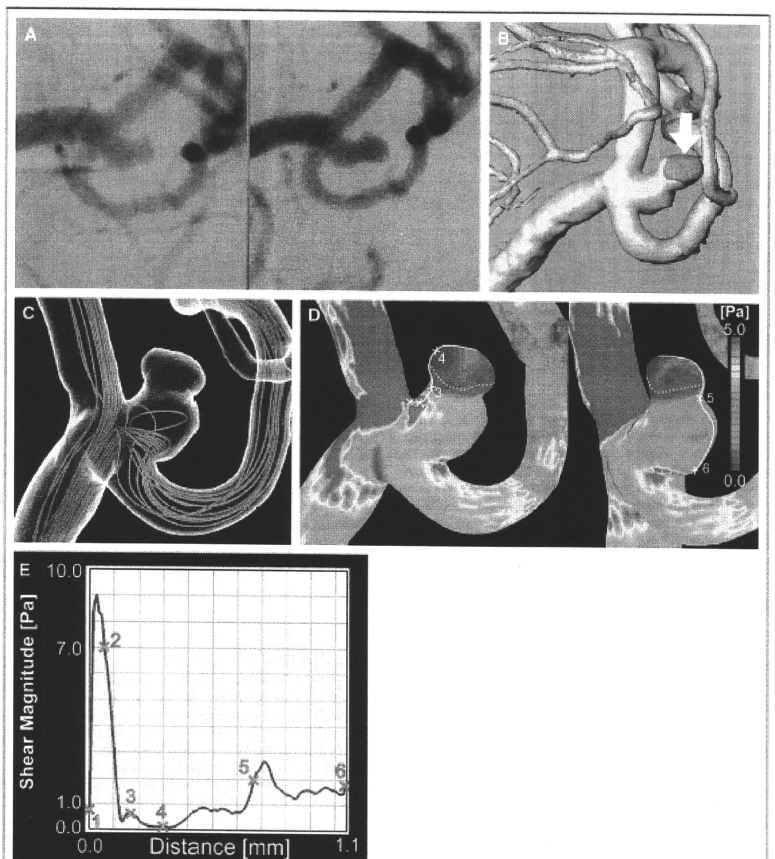

FIGURE 2. *Case 1. Left MCA aneurysm (enlarged). A, angiographic images focusing on the left MCA aneurysm before (right) and after (left) blister formation. B, reconstructed 3D surfaces of the aneurysm before (yellow) and after (red) blister formation. White arrow indicates the location of blister formation. C, Streamline visualization of intra-aneurysmal flow. D, colored contour of shear magnitude distributions. Dotted white line indicates the area of blister formation. E, plot of the shear magnitude along the white line in C. The numbers marking location on the white line in C correspond to those in E. Yellow band indicates the physiological level of shear magnitude. MCA, middle cerebral artery.*

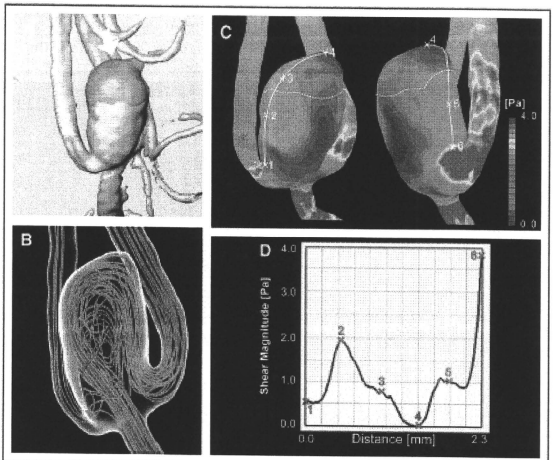

FIGURE 3. *Case 2. AComA aneurysm (ruptured). A, coregistrated 3D surfaces of the aneurysm before (yellow) and after (red) blister formation. White arrow indicates the location of blister formation. B, streamline visualization of intra-aneurysmal flow. C, colored contour of shear magnitude distributions. Dotted white line indicates the area of blister formation. D, plot of the shear magnitude along the white line in C. The numbers marking location on the white line in C correspond to those in D. Yellow band indicates the physiological level of shear magnitude. AcomA, anterior communicating artery.*

can lead to aneurysm formation,[2,11] and low shear magnitude at focally dilated segments can trigger degeneration of the vessel wall by promoting macrophage-related chronic inflammation and atherosclerotic remodeling.[9,10,12] Aoki et al[4] found that the macrophage-mediated chronic inflammation played an essential role in the progression of cerebral aneurysms in mice. Frösen et al[13] compared the pathology of the surgically resected aneurysm wall between the ruptured and unruptured cases and found that atherosclerotic changes, such as intimal hyperplasia and proliferation of disorganized smooth muscle cells, were seen more frequently in the wall of ruptured cases. These findings, in conjunction with our findings that the shear magnitude of the aneurysm wall was subphysiological and that of the blister-forming area was extremely low, imply that the progression and the rupture of the cerebral aneurysms are associated with low shear magnitude.

The present study demonstrated that the shear magnitude dropped precipitately to subphysiological levels (<1 Pa) near the border of the area of subsequent blister formation, resulting in high shear gradient at the edge of the blister-forming area. Previous reports suggest that high shear gradient has the same biological effect on the endothelium compared with low shear magnitude,[10] although endothelial cells may be more sensitive to high shear gradients than to low shear magnitude.[10] This provides a mechanistic explanation for the development of blisters at a specific area within a large area of low shear magnitude on the aneurysm wall. Cebral et al[14] indicated that small and concentrated flow impact might be an indicator of rupture-prone aneurysm; such flow impact would produce a high shear gradient near the flow impact zone and thereby accelerate the low shear-mediated degenerative process on the aneurysm wall.

Blister formation results from local weakness of the aneurysm wall and is strongly related to aneurysm rupture.[15] Blister formation is often used as an indicator of the culprit bleeding lesion when multiple aneurysms are present.[16] In 2 of the 3 present cases, rupture events coincided with blister formation. In these

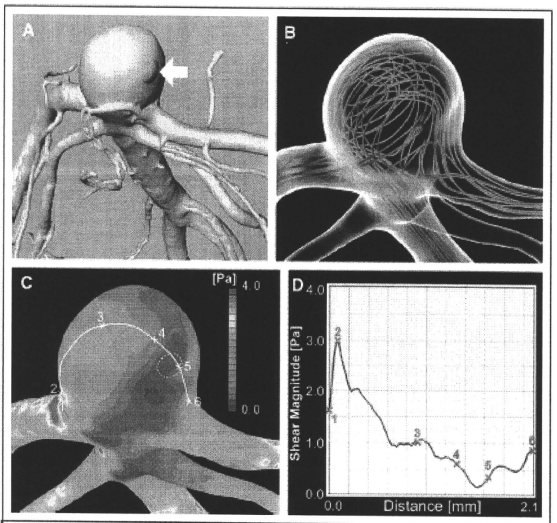

FIGURE 4. *Case 3: Basilar tip aneurysm (ruptured). A, coregistrated 3D surfaces of the aneurysm before (yellow) and after (red) blister formation. White arrow indicates the location of blister formation. B, streamline visualization of intra-aneurysmal flow. C, colored contour of shear magnitude distributions. Dotted white line indicates the area of blister formation. D, plot of the shear magnitude along the white line in C. The numbers marking location on the white line in C correspond to those in D. Yellow band indicates the physiological level of shear magnitude.*

cases, the rupture might have occurred at the blister, and our findings might also refer to the hemodynamic characteristics associated to the aneurysm rupture.

