2. 背景

脳ドックなどで未破裂脳動脈瘤が発見された場合、その対応として破裂を予防するためのクリッピング術、血管内塞栓術、または無治療のまま経過観察という選択肢が存在する。それぞれの選択肢のリスク・ベネフィットが定量的に明らかでない現状で、未破裂脳動脈瘤を持つ患者に脳動脈瘤自体や治療の選択肢について納得の得られる説明をすることは難しい。臨床医がその対応に最善の努力を尽くした場合でも、患者の理解は十分とは言えない場合が多い。しかし患者が、未破裂脳動脈瘤、そして、それに対してどのような治療の選択肢が存在するか、それらにどのようなリスクが伴うのかについて知識を得たいと希望していることは事実である 1-4)。また、このような情報提供により、不安を増長させることなく患者自身が治療計画に前向きに関わり、治療アウトカムを改善できる可能性がある 3-5)。一方で、情報提供自体は患者のほとんどすべてが望むのとは対照的に、どのような治療方針を採るかの意思決定への主体的な関与については患者間でばらつきがある。一般的には若い患者ほど積極的参加を望み、中高年患者は必ずしも積極的ではないことが多い 4-6)。しかし、具体的に、患者が未破裂脳動脈瘤の治療の選択肢について、どのような認識を持っているかに関する知見は乏しい 7)。

3. 目的

未破裂脳動脈瘤の自然経過、各治療選択肢に予期されるアウトカムについて、脳神経外科医が患者に提供したと考えている情報、患者が提供されたと感じている情報、医師および患者がそれをどのように認識しているかを明らかにする。

4. 調査方法

未破裂脳動脈瘤を指摘された患者、その主治医(脳神経外科医)を対象とした質問票調査
滋賀医科大学付属病院脳神経外科または関連病院の外来で実施

4-1. 選択基準

[患者]

1) 3年以内に未破裂脳動脈瘤を指摘された成人男女で、2010年2月から2010月5月に滋賀医科大学付属病院脳神経外科または関連病院を受診
2) 医師との間で疾患の危険性や治療方針について複数回以上にわたり説明が行なわれて

いる

3）未破裂脳動脈瘤に対する予防的治療の有無は問わない

4）本研究の趣旨を理解し、参加へのインフォームドコンセントが得られている

［脳神経外科医］

1）滋賀医科大学付属病院脳神経外科または関連病院の脳神経外科専門医

2）本研究の趣旨を理解し、参加へのインフォームドコンセントが得られている

4-2．質問票

下記の内容を含む質問票を作成し、患者と脳神経外科医から回答を求める。

(1) 治療選択肢に対する患者の理解

治療選択肢の適切性、ならびにこれらの治療選択肢に対する患者の理解度を評価するために、「大いにそう思う」から「まったくそう思わない」の6段階リッカート尺度を使用

(2) 患者と脳神経外科医との間で合意した最善の治療

(3) 治療中の脳卒中または死亡のリスク、無治療のまま放置した場合の将来的な死亡および脳卒中のリスクに関する認知

クリッピング術や血管内塞栓術に伴う患者の脳卒中や死亡リスク、動脈瘤を治療せず放置した場合の今後20年間の累積リスクを0～100%の範囲で推定し、10 cmの視覚アナログ尺度（VAS）にマーキング

4-3．症例数

Kingらの先行研究 7)を参照し、患者・脳神経外科医の各30名の協力を得て、30ペアとする。

5．予想される有害事象

身体的な侵襲は無く、また患者と脳神経外科医のコミュニケーションを支援する目的での質問票調査であり、有害事象の発生は考えにくい。

6．解析方法

人口統計、教育、認知機能、病歴、習慣、動脈瘤の特徴および治療の記述的解析。

患者と脳神経外科医のリッカート尺度の回答をペアにしたもの、ならびに合意した治療に関する回答の一致状況をκスコアにより比較。

κスコア・・・2名の評価者間で単なる偶然以上の合意がどの程度取れたかを評価し、合意の

程度を定量化する指標。0～0.20：わずかな一致、0.21～0.40：やや一致、0.41～0.60：中程度の一致、0.61～0.80：かなりの一致、0.81～1.00：ほぼ完全な一致 とする 8)。

患者と脳神経外科医のVASへの回答のペアはWilcoxon 検定、脳神経外科医の回答における差異は、Kruskal-Wallis検定で評価。いずれも両側検定のp値は0.05で統計学的に有意とする。

7. 費用負担および謝礼

費用負担は生じない。また参加患者および脳神経外科医への謝礼は行わない。

8. 倫理的配慮

ヘルシンキ宣言(2008年ソウル修正)、厚生労働省・文部科学省「疫学研究の倫理指針(2007年11月施行修正版)」と「臨床研究の倫理指針(2009年4月施行修正版)」を遵守し、主任研究者の所属機関での倫理審査を受ける。研究対象者の個人情報保護やインフォームドコンセントに十分留意して研究を実施する。

9. 研究費用

平成21年度厚生労働科学研究費補助金(医療技術実用化総合研究事業)
未破裂脳動脈瘤の治療の評価技術の開発に関する研究
(H21- 臨床研究- 一般- 008: 主任研究者: 野崎和彦)

10. 研究組織

主任研究者:
野崎和彦　滋賀医科大学脳神経外科学講座 教授

分担研究者:
中山健夫　京都大学大学院医学研究科 社会健康医学系専攻健康情報学分野 教授

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未破裂脳動脈瘤と診断された患者さんへ

記入日　平成22年＿＿月＿＿日　　　お名前＿＿＿＿＿＿＿＿＿＿

本日の診察を受けられて、現在のお気持ちについてお教え下さい。

それぞれの質問について、もっとも当てはまる回答を一つ選び、その数字に○をつけて下さい。

[1] 自分の脳動脈瘤のための最善の処置は、手術である。

1 大いにそう思う　　2 そう思う　　3 どちらかというとそう思う
4 どちらかというとそう思わない　　5 そう思わない　　6 まったくそう思わない

[2] 自分の脳動脈瘤のための最善の処置は、コイル塞栓術である。

1 大いにそう思う　　2 そう思う　　3 どちらかというとそう思う
4 どちらかというとそう思わない　　5 そう思わない　　6 まったくそう思わない

[3] 自分の脳動脈瘤のための最善の処置は、治療せずに経過を見ていくことである。

1 大いにそう思う　　2 そう思う　　3 どちらかというとそう思う
4 どちらかというとそう思わない　　5 そう思わない　　6 まったくそう思わない

[4] 自分の脳動脈瘤のための最善の処置は、MRI および CAT スキャン、血管造影などで経過を見ていくことである。

1 大いにそう思う　　2 そう思う　　3 どちらかというとそう思う
4 どちらかというとそう思わない　　5 そう思わない　　6 まったくそう思わない

[5] 今日の診察の終わりには脳動脈瘤の治療選択肢が理解できた。

1 大いにそう思う　　2 そう思う　　3 どちらかというとそう思う
4 どちらかというとそう思わない　　5 そう思わない　　6 まったくそう思わない

[6] 今日の診察の終わりには脳動脈瘤のための最善の処置が理解できた。

1 大いにそう思う　　2 そう思う　　3 どちらかというとそう思う
4 どちらかというとそう思わない　　5 そう思わない　　6 まったくそう思わない

それでは、どうぞお大事にされてください。(2010年1月)

[医師向け質問票]未破裂脳動脈瘤の患者さんの診療に関して

記入日　平成22年＿＿月＿＿日　　医師名＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

患者名＿＿＿＿＿＿＿＿＿＿＿

該当の患者さんに関して、次のそれぞれの質問について、主治医としてもっとも当てはまる回答を一つ選び、その数字に○をつけて下さい(同様の質問を該当患者さんにも回答頂いています)。

[1]（この患者さんの。以下同様） 脳動脈瘤のための最善の処置は、手術である。

1 大いにそう思う　2 そう思う　3 どちらかというとそう思う
4 どちらかというとそう思わない　5 そう思わない　6 まったくそう思わない

[2] 脳動脈瘤のための最善の処置は、コイル塞栓術である。

1 大いにそう思う　2 そう思う　3 どちらかというとそう思う
4 どちらかというとそう思わない　5 そう思わない　6 まったくそう思わない

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1 大いにそう思う　2 そう思う　3 どちらかというとそう思う
4 どちらかというとそう思わない　5 そう思わない　6 まったくそう思わない

[4] 脳動脈瘤のための最善の処置は、MRI および CAT スキャン、血管造影などで経過を見ていくことである。

1 大いにそう思う　2 そう思う　3 どちらかというとそう思う
4 どちらかというとそう思わない　5 そう思わない　6 まったくそう思わない

[5] 今日の診察の終わりには脳動脈瘤の治療選択肢が理解できた。

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1 大いにそう思う　2 そう思う　3 どちらかというとそう思う
4 どちらかというとそう思わない　5 そう思わない　6 まったくそう思わない

医師および患者さんに対する質問

下記について起こる確率はどのくらいと考えていますか。適当な場所に○をつけてください。

動脈瘤を治療せず経過観察した場合、今後20年間の脳卒中や死亡の可能性

（20年の**間に重篤な後遺症を起こしたり死亡する確率**）

[------|------|------|------|------|------|------|------|------|------]

0　10　20　30　40　50　60　70　80　90　100%

クリッピング術や血管内塞栓術などの治療に伴う脳卒中や死亡の可能性

[------|------|------|------|------|------|------|------|------|------]

0　10　20　30　40　50　60　70　80　90　100%

入力フォーム　動脈瘤情報

患者氏名：

研究参加日	平成　　年　　月　　日		
破裂または未破裂脳動脈瘤の部位・形状	(1) 脳動脈瘤　の部位 (以下の①から⑨の数値を記入) 前の方にある動脈瘤 ① 前大脳動脈 ②前交通動脈 ③中大脳動脈 ④内頚動脈 ⑤内頚動脈後交通動脈 後ろの方にある動脈瘤 ⑥椎骨動脈 ⑦脳底動脈 ⑧後大脳動脈 硬膜の外側にある動脈瘤 ⑨内頚動脈海綿静脈洞部	(2) 脳動脈瘤の大きさ・最大径 (数値を記入)	(3) 形の不整の有無 (ブレブの有無)
一つ目の脳動脈瘤 (SAH 例では破裂瘤)	(　　　)	(　　　) mm	有　　無
二つ目の脳動脈瘤	(　　　)	(　　　) mm	有　　無
三つ目の脳動脈瘤	(　　　)	(　　　) mm	有　　無
家族歴の有無	親、兄弟に脳動脈瘤を有する人が　　いる　　いない		
SAH 既往の有無	有 (年月日：　　　　　)　無		
脳動脈瘤発見時期	平成　　年　　月　　日		
脳動脈瘤診断方法	MRA (MRI), 3D-CTA (CT), DSA, その他 (　　　　　)		
未破裂脳動脈瘤の場合、増大の有無	有　　無 有の場合　増大　　　mm/　　　ヶ月		

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Practical Decision-Making in the Treatment of Unruptured Cerebral Aneurysm in Japan: The U-CARE Study

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Key Words
Practical decision-making · Cerebral aneurysm · Clipping · Coiling

Abstract

Background: Decision-making during the management of unruptured cerebral aneurysms is a delicate process for both neurosurgeons and patients. Guidelines are evidence-based references that can aid in making decisions. However, neurosurgeons do not always follow guidelines in clinical practice. The purpose of this study is to verify the hypothesis that there is substantial dissociation between treatment guidelines and practical decision-making due to a bias in treatment selection for unruptured cerebral aneurysms. This bias is dependent upon clinician-driven factors such as experience and specialty, and patient-driven factors such as patient preference. ***Methods:*** This study was performed using internet questionnaires. A total of 282 randomly selected, qualified Japanese neurosurgeons (out of approx. 6,000 registered neurosurgeons), including 45 endovascular specialists, participated in this study. Radiological and demographic data from 88 cases of unruptured cerebral aneurysm were opened on the Web. Participating neurosurgeons decided on the treatment for each case (clipping, coiling or observation). ***Results:*** Variations in treatment selection were not significant between neurosurgeons and endovascular specialists, except for aneurysms such as anterior choroidal artery aneurysm. However, contrary to the guidelines, aneurysms larger than 10 mm tended to be treated conservatively because the risk of treatment is high, while aneurysms smaller than 5 mm in diameter were often selected for intervention (clipping or coiling). ***Conclusions:*** This study revealed that in real-world clinical practice, physicians are not always faithful to the current guidelines. In making practical treatment decisions for unruptured cerebral aneurysms, the patient's will and the recognition of unavoidable, treatment-related risks seriously influence neurosurgeons' decisions.