In our computational fluid dynamic simulations, several biological properties such as the viscoelasticity of the vessel wall and the non-Newtonian property of the blood are simplified for technical reasons. The main hemodynamic features are supposed to be preserved despite such simplifications[17]; however, they might lead to the differences between the calculated flow dynamics and the in vivo state in detail.

Limitations of the present study also include the limited number of cases examined, and that detailed 3D images of the aneurysm suitable for fluid dynamic simulations were rarely obtained before blister formation. Furthermore, the assumption that the progression of cerebral aneurysms is mediated by the low shear magnitude should be validated with in vivo study.

CONCLUSIONS

These data demonstrate that the blisters of cerebral aneurysms are formed within the areas of low shear magnitude and high shear gradient, and suggest that the low shear-associated endothelial dysfunction may trigger the progression of cerebral aneurysms.

Disclosure

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COMMENTS

Shojima et al present a well-written report using computational fluid dynamic (CFD) simulations to propose a mechanistic role for wall shear stress in the progression of cerebral aneurysms. Wall shear stress is the tangential force exerted on the arterial walls by flowing blood. The authors suggest that low shear stress may serve as a trigger for aneurysm progression represented by blister formation, and distinguish this from the hemodynamic factors related to aneurysm formation. Of 82 unruptured aneurysms studied with 3-dimensional (3D) rotational angiography and followed with serial magnetic resonance angiography, 2 enlarged and 2 ruptured with blister formation during the mean observation period of 10.1 months. In these aneurysms with documented blister formation, 1 that enlarged (MCA) and 2 that ruptured (AComA and basilar apex) comprise the subject of this report. Three-D rotational angiogram images obtained before and after blister formation were overlaid to characterize the regions of blister formation. The aneurysm geometry before blister formation was then analyzed with phase contrast magnetic resonance velocimetry to simulate 3D pulsatile blood flow and to model shear magnitude at various sites within segmented parent arteries, whole aneurysms, and areas of blister formation on the aneurysm wall. Since shear magnitude values less than 1 Pa were defined as subphysiologic, the spatially averaged shear magnitude at the area of blister formation on these 3 aneurysms was concluded to be low, as measurements ranged from 0.40 to 0.61 Pa. The authors conclude that low shear magnitude at the blister-forming area is associated with progression and rupture of cerebral aneurysms.

This report adds to the growing amount of image-based data implicating intra-aneurysmal hemodynamic characteristics in aneurysm growth and rupture. These 3 cases extend the previous work by these authors describing low wall shear stress in MCA aneurysms, and is unique in focusing upon the areas of the aneurysm walls that subsequently form blisters. The effects of patient-specific flow characteristics upon CFD simulations are becoming increasingly clarified. Despite limitations of these modeling techniques, as evidenced by the exclusion of the anterior communicating artery aneurysm that enlarged in this series owing to the presence of inflow from both anterior cerebral arteries, this field of hemodynamic research is immensely exciting in its potential for improving our understanding of the natural history of this disease. Substantial efforts have already been targeted at elucidating the mechanisms of mechanotransduction, namely the interaction between hemodynamic biomechanical forces and endothelial cell function, and further studies focusing upon these mechanisms in cerebral aneurysms will likely lead to enhanced insights into the risk of aneurysm growth and rupture.

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The role of hemodynamic forces in blister formation on cerebral aneurysms is currently poorly understood. To complicate matters, recent data have suggested that the forces that promote aneurysm formation (high shear magnitude) may, in fact, be opposite to those that promote blister formation. Shojima et al have retrospectively evaluated 3 cerebral aneurysms that have undergone blister formation among their series of 82 unruptured aneurysms. A middle cerebral artery, anterior communicating artery, and basilar artery aneurysm with blister formation were isolated. Using elegant CFD simulations, the authors have demonstrated markedly subphysiologic shear magnitudes in the regions bordering blister sites in all 3 cases. These findings suggest that regions of low shear stress, resulting in an adjacent high shear gradient, may result in endothelial changes that weaken the vessel wall and, over time, promote degeneration and ultimately blister formation.

The present study has several important limitations including small sample size, lack of some critical preblister formation data, and typical CFD limitations regarding the assumptions made for model generation

and analysis. Nonetheless, Shojima et al have provided interesting data not previously evaluated. The continued refinement of CFD techniques and their application to neurosurgical disease provides a very real opportunity for substantial knowledge gains in cerebrovascular pathophysiology. Investigators, such as Shojima et al, who contribute to this burgeoning field, should be commended; however, we would also emphasize the importance of developing reliable ways to correlate these virtual findings with actual biologic cascades and events.

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Unruptured Intracranial Aneurysms: Current Perspectives on the Origin and Natural Course, and Quest for Standards in the Management Strategy

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Abstract

Unruptured intracranial aneurysms are relatively common, and can cause subarachnoid hemorrhage. Management of unruptured intracranial aneurysms requires knowledge of the natural course and management risks of individual aneurysms. Current knowledge on the natural course and management risks is summarized and our current management strategy presented. Extensive literature review was conducted to identify risk factors influencing the natural course and management outcome of unruptured intracranial aneurysms. Our consecutive surgical series from October 2006 through June 2009 were reviewed retrospectively. The risk factors for rupture were size and location, as well as history of subarachnoid hemorrhage in small aneurysms. Management morbidity was significantly influenced by the size, location, and patient's age. Since 2006, we have monitored motor evoked potentials in all surgeries of cerebral aneurysms and utilized endoscope control, and skull base and bypass techniques in selected cases. In 133 consecutive surgeries, two patients (1.5%) suffered severe neurological morbidity. Unruptured intracranial aneurysms have various clinical characteristics and we need to stratify management strategy according to the aneurysm features such as size, location, shape, and patient's clinical status. In Japan, with national efforts to elevate management standards, morbidity associated with the treatment of the unruptured intracranial aneurysms is relatively low. To improve future care further, we need to continue seeking better and less invasive management modalities and technique.

Key words: unruptured intracranial aneurysm, natural course, rupture, growth, management

Introduction

Unruptured intracranial aneurysms are relatively common, occurring in 2-6% of the adult population,[23] and can have grave consequences after rupture resulting in subarachnoid hemorrhage. Surgical intervention significantly reduces the risk of rupture but the risk of such prophylactic treatment cannot be ignored. To determine management strategy, we need to assess the natural history and management risks of individual aneurysms. Since the majority of the patients with this pathology are asymptomatic, management must minimize the interventional risks as far as possible.