Introduction

It is well known that the rupture of intracranial cerebral aneurysm is a major cause of subarachnoid hemorrhage, resulting in serious mortality and morbidity. Therefore, it is theoretically rational that the detection and preventive management of unruptured cerebral aneurysms may decrease the incidence of subarachnoid hemorrhage and its consequent mortality and morbidity.

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Unruptured cerebral aneurysms can be divided roughly into 2 types: asymptomatic and symptomatic. The former is often discovered by 'Brain Docs', a medical check-up system developed in Japan, or a detailed inspection of other cerebral disorders such as cerebral infarctions. The development and spread of high-resolution image modalities such as magnetic resonance angiography (MRA) and computed tomography angiography in Japan have increased the frequency with which asymptomatic unruptured cerebral aneurysms are now discovered.

The prevalence of unruptured cerebral aneurysm is assumed to be 2–6% in adults in Japan. While the rupture rate of unruptured cerebral aneurysms is estimated to be 1%, subarachnoid hemorrhage is presumed to occur in 20–60 patients per 100,000 people per year. Moreover, the mortality and morbidity rates of subarachnoid hemorrhage (50 and 25%, respectively) translate into 10–30 patient deaths and 5–15 severe physical disabilities resulting from subarachnoid hemorrhage per 100,000 people per year.

The preventive management of unruptured cerebral aneurysms can substantially decrease morbidity and mortality due to cerebral aneurysm rupture. There are many complex issues surrounding unruptured cerebral aneurysms. Among them, treatment selection is a primary concern. Evidence-based guidelines function as a reference for treating unruptured cerebral aneurysms. However, decision-making is not always straightforward in particular cases in daily clinical practice. It is unlikely that physicians and patients simply follow these guidelines without exception.

We conducted this study to reveal the practical decision-making processes employed by neurosurgeons in cases of unruptured cerebral aneurysms, and the primary factors that influence their decisions. This study is the first in the literature regarding unruptured cerebral aneurysm that can be classified as a practice variation study, although such studies have been undertaken in other fields.

Methods

Study Design

This study was performed as one of the substudies of the Unruptured Cerebral Aneurysm Study on Risk Communication and Evidence-Based Decision-Making (U-CARE), a comprehensive study on unruptured cerebral aneurysm supported by a grant from the Japanese Ministry of Health, Welfare and Labor (No. H16-03, chief researcher: Nobuo Hashimoto). We have opened a website (http://u-care.sapmed.ac.jp/cgi-bin/WebObjects/u-TREAT) that is accessible only to selected members with a password. Eighty-eight selected patients with unruptured cerebral aneurysms who had consulted the Sapporo Medical University and Kyoto University were enrolled from 2005 to 2006. Patients' demographic data, such as their gender, age, occupations, symptoms, present illness, personal and family history and preferences, and radiological data, such as magnetic resonance imaging (MRI), CT and/or MRA, were posted on the website in accordance with personal information protection laws (fig. 1).

Two hundred eighty-two neurosurgeons, randomly selected from approximately 6,000 neurosurgeons certified by the Japanese Society of Neurological Surgeons, have joined this study. Of these, 45 were also licensed endovascular specialists certified by the Japanese Neuroendovascular Society.

Participating neurosurgeons proffered decisions for each case, selecting the following 3 choices of (1) surgical treatment, (2) coiling and (3) conservative observation, via the Internet. Basic attitudes toward the Japanese guidelines for treating unruptured cerebral aneurysms were also surveyed.

Patients' Data and Physicians' Data

Patients were aged from 29 to 77 years (median 62.5). Presented aneurysms included internal carotid artery (ICA, n = 34), middle cerebral artery (MCA, n = 38), anterior cerebral artery (ACA, n = 17), vertebral artery (VA, n = 6), basilar artery (BA, n = 11) and posterior cerebral artery (PCA, n = 4) aneurysms. The distribution of the aneurysm locations in this study seemed to be similar to the distribution occurring in the general practice. Patient demography included personal history, family history and requests regarding the aneurysm management (clipping, coiling, conservative and reliance on doctors' expertise).

Physicians' data included subspecialty, working facility (e.g. location, hospital size, University hospital) and experience (number of annual cases of unruptured cerebral aneurysms).

Data Analysis

We calculated that if all 327 doctors responded completely to all 88 cases, there would be 28,776 total answers. The real average response rate has reached approximately 80%, and consequently enormous data (as much as 23,000 answers) have been collected. The data consist of many factors, including both clinician-driven and patient-driven factors. Analysis in this study focused on 5 factors significant to daily practice: (1) aneurysm location and subspecialty; (2) aneurysm size and doctor's decision; (3) patient's preference, and (4) basic attitudes toward the guidelines. All data were collected via the Internet and analyzed with software SPSS version 16.0 (SPSS Inc., Chicago, Ill., USA).

Ethical Considerations

All of these lines of inquiry have been executed with strict attention to the protection of individual information and the informed consent of the persons being studied, in accordance with the Ethics Indicator of Epidemiologic Study by the Ministry of Health. This study design was approved by the ethical committees at Sapporo Medical University and Kyoto University. All patients have agreed to join this study and have provided written informed consent.

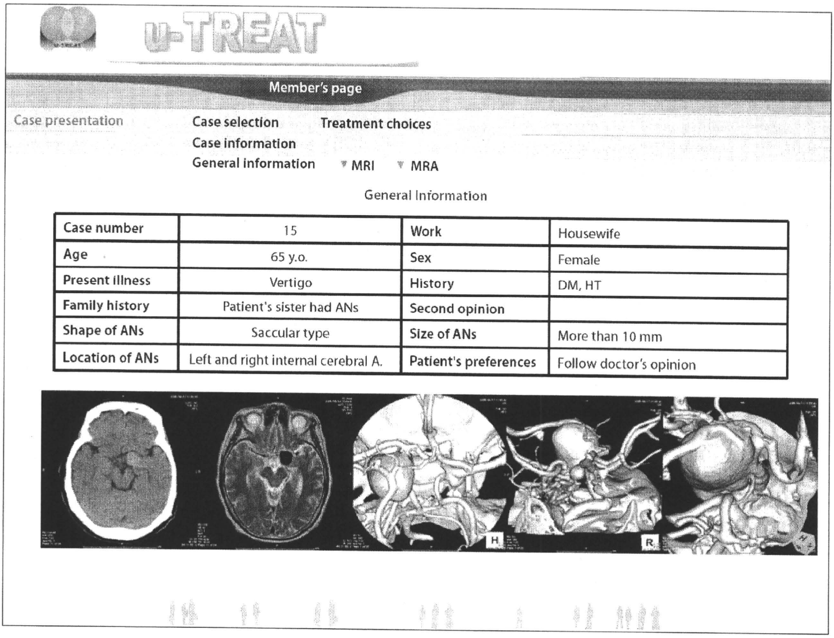

Fig. 1. Representative picture of the website of this study. General and radiological information are shown. ANs = Aneurysms; DM = diabetes mellitus; HT = hypertension.

Results

Demonstrative Data

In an ACA aneurysm, endovascular surgeons preferred coiling to treat it (fig. 2). The huge aneurysms tended to be conservatively observed by both neurosurgeons and endovascular specialists (fig. 3). A large MCA aneurysm and an internal cerebral/posterior communicating artery aneurysm tended to be aggressively treated with operative and endovascular treatment, respectively (fig. 4).

Aneurysm Location

In MCA, BA, VA and PCA aneurysms, there was no significant selection bias in terms of subspecialty (fig. 5). However, endovascular surgeons significantly preferred coiling to treat ICA and ACA aneurysms. In particular, there was a significant difference in the treatment of ICA/anterior choroidal artery aneurysms depending on subspecialty. Unsurprisingly, there was no significant variation in treatment practices for BA and VA aneurysms between neurosurgeons and endovascular surgeons. Endovascular surgeons significantly preferred coiling to treat internal cerebral artery and ACA aneurysms.

Aneurysm Size

The relationship between aneurysm size (fig. 6) and treatment decision was analyzed only in ICA aneurysms, since the number of aneurysms in this location was large

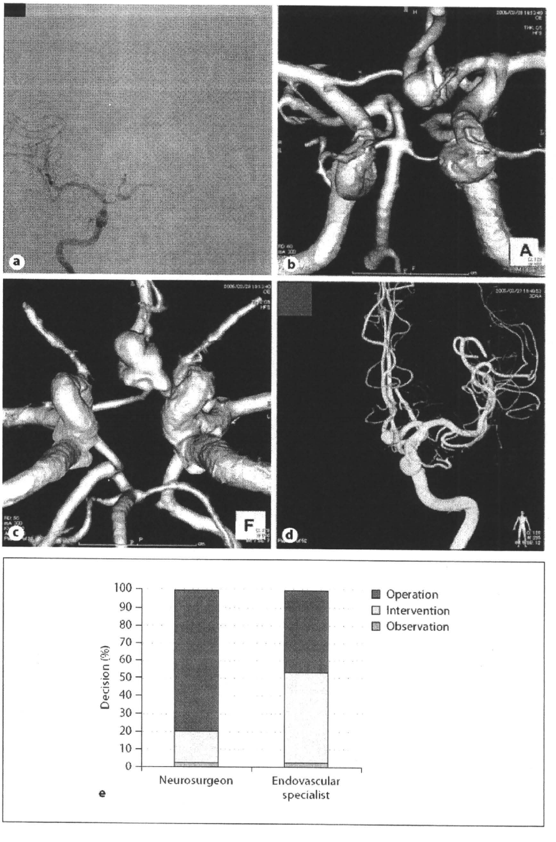

Fig. 2. A 57-year-old female consulted a doctor because of her headache. She had a family history: her father and brother died of subarachnoid hemorrhage. She had a 10-year history of hypertension and hyperlipidemia. Her wish for treatment of her aneurysm was subjected to her doctor's opinion. In an ACA aneurysm, endovascular surgeons preferred coiling to treat it. A = Anterior; F = foot.

enough for analysis to produce statistically significant results. ICA aneurysms with diameters less than 4 mm were often considered as a subject for treatment, while aneurysms larger than 10 mm often tended to be conservatively observed. Clinicians tended to choose interventions such as clipping or coiling for the treatment of intermediately sized aneurysms (5–9 mm diameter).

Patient Preferences

Most doctors generally followed their patients' requests (fig. 7) that their aneurysms be managed with conservative observation. However, doctors did not always adhere to their patients' requests for aggressive treatments such as clipping or coiling.

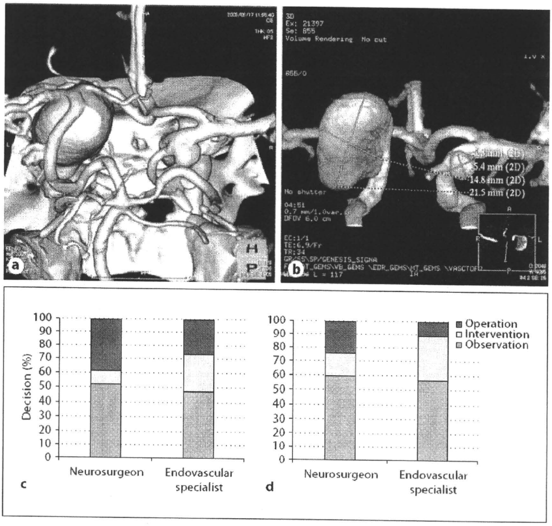

Fig. 3. A 66-year-old female consulted a doctor because of her headache. She had had an operation for a lung carcinoma 5 years before this consultation. She had a medical screening for brain metastasis. Two aneurysms were found incidentally in the left (**c**) and right (**d**) internal cerebral arteries. She entrusted the treatment of her aneurysms to her doctor. Huge aneurysms tended to be conservatively observed by both neurosurgeons and endovascular specialists. H = Head; P = posterior.