This review summarizes the current knowledge of the origin and the natural course, and standard management strategy of unruptured intracranial aneurysms.

Characteristics of Unruptured Intracranial Aneurysms

I. Origin and rupture

The origin and cause of rupture of cerebral aneurysms remain unclear. The impact of the blood stream may damage the arterial wall, especially at the arterial bifurcation, and cause the aneurysm. However, a recent hemodynamic study has proven that the impact force at the originating site is not significantly different from other sites.[35] On the other hand, the shear stress was relatively high adjacent to the origin of the aneurysm, which is thought to work as the force tearing the vessel wall. The aneurysm then grows with physiological remodeling of the arterial wall caused by the relatively low shear stress at the aneurysm dome.[34] Histological studies of intracranial aneurysms have demonstrated that both symptomatic unruptured and ruptured aneurysms

incorporate degenerative processes of the arterial wall similar to atherosclerosis, and such features are not commonly seen in asymptomatic unruptured intracranial aneurysms.[5] Recently, atherosclerosis has been considered to originate in inflammation of the arterial wall. Such inflammatory processes are considered to be important in the growth and rupture of the aneurysms. A recent experimental study showed statins inhibit the growth of experimental cerebral aneurysms.[31] Development of medical treatments for unruptured intracranial aneurysms are awaited.

II. Natural course of unruptured intracranial aneurysms

Many studies have investigated the natural course (analysis of risk of rupture) of unruptured intracranial aneurysms.[8,10,20,30,37,38,41,42,45,46] Most studies were retrospective and some were prospective, but no randomized clinical trials have been published. In general, higher rupture risks have been reported in retrospective studies than in prospective studies. Also, the independent risk factors are rather difficult to clarify in retrospective series. Table 1 summarizes the natural course of unruptured intracranial aneurysms from retrospective series. The annual rupture risk of all intracranial aneurysms was reported as between 1% to 3% in retrospective studies. However, there is inevitable selection bias in the included patients. Elderly, sicker patients or patients with aneurysms carrying high management risks tend to be observed conservatively.

Table 2 shows the three prospective studies published. The international study of unruptured intracranial aneurysms (ISUIA) including 1,692 prospective cases demonstrated the rupture rate is about 0.78% annually, and is strongly related with aneurysm size and anterior or posterior location (Table 3).[42] Small anterior circulation aneurysms rarely ruptured (0% for <7 mm aneurysms located in the anterior circulation without history of subarachnoid hemorrhage). On the other hand, large aneurysms frequently ruptured (8% or more annually). The SUAVe study in Japan included all small aneurysms less than or equal to 5 mm, and demonstrated that even small aneurysms can grow and rupture.[46] The annual rupture rate in the follow-up period of 375 aneurysm-years was 0.8%. An additional 18 aneurysms (4.7%) grew more than 2 mm, and 5 of them underwent repair of the aneurysm before its rupture. Considering the growing aneurysm

Table 1 Natural history of unruptured intracranial aneurysms from retrospective series

Author (Year)	No. of cases	Mean age (yrs)	Follow up	Annual rupture rate (%)	Factors affecting rupture
Yasui et al. (1997)[45]	234 pt, 303 an	59.6	75.1 mos	2.3	multiplicity
Rinkel et al. (1998)[20]	3907 pt·yr	—		1.9 (1.5–2.4); 0.7: <1 cm, 4.0: >1 cm	symptomatic, sex, size, location
ISUIA (1998)[38]	727 pt, 977 an	56	8.3 yrs, 12,023 pt·yr	0.05: <1 cm, 0.5: >1 cm	size
	722 pt, 960 an	49.4		0.5	
Juvela et al. (2000)[30]	142 pt, 181 an	41.9	19.7 yrs, 2575 pt·yr	1.3	smoking, older age, size
Tsutsumi et al. (2000)[37]	62 pt	70.8	4.8 yrs	2.3	size
Moritu et al. (2005)[28]	911 pt		3801 pt·yr	2.7	size, posterior, symptom
Wermer et al. (2007)[41]	4705 pt, 6556 an		26122 pt·yr	1.2: <5 yrs, 0.6: 5–10 yrs, 1.3: >10 yrs	age >60 yrs, female, Japanese or Finnish, size >5 mm, posterior, symptom

an: aneurysms, pt: patients, pt·yr: patient·year.

Table 2 Natural history of unruptured intracranial aneurysms from prospective series

Author (Year)	No. of cases	Mean age (yrs)	Follow up	Annual rupture rate (%)	Factors affecting rupture
ISUIA (2003)[55]	1692 pt, 2686 an	55.2	4.1 yrs, 6544 pt·yr	0.78	size, posterior location, history of SAH
Yonekura (2004)[49]	329 pt, 380 an, all ≤5 mm	62	375 an*yr	0.8 (0.2–3)	multiple, female, ACom, basilar location, age >70 yrs
Ishibashi et al. (2009)[9]	419 pt, 529 an		2.5 yrs, 1039 pt·yr	1.4	history of SAH, size, posterior location

ACom: anterior communicating artery, an: aneurysms, an*yr: aneurysm-year, pt: patients, pt·yr: patient·year, SAH: subarachnoid hemorrhage.

Table 3 Risk specific natural history (annual rupture rate) according to the prospective cohort of ISUIA II

ISUIA II	Size				
	<7 mm		7–12 mm	13–24 mm	≥25 mm
	Group I	Group II			
Cavernous IC (n=210)	0	0	0	3.0%	6.4%
AC/MC/IC (n=1037)	0	0.3%	0.5%	2.9%	8%
Post-PCom (n=445)	0.5%	0.7%	2.9%	3.7%	10%

AC: anterior cerebral, Group I: not associated with subarachnoid hemorrhage, Group II: aneurysm found in patients with previous subarachnoid hemorrhage, IC: internal carotid, ISUIA II: International Study of Unruptured Intracranial Aneurysms Investigators published in 2003, MC: middle cerebral, PCom: internal carotid-posterior communicating, Post: posterior circulation.

Table 4 Summary of reports on the growth of unruptured intracranial aneurysm

Author (Year)	No. of cases	Follow up	Enlargement rate	Factors affecting rupture
Matsubara et al. (2004)[18]	140 pt, 166 an	17.7 mos	10 (6.4%): 2.4%: <5 mm, 8.8%: 5–10 mm, 50%: >10 mm; 2.5%: <1 yr, 8%: 2 yrs, 17.6%: 3 yrs; 40%: BA, 0%: MCA	size, location (BA), follow-up period
Yonekura (2004)[48]	329 pt, 380 an, 375 an*yr	12 mos	18 (4.7%)	age >70 yrs, ACom, BA location, multiplicity, female
Burns et al. (2009)[3]	156 pt, 191 an	47 mos	10%: 6.9%: <6 mm, 25%: 8–12 mm, 83%: >13 mm	size, location, multiplicity

ACom: anterior communicating artery, an: aneurysms, an*yr: aneurysm-year, BA: basilar artery, MCA: middle cerebral artery, pt: patients, pt·yr: patient·year.

could have ruptured unless treated, the annual rupture rate is not negligible in such patients. A follow-up study on untreated 419 patients at a single institution[6] found the rupture rate was 1.4% per year and was significantly influenced by history of subarachnoid hemorrhage, posterior location, and size of the aneurysm. Currently, in Japan, two prospective studies (UCAS Japan and UCAS II) have being conducted, and the preliminary results indicate that the natural course is significantly related to size as well as specific locations of the aneurysms. Aneurysms located at the anterior communicating and internal carotid-posterior communicating arteries tended to rupture more frequently than other locations, even if small (unpublished data).