Basic Attitudes toward the Guidelines

The basic attitudes toward the Japanese guidelines are shown in figure 8. It was revealed that only 33% of participating neurosurgeons and endovascular specialists (92 out of 282 neurosurgeons) strictly followed these guidelines.

Discussion

Unruptured cerebral aneurysms are frequently diagnosed by the Brain Docs system, which is run by many hospitals in Japan. The purpose of the Brain Docs system is not only to find unruptured cerebral aneurysms, but also to detect asymptomatic brain disease. This system has developed in the context of the spread of high-performance MRI/MRA. It is reported that cerebral aneurysms are detected in, at most, 6–7 per 100 persons that have medical check-ups using high-resolution MRI/MRA [1]. According to the statistics of the Society of Japanese Neurosurgeons, approximately 10,000 unruptured cerebral aneurysms are treated in Japan per year. Among these 10,000 aneurysms, 8,500 are treated by craniotomy and clipping or other surgical procedures, 1,500 are treated by endovascular techniques and some aneurysms are treated by both surgical and endovascular treatment [2]. It is estimated that medical expenses for these treatments total approximately 20 billion yen (200 million USD) per year.

The main purpose of treatment of unruptured intracranial aneurysms is the prevention of rupture, since the prognosis for ruptured cerebral aneurysms is not always optimistic and ruptures frequently result in high rates of mortality and morbidity [3]. However, this logic can be rationalized when the benefit obtained by the treatment overcomes the risk and mortality/morbidity that accompany treatment. Therefore, decisions regarding the treatment of unruptured cerebral aneurysms are made by the integrated evaluation of the natural course of each aneurysm and the predicted risk of each treatment.

The management guidelines regarding unruptured cerebral aneurysms are primarily evidence-based facts about the risk of aneurysm rupture and the treatment-associated risks. It is well known that the guidelines differ

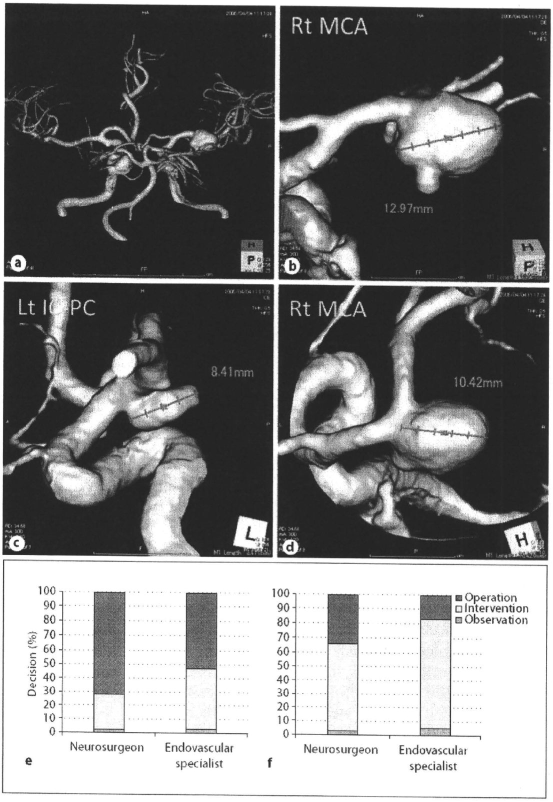

Fig. 4. A 57-year-old male consulted a doctor because he had a head injury. A right MCA (**e**) and a left internal cerebral/posterior communicating artery (**f**) aneurysm were found incidentally. His wish for the treatment of his aneurysms was endovascular treatment. In internal cerebral/posterior communicating artery aneurysm, both neurosurgeons and endovascular specialists chose endovascular treatment. However, in the MCA, both surgeons and endovascular specialists chose operative treatment even if the patient wanted endovascular treatment. P = Posterior; H = head; L = left.

subtly among countries, since there are differences in health care systems and epidemiological factors. In Japan, for example, according to the guidelines of the Japanese Brain Doc Society, unruptured cerebral aneurysms in patients younger than 70 years and aneurysms larger than 5 mm in diameter should be considered for treatment based on the comprehensive evaluation of several other medical conditions. Meanwhile, aneurysms smaller than 3 mm in size should be conservatively observed, and aneurysms larger than 7 mm in size are generally considered subject to treatment. The guidelines of the American Heart Association contain many cautious descriptions based on extensive evidence, although the numerical values for the treated aneurysms are not always described in these guidelines. Treatment is generally recommended for aneurysms larger than 10 mm in diameter [4].