Several studies compared three-dimensional (3D) images between groups of ruptured and unruptured intracranial aneurysms. Aneurysms with large height and high ASPECT (dome height /neck width) ratio, and located on the posterior communicating artery and anterior communicating artery, as well as the posterior circulation are more commonly ruptured.[25] Irregular shape and coexistence of bleb are also found more in ruptured aneurysms.[29] These findings suggest that the aneurysms with such features can rupture easily.

Table 4 summarizes the reports on aneurysm growth. Larger aneurysms often grew more than smaller aneurysms.[3,17,46] Posterior location and multiple aneurysms also tended to grow frequently. Rate of growth is exponentially increased along with the follow-up year. Such findings coincide with the risk factors found for aneurysm rupture.

III. Management outcome and risks

Numerous studies on the management outcome for unruptured intracranial aneurysms are summarized in Table 5.[9,14,22,28,42,43] Reported and published clinical outcomes are significantly different between various types of studies.[47] The ISUIA[42] found that mortality was 1.6% and significant morbidity (modified Rankin scale 3 or below or mini-mental state examination (MMSE) score below 25) was 10.9% at the one month follow-up. Decline of cogni-

Table 5 Outcome of management of unruptured intracranial aneurysms

Author (Year)	No. of cases	Type of study	Risk	Risk factors
Wirth et al. (1983)[51]	107 pt, 119 an open surgery	multicenter retrospective cohort, 12 centers	mortality: 0%; morbidity: 6.5%	size, location
King et al. (1994)[6]	733 pt open surgery	meta-analysis, 28 studies	mortality:1.0% (0.4–2.0%); morbidity: 4.1% (2.8–5.8%)	none
Raaymakers et al. (1998)[28]	2,460 pt open surgery	meta-analysis, 61 studies	mortality: 2.6% (2.0–3.3%); morbidity: 10.9% (9.6–12.2%)	old publication, giant an., posterior circulation
Murayama et al. (1999)[22]	115 pt, 120 an endovascular	case series retrospective	morbidity: 4.3%; complete occlusion: 91%, unsuccessful coil: 5%, delayed rupture: 1%	early series
Johnston et al. (2001)[9]	2,069 pt 1699: open surgery, 370: endovascular	multicenter retrospective cohort	mortality: 3.5% (open surgery), 0.5% (endovascular); morbidity: 25% (open surgery), 11% (endovascular)	open surgery
ISUIA (2003)[29]	1917 pt open surgery	multicenter prospective cohort, 61 centers	mortality: 1.5%; morbidity: 11.7% (1 mo)	size, age, location, ischemic disease, symptom
	451 pt endovascular		mortality: 1.7%; morbidity: 7.3% (1 mo); complete occlusion: 51%, unsuccessful: 5%	

an: aneurysms, pt: patients.

tive function accounted for the major part of the morbidity, and the importance of measuring high cognitive function for the clinical assessment of surgical outcome of the patients was stressed. Risks were higher in elderly patients and patients with posterior circulation aneurysms. Endovascular treatment had better outcomes in the group of elderly patients. Survey of the outcomes of aneurysm surgery in Japan found the surgical mortality of 4,396 UIAs was 0.2%.[7] The case volume of the institution did not affect the surgical outcome in this survey. Quality of life (QOL) score was also analyzed in several outcome studies.[27,39,44] Some reported significant decline of QOL long time after aneurysm repair. However, preoperative anxiety was relieved by the repair of the aneurysm and QOL also improved.[44] Meticulous surgical repair resulted in decline of cognitive function in only a minimal number of cases.[24] Our recent study (UCAS II) also followed the QOL of patients (unpublished data). QOL scores measured by SF-8 and EQ5D immediately after treatment did not show any decline compared to prior to surgery. Depression score measured by SF36 mental health and vitality domain was low compared to the Japanese normal population and did not show change immediately after the treatment. We are following these scores in the longer term.

Surgical Strategy and Case Series in Our Institution

1. Surgical strategy

To accomplish the safest intervention, we need to carefully assess the patient and involve updated surgical technique and assist devices. In our institution, we follow the recommendations of the Japanese Society of Screening of Asymptomatic Cerebral Disorders in deciding on repair of unruptured intracranial aneurysms. Basically, aneurysm repair is indicated in patients with management risks considered lower than the natural risks for rupture or physical factors for the next 10 years. When we decide to treat the aneurysm of specific patients, either open craniotomy and clipping or endovascular coiling is selected individually according to the following strategy.

A: Clipping is the preferred method when the surgical risk in the specific patient is similar or lower to that of coiling. Aneurysm repair in the location of the basilar tip or in patients with very high medical risks is often managed better by endovascular methods. However, wide-based basilar aneurysms are repaired by open clipping after thorough discussion with endovascular specialists.

B: If the patient strongly prefers endovascular management after thorough discussion, endovascular treatment is indicated.

In our institution, surgical managements are as-

sisted by the following advanced techniques to diminish surgical morbidity: Pre-operative thorough evaluation of aneurysm images including 3D angiography, 3D computed tomography (CT) angiography and magnetic resonance (MR) angiography, MR imaging with Fast Imaging Employing STeadystate Acquisition (FIESTA), and Preoperative 3D simulation.

The gold standard for the diagnosis of cerebral aneurysms is digital subtraction angiography. This technique is still essential for assessing cerebral circulation and obtained details of the cerebral vascular anatomy including the venous system. However, recent advances in CT and MR angiography have reduced the needs for catheter angiography. With advanced imaging techniques, we now can visualize and anticipate perforators around the aneurysm, and imagine the space between the aneurysm and the adjacent parent arteries. CT and MR angiography provide the internal shape of the aneurysm and FIESTA images provide the external shape of the aneurysm, and detect adjacent perforator and cranial nerves.[32] More accurate imaging incorporating heart beat influence will provide information on the distortion of the aneurysm by the heart beat and the wall thickness of the aneurysm. Combination of such 3D images can provide very useful virtual reality simulations for surgical procedures.[13] Currently, we can create an actual-sized elastic hollow model of individual aneurysms from the preoperative 3D images. These models were very useful in deciding how to apply clips to occlude the closure line of the aneurysm and combination of aneurysm clips for complex-shaped aneurysms.[11]

Electrophysiological monitoring: Electrophysiological monitoring is essential to reduce operative complications. Motor evoked potential monitoring is very useful for reducing managing morbidity during aneurysm surgery, especially around the perforating branches such as the anterior choroidal, posterior communicating, M_1, and vertebro-basilar arteries.[31] Visual evoked response is also very useful in reducing risks to visual acuity during intervention for paraclinoid aneurysms.[6]

Meticulous microsurgical, skull base surgical and bypass technique: For open aneurysm surgery, the basic surgical technique involves meticulous microsurgical procedures preserving all possible venous and arteriolar structures. To accomplish appropriate clipping, we need to fully dissect and expose the aneurysm dome and neck with sharp dissection. Also, with the widespread availability of endovascular technique, open surgeons are now facing more complex cerebral aneurysms, which cannot be simply obliterated using the usual microsurgical techniques. We should be able to utilize skull base and bypass techniques as routine additional microsurgical techniques. The anterior clinoid process including optic canal unroofing and/or posterior clinoid process should be drilled in treating paraclinoid aneurysms or basilar aneurysms to widely expose the adjacent anatomical structures and create extra room for safe access. Such procedures can be safely performed using the SONOPET ultrasonic bone curettage instrument (UST-2001; Stryker Japan, Tokyo) without the fear of causing rolling-up injury to the important structures by the drills.[4] Other cranial base approaches including anterior petrosectomy and combined petrosal approach, and transcondylar approaches are utilized in managing vertebrobasilar complex aneurysms. Bypass technique including superficial temporal artery (STA) to middle cerebral artery, A_3-A_3 anastomosis or high flow technique, is often required in the management of some wide neck aneurysms to salvage parent arteries, especially aneurysms incorporating wide or thrombosed wall.[12,33,36]

Combination of open and endovascular technique in selected cases: If cases present possible difficulty for both open and endovascular techniques, we should combine both techniques. Especially in cases with wide neck aneurysm combined with vessel wall calcification, or adjacent perforator difficult to dissect from the neck, we can intentionally partially occlude the aneurysm neck with clips and obliterate the aneurysm completely with endovascular coils. Endovascular procedure can be achieved safely after the aneurysm neck is narrowed and the clipping can be done without sacrificing the perforators. In Japan, advanced intracranial stent technique is currently under trial and only performed in selected institutions. When such endovascular techniques including the soft flexible stenting method are available widely, we should actively incorporate such techniques.[16,40] However, we need to carefully assess the long term outcome of such endovascular procedures, since the ISAT showed frequent rebleeding after endovascular procedures.[18] Current endovascular technique is not completely reliable protection against bleeding from aneurysms.

Application of endoscopy and Indocyanine Green (ICG) angiography: Endoscopy and ICG are very useful techniques in assessing the patency of adjacent perforating and parent arteries. In selected cases, clipping can be accomplished under the control of the endoscope to prevent occlusion of the perforating vessels.[15,21] Recently developed ICG technique is useful in assessing the patency of adjacent arteries.[26]

Cosmetic skin incision and craniotomy repair: To

reduce patient's burden in social life, we should always consider cosmetic concerns in assessing surgical outcome. We should avoid facial nerve palsy after craniotomy and minimize surgical depression of the temporal area. Muscle atrophy should be avoided by meticulous dissection technique, avoiding injury to the temporal muscle nerves and vasculature, and reduce the bone defect caused by the craniotomy.

II. Our series of open aneurysm surgeries

From October 2006 through June 2009, 133 open aneurysm surgeries for unruptured intracranial aneurysms were performed by the authors utilizing the above mentioned techniques. Bypass surgery was included in 13 procedures and cranial base technique was involved in 18 cases (anterior clinoidectomy in 13, posterior clinoidectomy in 3, anterior petrosal approach in 1, and combined posterior petrosal approach in 1). Endovascular procedures (coiling) were added in 2 cases for planned incomplete occlusion of the aneurysm. The endoscope was used in all cases except for middle cerebral aneurysms. Electrophysiological monitoring was applied in all cases. At discharge, two patients (1.5%) suffered severe morbidity (modified Rankin scale less than or equal to 2, or Mini-mental State Examination Score less than or equal to 25). Both patients had giant thrombosed aneurysms (Table 6).

Postoperative MR imaging, obtained in all open surgical cases, showed unexpected T_2 hyperintensity in 6 cases. In addition to the severe morbidity, four patients experienced four subdural hematomas, which required surgical evacuation one to 3 months after surgery. Seizure occurred in 5 patients, which was controlled with antiepileptic medication. Wound complication was found in 2 patients, including one patient who required surgical repair for CSF leak. No other clinical complication was noted.

Table 6 Morbidity of 133 consecutive open surgical procedures on unruptured intracranial aneurysms in Kanto Medical Center, NTT Ec during October 2006 through June 2009 (mRS ≥2, or MMSE ≤25 at discharge)

Location	Size	
	< 10 mm	≥ 10 mm
Anterior circulation	0/92	1/26 (3.8%)
Posterior circulation	0/3	1/2 (50%)

MMSE: mini-mental state examination, mRS: modified Rankin scale, NTT Ec: Nippon Telegraph and Telephone East Corporation.

III. Illustrative cases

Case 1 (Fig. 1): This 63 year-old female presented with a left asymptomatic small posterior communicating artery aneurysm. Left pterional craniotomy was performed and clipping was performed under endoscopic control. After initial clipping, her right upper-extremity motor evoked potential diminished and endoscopic imaging showed the clip had occluded a perforator from the posterior communicating artery. The clip was repositioned to not constrict the perforator circulation. Motor evoked response returned and the patient recovered uneventfully.

Case 2 (Fig. 2): This 72-year old female presented with a large left basilar superior cerebellar artery aneurysm. Preoperative FIESTA MR imaging demonstrated several perforators on the right back side of the aneurysm. Endovascular intervention was not indicated because the left superior cerebellar artery was at risk of occlusion. Surgery was performed through the left modified pterional-anterior temporal approach involving anterior and posterior clinoid resection using SONOPET. During surgery,

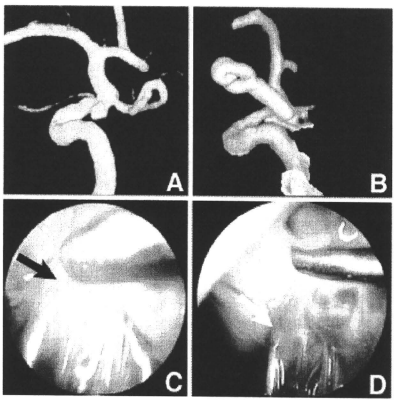

Fig. 1 Illustrative Case 1. A, B: Pre- and post-operative three-dimensional angiograms showing a small left internal carotid-posterior communicating aneurysm successfully occluded by a clip graft. C: Endoscopic image after initial clipping showing occlusion of the perforating vessel (*arrow*). D: After repositioning the clip, the perforators were spared (*arrow*) and motor evoked potential recovered.