In this study, the variations in practice between the neurosurgeons (who primarily prefer clipping) and the

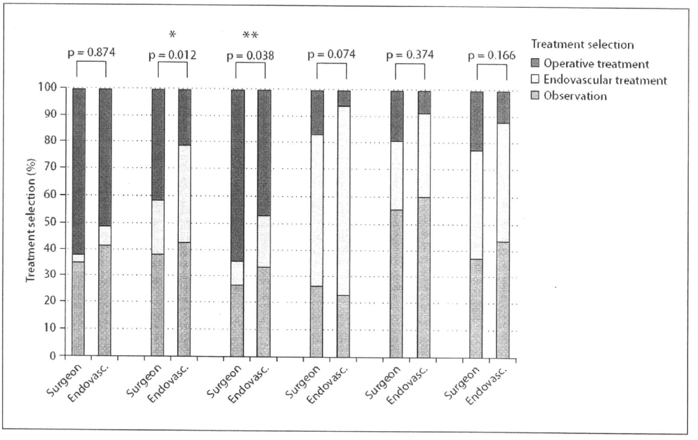

Fig. 5. Relation between aneurysm location and treatment selection by neurosurgeons and endovascular specialists (endovasc.). Endovascular surgeons significantly preferred coiling to treat internal cerebral (IC) and ACA aneurysms. There was no significant difference between neurosurgeons and endovascular specialists in MCA, BA, VA and PCA. * $p < 0.03$, ** $p < 0.05$.

endovascular specialists are not necessarily significant, except in the cases of some particular aneurysm locations, such as the anterior choroidal artery aneurysm, which is becoming controversial regarding treatment selection. It is therefore quite conceivable that the decision-making for the treatment of the ACA aneurysm differs according to subspecialty. Indeed, as far as the choice of aneurysm treatment (clipping or coiling) is concerned, there is not necessarily a well-established guideline at this point.

The most interesting variation in practice that has been revealed in this study is that of the relationship between aneurysm size and treatment decision. In both the Japanese and American Heart Association guidelines, treatment of small aneurysms (less than 4 mm in diameter) is not recommended, while large aneurysm size (more than 10 mm in diameter) is considered a good indication for treatment. However, this study revealed that the size recommendations in these guidelines are not always followed in practice.

Risk factors concerning rupture have been well investigated, including but not limited to age, sex, smoking, hypertension, symptomatology and family history of subarachnoid hemorrhage [5–8]. Among these predictable risk factors, it is well known that aneurysm size and location are among the most reliable predictors for rupture. Larger aneurysms have a much higher rate of rupture, as has been reported by many authors, including Juvela et al. [5], who demonstrated that aneurysms greater than 7 mm in diameter are twice as likely to rupture as those less than 6 mm in diameter. Additionally, Rinkel et al. [6] demonstrated a 5.5-fold higher rate of rupture in aneurysms over 10 mm in diameter compared to smaller aneurysms. Wiebers et al. [7] also demonstrated that aneurysms over 10 mm in diameter are easier to rupture than smaller aneurysms.

The reason why this strong evidence is not well reflected in clinical decision-making is quite apparent. The treatment outcomes regarding the smaller aneurysms are excellent. However, the surgical risk of complications with permanent consequences is not low enough in the treatment of large aneurysms. Raaymakers et al. [9] reported that giant aneurysms in the anterior circulation demonstrated a 7.4-fold higher mortality and 26.9% morbidity, while giant aneurysms in the posterior circulation

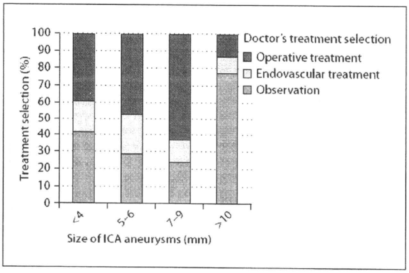

Fig. 6. Aneurysm size and treatment selection in the ICA. Aneurysms even less than 4 mm were often treated with surgical or endovascular interventions. Most neurosurgeons in Japan tend to choose conservative observation for aneurysms larger than 10 mm in diameter.

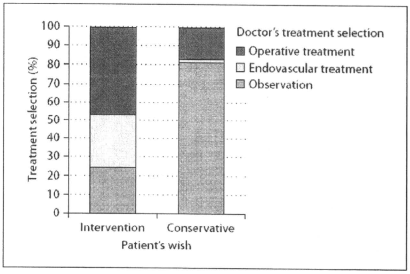

Fig. 7. Patient's wish and doctor's treatment selection. Most doctors generally followed their patients' requests that their aneurysms be managed with conservative observation. However, doctors did not always adhere to their patients' requests for aggressive treatments such as clipping or coiling.

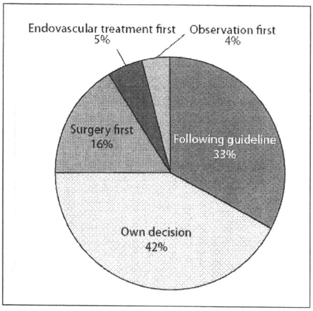

Fig. 8. Basic attitude of doctors to the official guidelines concerning unruptured cerebral aneurysms in Japan. Note that only 33% of neurosurgeons and endovascular specialists in Japan follow the guidelines.

demonstrated 9.6% mortality and 37.9% morbidity. On the other hand, nongiant aneurysms in the anterior circulation had 0.8% mortality and 1.9% morbidity [9]. We believe this study clearly demonstrates that there is a defensive tendency to avoid high-risk aneurysm treatments [10]. This tendency is likely influenced by the steadily increasing rates of malpractice and lawsuits in Japan.

It is unsurprising that the management guidelines for unruptured cerebral aneurysms are not always well established compared to the guidelines of other diseases. The whole scheme of natural history and treatment risk of unruptured cerebral aneurysms has not been defined clearly enough to support the establishment of a practically reliable set of guidelines. As a result, decisions made by physicians in clinical practice are dissociated from the official guidelines. Our data indicate that only 33% of participating neurosurgeons and endovascular specialists (92 out of 282 neurosurgeons) strictly followed these guidelines. This does not mean that evidence-based guidelines are not amenable to clinical usage. However, in real-time clinical situations, the tendency to avoid high-risk treatment options dominates the decision-making processes of both doctors and patients. In conclusion, this study revealed that the present guidelines are not always used as a gold standard in practical decision-making when treating unruptured aneurysms. Recognition of unavoidable risks related to treatment seriously influences the practical decision-making of neurosurgeons.

Acknowledgment

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Role of Shear Stress in the Blister Formation of Cerebral Aneurysms

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BACKGROUND: The development of cerebral aneurysms is related to hemodynamic stress.

OBJECTIVE: To elucidate the role of shear stress in the blister formation of cerebral aneurysms.