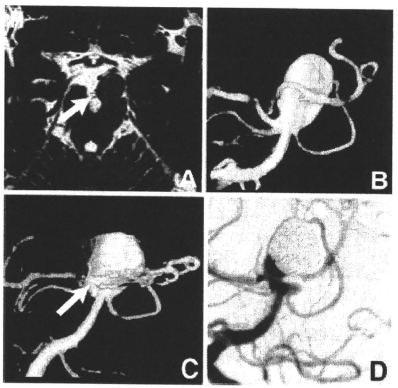

Fig. 2 Illustrative Case 2. A: Preoperative magnetic resonance image using the Fast Imaging Employing STeadystate Acquisition sequence showing several perforators in the right back side of the aneurysm (*arrow*) and the left P_1 segment attached to the aneurysm dome. B: Three-dimensional angiogram showing the large basilar-superior cerebellar artery aneurysm with a relatively wide neck through the narrowed neck (*arrow*). C: After partial clipping across the neck, the aneurysm dome was still patent. D: Endovascular coiling was performed to occlude the majority of the dome.

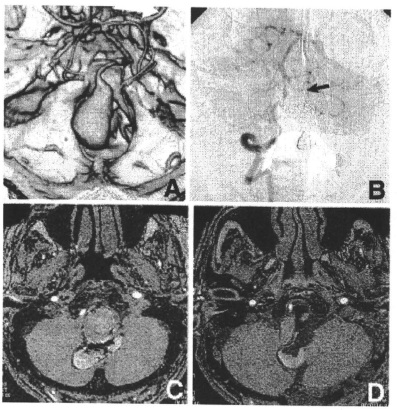

Fig. 3 Illustrative Case 3. A: Three-dimensional angiogram showing a large left vertebral artery aneurysm. B: After coil obliteration of the aneurysm, there is back flow from the distal left vertebral artery to the top of the aneurysm (*arrow*). C: Magnetic resonance angiogram showing a large mass compressing medulla. D: After clipping of the distal and proximal left vertebral artery, aneurysm mass and coil substance was partially removed and the brain stem was decompressed.

the clip could not be pushed across the neck due to the toughness of the wall and adhesion of the left P_1 segment to the aneurysm wall. So the clip was intentionally placed partially over the neck to produce a narrow aneurysm neck. Since this aneurysm did not occlude spontaneously, the remaining dome was filled with coils through the smaller aneurysm neck. She suffered temporary left oculomotor palsy, which subsided in 2 months. No other complication was noted and follow-up MR imaging findings have been stable.

Case 3 (Fig. 3): This 50-year-old male presented with a left giant vertebral artery aneurysm with progressive brainstem signs after coil embolization in another hospital. He initially presented with subarachnoid hemorrhage 10 years ago. He was found to have left vertebral artery dissecting aneurysm and was conservatively managed. In 2005, he developed progressive right heaviness and giant vertebral aneurysm was diagnosed. Aneurysm obliteration was performed using detachable platinum coils in another hospital. However, even after the occlusion, the aneurysm continued to grow by blood back flow from the distal vertebral artery and his neurological function deteriorated including dysphagia, dizziness, and right hemiparesis. Endovascular trial to occlude the left distal vertebral artery was unsuccessful. We planned to occlude the distal vertebral artery by clipping and decompression of the aneurysm at the second stage surgery. Left anterior petrosectomy was chosen and the clip was placed on the left distal vertebral artery just above the aneurysm. There were several perforators from the vertebral artery, which were spared. Three weeks later, the aneurysm mass with coils compressing the medulla was removed after proximal left vertebral artery clipping. Postoperative course was complicated with hydrocephalus, pneumonia, and persistent orthostatic hypotension. He was transferred to a rehabilitation facility and resumed his job 7 months after surgery. At the last follow-up examination, he was ambulatory and dysphagia was improved. At the last clinical visit, his modified Rankin scale was 1. (This case was managed in collaboration with the Endovascular Unit at Jikei Medical School.)

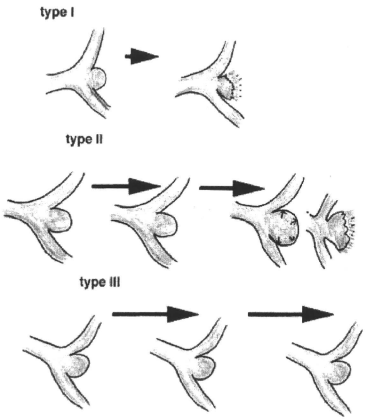

Fig. 4 Conceptual types of the natural course of intracranial aneurysms. Three types of natural course occur after the formation of intracranial aneurysms.[46] In type I, the aneurysm continues to enlarge till the phase of rupture. Most subarachnoid hemorrhage (SAH) could be caused by such aneurysms, since many small aneurysms cause SAH, whereas small unruptured aneurysm rarely ruptures. In type II, the aneurysm stops growing, but with some physiological or some other external stimuli, regrowth starts and eventually ruptures. There might be several steps repeating these grow and halt phases. In type III, the aneurysm stops growing and remains stable.

Discussions

Current knowledge on the origin and growth of the cerebral aneurysms suggests three types of origin and natural course of unruptured intracranial aneurysms (Fig. 4[46]). Type 1 is an aneurysm which ruptures immediately after formation. Type 2 is an aneurysm which stops enlarging sometime after formation, but grows due to some inflammatory process and ruptures. Type 3 is an aneurysm which stops growing after formation, but still may start regrowth due to some unknown biological cues. Type 1 should present as ruptured aneurysm, so unruptured intracranial aneurysms are likely to be type 2 or 3. To determine whether an aneurysm should be treated, we need to know the type of the individual aneurysm and the process that induces the growth of the aneurysm.

The risk factors influencing the growth and rupture of intracranial aneurysms can be summarized as follows: Group 1 risk factors (evidenced by high level prospective studies), size (≥7 mm), location (posterior circulation>anterior circulation), specific locations such as anterior communicating, posterior communicating and basilar artery aneurysms, and history of subarachnoid hemorrhage; Group 2 risk factors (evidenced by retrospective case series and studies), history of smoking, multiplicity of aneurysms, higher age, symptomatic aneurysm, Japanese or Finnish population, and shape of aneurysm (irregular or high dome/neck ratio). Such evidence leads us to believe that unruptured intracranial aneurysms should not be considered as a single disease entity. We should stratify unruptured aneurysms according to the specific features such as location, size or shape, and patient factors.

Risk factors that influence management outcomes can be summarized as follows: Group 1 management risk factors (evidenced by high level prospective studies), size, location (vertebro-basilar>anterior circulation), history of subarachnoid hemorrhage, and age; Group 2 management risk factors (evidenced by retrospective case series, studies), history of ischemia, and type of management. The management of unruptured intracranial aneurysms is not risk free and the published outcomes vary according to the study design and the measurement of outcome. We should not apply published outcomes to our own decision making. Before discussing risk communication, we should clarify our own clinical outcome. Thereafter, we need to carefully decide the indications for management by assessing the natural course and institutional outcome in managing individual aneurysms.

According to the ISUIA study, recent management recommendations for unruptured intracranial aneurysm did not advocate surgical management for incidental small intracranial aneurysms unless the patient is young or has other specific hemodynamic features.[2] However, a recent study of the long-term outcome of ISUIA cases with mean follow-up of 9.2 years reported that the overall outcome was better in treated than untreated patients. Relatively risk-matched patient groups were extracted from the prospective patient cohort of ISUIA using propensity analysis score and compared untreated and treated patients (ISUIA report at the AANS 2010, unpublished data). Although the case risks in both groups matched relatively well, there might be hidden bias as sicker patients may not be indicated for treatment. Nevertheless, we need to realize the importance of long term assessment to evaluate the real outcome and benefit of treatment of unruptured in-

tracranial aneurysms.

In Japan, even carefully designed prospective studies showed relatively low overall morbidity and mortality in managing unruptured intracranial aneurysms.[19] To achieve low-risk intervention, meticulous care in preoperative assessments and involvement of advanced surgical and interventional techniques are mandatory, including high resolution MR imaging, preoperative 3D simulation, meticulous surgical technique, skull base technique, bypass surgery, advanced neuro-physiological and neuro-imaging monitoring, and collaboration with neuro-interventional techniques. In illustrative Case 1, the authors demonstrated the need for electrophysiological monitoring and endoscopic control in managing simple small aneurysms. In Cases 2 and 3, we illustrated the need for cranial base approaches as well as combination of surgery and endovascular techniques in managing difficult cases. Brain stem compression caused by the mass effect of the aneurysm and endovascular material must be decompressed to alleviate clinical signs, and can be effective even after months of progressive symptoms. Well organized and dedicated rehabilitation efforts and physical care is mandatory to obtain good recovery.

In 2008, the revised guidelines of the Society of Screening of Asymptomatic Cerebral Disorders in Japan were published. Recommendations were made according to the published series of natural course and management outcome. The Japanese experiences were stressed rather than reports from western countries since the natural course of UIA might be slightly different between Japan and other western countries.[41] The management outcomes in our prospective series are also relatively better than those reported by ISUIA.

The recommendations for managing unruptured intracranial aneurysms are as follows (http://www.snh.or.jp/jsbd/pdf/guideline2008.pdf).

i) Interventions for unruptured cerebral aneurysms should be determined by the age and health status of the patient, size, location and nature (shape and other characteristics) of the aneurysm, the expected natural course of the aneurysm, and the institutional or surgeon's management outcome. Full detailed informed consents should be obtained and good risk communication between caregivers and patients should be created before deciding on intervention or careful follow up.

ii) Surgical or endovascular management is recommended for patients with the following aneurysms with life expectancy of more than 10–15 years.

ii-i) Aneurysms more than or equal to 5 to 7 mm

ii-ii) Smaller than above but

ii-ii-i) Symptomatic

ii-ii-ii) Located at anterior communicating, internal carotid-posterior communicating arteries or posterior circulation.

ii-ii-iii) Aneurysm with daughter sac, irregular shape, or large dome-neck aspect ratio.

iii) Risk benefit analysis based on large previously published cohort studies can be a useful indicator in deciding the management of unruptured cerebral aneurysms in general. However, the natural course, quality of life, mental status of each patient and aneurysm, and institutional surgical outcome should be carefully assessed.

iv) If the unruptured cerebral aneurysm is to be followed up without surgical intervention, smoking and excessive alcohol intake should be avoided and hypertension needs to be treated. Aneurysm should be carefully followed every half or one year by high quality imaging devices.

v) If any change of shape or increasing size is detected by the follow-up imaging, management of aneurysms should be re-assessed.

vi) Long-term follow up is mandatory after endovascular and surgical clipping of aneurysms.

Conclusions

Unruptured intracranial aneurysms show various clinical characteristics and risk analysis should be based on their features. Indication and decision of management should be decided carefully based on the aneurysm features and updated institutional management risks. All possible measures to achieve safe surgery for this disease, which is mostly asymptomatic, should be deployed. To advance future care of the unruptured intracranial aneurysms, we need continue to obtain more accurate data on the natural course by well designed prospective studies and develop less invasive management measures with minimal morbidity including medical treatment.

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特集 脳動脈瘤の治療―最近のトピックス

脳動脈瘤治療薬としてのスタチン製剤の可能性

Therapeutic Potential of Statins for Cerebral Aneurysm Treatment

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KEY WORDS

脳動脈瘤
炎症反応
NF-κB
スタチン製剤
治療薬

SUMMARY

脳動脈瘤は社会的に重要な疾患である．しかし，現在有効な薬物治療法は存在しない．我々は，脳動脈瘤の形成機序を明らかにするためにモデル動物を使用した検討を行い，結果，脳動脈瘤形成に血管壁の慢性炎症反応が深く寄与することを見い出した．この研究結果を踏まえ，抗炎症作用を有するスタチン製剤がモデル動物に対して脳動脈瘤抑制作用を有することを証明した．スタチン製剤の安全性は確立しているため，脳動脈瘤治療薬として有望である．今後臨床治験を経て臨床応用が切望される．

はじめに

脳動脈瘤は，重篤な疾患であるくも膜下出血の主要な原因である．また，脳動脈瘤の有病率は一般人口の数%と高率である[1][2]．さらに，未破裂脳動脈瘤症例では破裂に対する不安からability of daily life（ADL）が低下しているとの報告もある[3]．すなわち脳動脈瘤は，くも膜下出血発症による損失というだけでなく，それ以上に社会的に大きな損失をもたらす病態である．これらの事実から，未破裂脳動脈瘤の治療が社会的に重要であることは明らかである．

現在，未破裂脳動脈瘤の治療は，その形態や部位などから個々の症例で破裂の危険性を推定し，結果として外科的リスクを越える高い破裂率が見込まれる症例に対して外科的治療が適応される．しかし，外科的治療の適応とならない小さな脳動脈瘤や治療リスクの高い症例も多く存在するが，これらの症例に対する有用な治療法は存在しない．そのため，非侵襲的な薬物治療の開発が求められる．

我々は，未破裂脳動脈瘤の薬物治療の開発を目標に，先に開発された脳動脈瘤モデル動物[4]を使用し，脳動脈瘤の発生増大機構の研究を行ってきた．その結果，脳動脈瘤の形成

には血管壁の慢性炎症反応が重要な役割を果たすことを見い出した[4-6]．また，この結果を踏まえ，抗炎症作用を有する薬剤が脳動脈瘤治療薬となり得るとの仮説のもと，さまざまな薬剤を検討した．この中で，pleiotrophic effectとしてコレステロール降下作用とは独立した抗炎症作用を有するスタチン製剤において[7]，脳動脈瘤治療薬としての可能性を示唆する結果を得た[8-10]．本稿では，動物実験から得られたスタチン製剤の脳動脈瘤抑制作用を概説し，その臨床応用への展望を示す．