METHODS: Among 82 aneurysms detected during catheter-based 3D rotational angiography (3DRA), 4 aneurysms enlarged with blister formation during a mean follow-up period of 10.1 month. Three of these 4 aneurysms were analyzed in this study. The regions of blister formation were characterized by comparing 3DRA before and after blister formation, and computational fluid dynamic simulations were performed based on the aneurysm geometry before blister formation.

RESULTS: The spatially averaged shear magnitude was lower in the aneurysm region (0.97 ± 0.39 Pa) than in the parent artery (2.75 ± 0.92 Pa). The spatially averaged shear magnitude of the blister-forming area was extremely low (0.48 ± 0.12 Pa), and the shear magnitude dropped precipitately to subphysiological levels, resulting in a high shear gradient near the border of the blister-forming area.

CONCLUSION: These data suggest that low shear magnitude may trigger the progression of cerebral aneurysms and that blister formation is associated with high shear gradient in the large region of low shear magnitude on the aneurysm wall.

KEY WORDS: Biomechanics, Computer simulation, Hemodynamics, Intracranial aneurysm, Shear stress

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Cerebral aneurysms typically arise at vascular branch points, most likely because of alterations in hemodynamic forces at these points. High and supraphysiological shear magnitudes lead to fragmentation of the internal elastic lamina,[1] thereby promoting aneurysm formation.[2]

However, the role of shear stress on aneurysm progression remains unclear. Intuitively, high shear magnitude would be expected to promote the enlargement and rupture of cerebral aneurysms, because that promotes the formation of cerebral aneurysms. However, the cellular and hemodynamic mechanisms related to aneurysm progression may differ from those involved in the aneurysm formation.[3,4] Several studies suggest that low shear magnitude might trigger aneurysm progression and eventual rupture.[5-7]

Our group has observed rare cases of aneurysms with subsequent blister formation leading to enlargement or rupture. Detailed 3-dimensional (3D) images were obtained before and after the blister formation in these cases. In the present study, computational fluid dynamic simulations were performed based on the aneurysm geometry before blister formation to characterize the hemodynamic features associated with the subsequent blister formation on cerebral aneurysms.

ABBREVIATIONS: AcomA, anterior communicating artery; **3D**, 3-dimensional; **3DRA**, 3D rotational angiography; **MCA**, middle cerebral artery

MATERIALS AND METHODS

Patient Population

From March 2007 to August 2008, 119 unruptured cerebral aneurysms among 93 patients were characterized with catheter angiography and 3D rotational angiography (3DRA) at Jichi Medical University Hospital. Within this population, 82 aneurysms among 62 patients were followed with magnetic resonance angiography over a mean period of 10.1 months (range, 1–25 mo). Among the cases with blister formation, 2 aneurysms enlarged and 2 aneurysms ruptured during the observation period. One anterior communicating artery (AComA) aneurysm that enlarged 17 months after the initial 3DRA was excluded from final analysis because the aneurysm was supplied by both anterior cerebral arteries and because 3DRA data quality was insufficient for fluid dynamic simulation. Thus, a total of 3 aneurysms were subjected to computational fluid dynamic simulation (Table).

Vessel and Aneurysm Modeling

Three-dimensional rotational angiography was performed using a C-arm angiography unit with flat detectors (Allura Xper FD 20/10; Philips Medical Systems, Best, Netherlands). During the 180° C-arm rotation, contrast medium (300 mgI/mL) was injected at a rate of 4 mL/s for 5 seconds via a catheter placed at the internal or vertebral artery, and 120 angiographic images with a matrix size of 1024 × 1024 pixels were obtained with a 17-inch field of view. These images were converted to isotropic 3D volume data with a voxel size of 0.28 mm in the equipped workstation.

Vessels and aneurysms were segmented by adjusting the threshold curve of the volume-rendered image on the workstation, resulting in the output of 3D surfaces. Thresholds were adjusted to keep the same reference diameter (ie, the diameter of the parent artery) when comparing images before and after the blister formation, thereby ensuring a consistent threshold policy.

The 3D surface was processed using a preprocessor equipped with a finite volume solver, SC/Tetra (Software Cradle, Osaka, Japan), to refine the fine irregularities of the 3D surfaces, to make planes for inlets and outlets, and to clear small branches from the region of interest. The computational meshes generated for the aneurysms before the blister formation consisted of 545 690 tetrahedral elements and the average resolution of the meshes was 0.32 mm. Regions of analysis encompassed the area from the cavernous segment of the internal carotid artery (cases 1 and 2) or from both of the vertebral arteries (case 3) to segments at least 15 mm distal to the aneurysms.

TABLE. Subject Characteristics and Results of Fluid Dynamic Simulation[a]

	Case 1	Case 2	Case 3
Age, y	58	49	59
Sex	Female	Female	Male
Aneurysm site	Left MCA	AComA	BA
Size, mm			
Before BF	3.8	6.6	9.7
After BF	5.7	7.1	9.7
Event	Enlargement	Rupture	Rupture
Interval, mo	15	2	1
Flow rate at inlets, mL/min	230	212	130
Reynolds number	322	191	189
Womersley number	2.53	2.35	1.95
Shear magnitude, Pa			
Parent artery	3.28	3.29	1.69
Whole aneurysm	1.41	0.69	0.80
Blister forming area	0.61	0.40	0.42

[a]MCA, middle cerebral artery; AComA, anterior communicating artery; BA, basilar artery; BF, blister formation.

Numerical Simulations

For aneurysm geometry before blister formation, 3D pulsatile blood flow was modeled with a finite volume solver (SC/Tetra) under governing equations of mass conservation and Navier-Stokes.

The flow rate and waveform at each of the inlets were derived from each case within 1 month after blister formation using phase contrast magnetic resonance velocimetry. Measured flow rates were imposed on the cross-sectional area of the inlets as velocity inlet conditions according to Womersley's analytic solution of oscillatory flow.[8] The average of the Reynolds number and Womersley number at the parent arteries of the aneurysms were 234 and 2.28, respectively, and laminar flow conditions were assumed for the fluid dynamic simulations.