血管壁の慢性炎症性疾患としての脳動脈瘤

脳動脈瘤形成に炎症反応が関与することは，ヒトの脳動脈瘤標本で病理学的に炎症細胞浸潤を証明した検討[11]や，脳動脈瘤壁での炎症関連因子の発現解析[12-15]の検討から示唆されてきた．しかし，ヒトの手術標本では，脳動脈瘤の形成過程を経時的に追跡することは困難であり，脳動脈瘤の形成機序の詳細な解析には適していなかった．その問題点を克服するため，脳動脈瘤モデル動物が開発された[4-6]．同モデルは，片側総頸動脈閉塞および全身的高血圧誘導により，対側脳動脈分岐部に血流ストレス負荷から脳動脈瘤を誘発するモデルである．近年，脳動脈瘤モデル動物を用いた解析から，脳動脈瘤の発生増大に血管壁の慢性炎症反応が寄与することが明らかとなった[4-6,16]．脳動脈瘤形成初期に，脳血管分岐部の内皮細胞層においておそらく血管壁への血行力学的なストレスとそれに起因する内皮細胞機能により，転写因子NF-κBが活性化される．引き続き活性化したNF-κBはさまざまな炎症関連遺伝子の発現を転写レベルで亢進させる[17-19]．その中でマクロファージの遊走因子であるmonocyte chemoattractant protein-1（MCP-1）は，マクロファージを脳血管分岐部へ動員し，慢性炎症反応を惹起することにより脳動脈瘤形成に重要な役割を果たす[4-6]．最終的には，血管壁の慢性炎症性反応の結果として蛋白分解酵素の発現亢進[5,20]，活性酸素産生[20]，サイトカイン分泌[18]やアポトーシス誘導[18,21,22]を介して血管壁の変性が生じ，脳動脈瘤が形成される．このような脳動脈瘤の形成に関与する因子のうちで，NF-κBは最も初期から活性化される因子の一つであり，転写因子として他の炎症関連遺伝子を制御誘導することから，主要な関連因子であると推測された．実際，NF-κB p50欠損マウスやdecoy oligonucleotidesによるNF-κB抑制は，脳血管において下流の炎症関連遺伝子群の発現抑制を介して脳動脈瘤発生を強力に抑制する[17,18]．

これらの研究結果から，NF-κBは脳動脈瘤の薬物治療を考える際に第一の標的となる．

抗炎症薬としてのスタチンの脳動脈瘤抑制作用

我々は，前述のように近年の脳動脈瘤研究の結果，抗炎症作用特に抗NF-κB作用を有する薬剤が脳動脈瘤治療薬となり得るとの仮説を立て，種々の薬剤につきその脳動脈瘤抑制作用を検討した[10,17,18]．その中で，スタチン製剤が強力な脳動脈瘤抑制作用を示し，治療薬として有望であることを確認したので，その結果を概説する．

本検討では脳動脈瘤モデルラットを使用した．スタチン製剤としてはピタバスタチンを使用し，経口投与を行った．本モデル動物においてピタバスタチンは血中コレステロールを低下させなかったため，本検討の結果はピタバスタチンのコレステロール降下作用とは独立した作用，すなわちpleiotrophic effectに起因すると判断できる．

ピタバスタチンは，ラットモデルの脳動脈瘤増大を有意に抑制した（図1A）．あわせて動脈瘤壁のひ薄化も有意に抑制した（図1B）．これら抑制作用の機序として血管壁内での炎症反応に注目し，解析を行った．ピタバスタチンは脳動脈瘤壁において，免疫染色による検討でNF-κB活性化を著明に抑制していた（図2A）．ピタバスタチンの抗NF-κB作用については，ゲルシフト法やリン酸化抗体を使用したwestern blot法でも確認した（data not shown）．また，脳動脈瘤壁での主要な炎症細胞であるマクロファージの浸潤[4]も有意に抑制した（図2B）．先の検討で，脳動脈瘤壁においてNF-κB依存的に発現が亢進する遺伝子群を同定している[17,18,22]．そのため，引き続きこれらの遺伝子群についてピタバスタチン投与の影響を確認した．RT-PCR法で，これらの炎症関連遺伝子群はピタバスタチンの抗NF-κB作用と一致して有意に発現が抑制されていた（図2C）．さらに我々は，いったん作製した既存の脳動脈瘤についても，ピタバスタチンがその増大を有意に抑制すること

を確認した．このことは，実際にヒトでの臨床症例では脳動脈瘤がすでに存在している状況を模しており，ピタバスタチンの臨床応用の可能性を強く示唆する結果である．

詳細については本稿では割愛するが，我々は別の種類のスタチン製剤であるシンバスタチンについても，同様のラットモデルを使用して脳動脈瘤抑制効果を検討した[9]．結果としては，シンバスタチンはピタバスタチン同様，脳血管壁の炎症反応を抑制し，脳動脈瘤増大を有意に抑制した．これらの結果から，スタチン製剤による脳動脈瘤抑制効果はピタバスタチンに特異的なものではなく，スタチン製剤に共通するものであることが示唆された．

臨床的には脳動脈瘤治療では破裂の予防，すなわちくも膜下出血の発症予防が重要である．しかし現在，我々の使用したモデル動物では脳動脈瘤の破裂率はわずか数%であり，統計的な解析が困難である．それゆえ，スタチン製剤による脳動脈瘤破裂予防効果については検討できていない．しかし，少なくとも脳動脈瘤の増大抑制効果を認めたことは，疫学的に動脈瘤が大きいほど破裂率が高いという事実と考え合わせると，スタチン製剤が破裂予防効果をもつことが推定される．あわせて，スタチン製剤が動脈瘤壁のひ薄化を抑制したことも，スタチン製剤が破裂予防効果をもつことを示唆している．

スタチンの臨床応用への展望

スタチン製剤は，現在世界中で最も広く使用されている薬剤の一つであり，その安全性は十分に確立している．そのため，スタチン製剤の脳動脈瘤抑制効果をみた動物実験の結果は，他の薬剤の場合に比較してより臨床応用に近いと考えられる．スタチン製剤の脳動脈瘤治療薬としての臨床応用を考慮する上で解決すべき問題は，脂質異常症が脳動脈瘤の危険因子でないため投与対象が主に非脂質異常症症例である点である[10]．この点，すなわち非脂質異常症症例に対するスタチン製剤投与の安全性が解決されるのであれば，スタチン製剤は脳動脈瘤治療薬として有望な薬剤である．

大動脈瘤は脳動脈瘤同様，主に外科的に加療をされてきた疾患である．大動脈瘤形成の分子機序は，脳動脈瘤とさまざまな差異はあるにしろ，血管壁の慢性炎症を基礎としており共通の部分も多い．大動脈瘤研究は脳動脈瘤研究に比較し進んでおり，抗炎症薬特にスタチン製剤の治療薬としての可能性が臨床的に検討されている．そして，その増大予防効果と破裂による死亡率低減効果が実際の臨床症例で証明されている[11-13]．大動脈治療において，今後の大規模な臨床研究の後，スタチン製剤が治療薬として確立することが見込まれている．脳動脈瘤においても，同様にスタチン製剤による大規模な臨床研究の実施が切望される．

結　語

本稿では，スタチン製剤がpleiotrophic effectである抗NF-κB作用を介して脳動脈瘤抑制効果を発揮するという最新の知見を紹介した．スタチン製剤は，脳動脈瘤治療薬として有望であり，臨床的検討が強く望まれる．

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