Blood was assumed to be an incompressible Newtonian fluid with a specific gravity of 1053 kg/m^3 and a viscosity of 4.0×10^{-3} N/m^2·s. The viscoelastic properties of the vessel walls were neglected and a rigid wall with a no-slip condition was assumed. Zero surface pressure was applied for the outlet boundaries.

The width of the time step for the calculation was adjusted by the solver to control the Courant number to ≤1. To confirm numerical stability, calculations were performed for 5 cardiac cycles, and the results from the 5th cycle were used for analysis.

Data Analysis

The area of blister formation on the aneurysm wall was determined precisely by overlaying the 3D surfaces before and after the blister formation using Avizo 5 (Mercury Computer and Systems, Inc., Chelmsford, Massachusetts). Coregistration of the 3D surfaces was performed in a semiautomatic fashion according to the normalized mutual information-based algorithm (Figure 1).

All instantaneous velocity fields calculated during 1 cardiac cycle were averaged to create time-averaged velocity fields for each case and the streamlines and the spatial distributions of shear magnitude were visualized using postprocessing software equipped with SC/Tetra. Results were analyzed with particular interest to the area of eventual blister formation. Shear magnitude of 1 to 7 N/m^2 [Pa] was considered as physiological in this study.[9]

RESULTS

Results of the fluid dynamic simulations are summarized in the Table.

The shear magnitude of the aneurysm region was within or lower than the physiological level (1-7 Pa) except for case 1, in which a small area with high shear magnitude >7 Pa was observed at the neck of the aneurysm. The shear magnitude of the whole aneurysm region was low (mean ± standard deviation, 0.97 ± 0.39 Pa) in all 3 cases when compared with the shear magnitude of the parent artery (2.75 ± 0.92 Pa). The shear magnitude dropped precipitately to the subphysiological level (ie, below 1 Pa) near the border of the blister-forming area, and the spatially averaged shear magnitude of the blister-forming area was extremely low (0.48 ± 0.12 Pa).

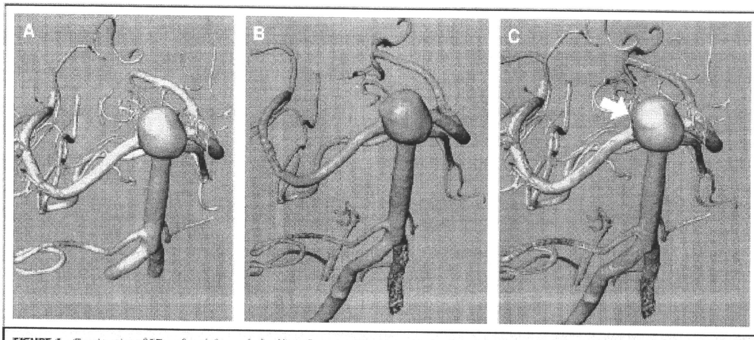

FIGURE 1. *Coregistration of 3D surfaces before and after blister formation. Three-dimensional surfaces before (A) and after (B) blister formation were coregistered in a semiautomatic fashion using Avizo 5 based on the normalized mutual information-based algorithm (C). White arrow indicates the location of blister formation.*

Case 1 (Figure 2)

An unruptured left middle cerebral artery (MCA) aneurysm (size 3.8 mm) in a 58-year-old female enlarged 15 months after initial 3DRA. Magnetic resonance angiography was obtained every 5 months, and no changes in size or shape were documented until the last examination. Repeat 3DRA showed aneurysm enlargement to 5.7 mm. Deformation was noted only in the upper portion of the aneurysm. The bloodstream of the parent artery did not impinge directly against the area of subsequent blister formation.

The spatially averaged shear magnitude of the blister-forming area was extremely low (0.61 Pa). The shear magnitude was moderately elevated in the area adjacent to the blister formation, and it dropped precipitately to subphysiological level (<1 Pa) near the border of the blister-forming area.

Case 2 (Figure 3)

A 49-year-old female with 2 unruptured aneurysms at the AComA (6.6 mm) and the left MCA (10.3 mm) developed subarachnoid hemorrhage 2 months after initial 3DRA. Repeated 3DRA after bleeding revealed newly formed blisters in the AComA aneurysm, which was confirmed as the culprit lesion during surgical clipping of both aneurysms. This AComA aneurysm was supplied by the left anterior cerebral artery.

Blood inflow from the parent artery was directed against the right lateral wall of the aneurysm, resulting in moderately elevated shear magnitude within physiological levels (~2 Pa), and the shear magnitude decreased to a subphysiological level (<1 Pa) near the border of the blister-forming area. The region of subsequent blister formation was located at the top of the aneurysm, where the shear magnitude was extremely low (0.40 Pa).

Case 3 (Figure 4)

A 59-year-old male with an unruptured basilar-tip aneurysm (size, 9.7 mm) developed a subarachnoid hemorrhage 1 month after initial catheter angiography and 3DRA. At repeat catheter angiography, no other aneurysms were documented, and 3DRA after bleeding showed a small, newly formed blister on the right posterolateral aspect of the aneurysm. Thus, this aneurysm was presumed to be the culprit lesion.

The bloodstream from the basilar artery entered into the aneurysm from the right side, creating an area of shear magnitude of approximately 3 Pa. The spatially averaged shear magnitude of the blister-forming area was extremely low (0.42 Pa).

DISCUSSION

In the present study, computational fluid dynamic simulations were used to characterize 3 aneurysms that enlarged or ruptured with blister formation during the observation periods. The shear magnitude dropped precipitately to subphysiological levels near the border of the blister-forming area, and blister formation occurred in the area with low shear magnitude.

Intuitively, high shear magnitude would be expected to promote the enlargement and rupture of cerebral aneurysms, because that promotes the formation of cerebral aneurysms. However, the shear magnitude of the area of subsequent blister formation was low in the subphysiological level in this study. This could be explained by the role of low shear magnitude in the endothelial functions and in the vascular disease processes. Prolonged nonphysiological shear conditions, including either excessively high or excessively low shear magnitude, may trigger vascular disease processes.[9,10] High shear magnitude near the vessel branch points