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

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11. 文献

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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

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[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

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[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

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[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

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[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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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

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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。

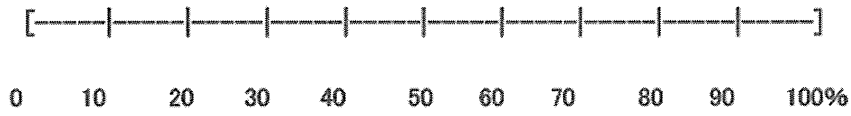
1 大いにそう思う　2 そう思う　3 どちらかというとそう思う
4 どちらかというとそう思わない　5 そう思わない　6 まったくそう思わない

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）**



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

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		

Title: Statin use and risk of cerebral aneurysm rupture: a hospital-based case-control study in Japan

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Cover Title: statin use and cerebral aneurysm rupture

Total number of tables: 3 tables

Key words: statin, cerebral aneurysm, subarachnoid hemorrhage, case-control study

Subject Code: [50] Cerebral Aneurysm, AVM, & Subarachnoid hemorrhage

Word count of manuscripts: 3535 words.

Abstract

Background and Purpose

Recent reports have showed that some statins have protective effects in experimental cerebral aneurysm models. We conducted a case-control study to investigate an association between statin use and the rupture risk of cerebral aneurysm in Japanese population.

Methods

This was a multi-hospital case-control study; cases and controls were collected from 15 hospitals in Japan. Cases consisted of patients with aneurysmal subarachnoid hemorrhage hospitalized from April, 2009 to March, 2011. Controls were selected from patients who had newly diagnosed unruptured saccular aneurysms from April, 2006 to March, 2011. The primary exposure of interest was statin use. Multivariable logistic regression was used to assess the relationship between stain use and the rupture risk of cerebral aneurysm.

Results

A total of 117 cases and 304 controls were included in the analyses. Statin was used in 9.4% of cases and 26.0% of controls. The use of any statin was associated with a significantly lower risk of cerebral aneurysm rupture after adjustment of potential confounders (adjusted odds ratio: 0.30, 95% confidence interval: 0.14-0.66). The association was similar in each stratum of total cholesterol level.

Conclusions

This observation from a hospital-based case-control study in Japan suggested that statin use reduces the risk of rupture of unruptured cerebral aneurysms.

Introduction

With the prevalent use of non-invasive neuroimaging techniques and spread of medical checkup of the brain, many incidental cerebral aneurysms are detected in the clinical practice, and the overall prevalence of cerebral aneurysms is estimated as 3.2% in a population without comorbidity with a mean age of 50 years.[1] Once incidental aneurysms are detected, careful observation and intervention should be continued to prevent their progression and rupture. Subarachnoid hemorrhage (SAH) is a serious disease that has high morbidity and mortality rate, and average onset of SAH is younger than that of other stroke subtypes,[2,3] which causes a greater productivity loss in the society. Therefore, SAH prevention has an important role from the public health perspective. Particularly in Japan and Finland, the risk of rupture from cerebral aneurysms is estimated to be higher than other countries.[4] Surgical clipping or endovascular treatment is performed to prevent SAH but there are constant morbidity and mortality.[5] To date, medical treatments to prevent a rupture of cerebral aneurysms are not available and non-surgical procedure, such as pharmacological treatments, are expected in this area. Several reports have showed that some statins (3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) have protective effects in experimental cerebral aneurysm models.[6-8] However, it remains uncertain whether statins are beneficial for the prevention of SAH in people with unruptured cerebral aneurysms.

We conducted a multi-hospital case-control study in Japan to investigate an association between statin use and the rupture risk of cerebral aneurysms. Results are reported here.

Participants and Methods

Case and control selection

Study participants were recruited from 15 hospitals in Japan which were located in Shiga (8 hospitals), Kyoto (5 hospitals), and Tokyo (2 hospitals). Cases were the patients who were aged 20 and over with aneurysmal SAH hospitalized from April 1, 2009 to March 31, 2011. SAH was diagnosed by aneurysmal bleeding pattern, with the additional condition that the presence of one or more saccular aneurysms was confirmed by diagnostic imaging in the hospital. We excluded SAH patients caused by trauma, dissecting aneurysms, infected aneurysms, autoimmune diseases and familial diseases. Controls were consecutively selected from the patients who were aged 20 and over with newly diagnosed unruptured saccular aneurysms from April 1, 2006 to March 31, 2011. Patients who had the past history of aneurysmal SAH were also excluded from cases (5 cases [11.5%] and 9 controls [13.5%]), because unruptured aneurysms in patients with a history of subarachnoid hemorrhage have higher rupture rate rather than those in patients without history of subarachnoid hemorrhage.

Data Collection

Demographic characteristics (age, sex, height, weight), information on cerebral aneurysms (aneurysm location, aneurysm diameter, bleb), past medical history (hypertension, diabetes mellitus, hyperlipidemia, heart disease, previous stroke), family history of SAH, and behavioral factors (smoking and alcohol consumption) were collected from medical record in each hospital. The smoking status was categorized into three (never, past, and current) and the drinking status was categorized into three (never, past, and current). Prescription information on statin use and other drugs (antihypertensive drugs, aspirin or other antiplatelet drugs, vitamin K antagonists, nonsteroidal anti-inflammatory drugs, steroids, and other lipid-lowering drugs, including fibrate, bile-acid binding resins, niacin, ethyl icosapentate)

were collected from doctors in each hospital and/or supplemented through medical record review.

This study was approved by the ethics committee of Shiga University of Medical Science(20-96). All participants gave written informed consent, including proxy respondents for case subjects who were severely ill, unconscious, or dead, in accordance with criteria established by the local ethics committees at each participating center.

From April, 2009 to March, 2011, 122 cases and 313 controls were collected from 15 hospitals.

Statistical Analysis

The relationship between stain use and rupture risk of cerebral aneurysms were examined by logistic regression and chi-square test. Multivariable logistic regression was used to calculate odds ratios adjusted for sex, age, hypertension, serum total cholesterol, smoking and alcohol consumption. Statistical significance was set in 0.05 and all statistical analysis was performed by SPSS 19.0 (IBM, Chicago, IL).

Results

A total of 117 cases and 304 controls were included in the analyses. Table 1 shows characteristics of the study participants. In the case group, age tended to be younger ($p=0.07$) and the aneurysm size was larger ($p<0.01$) than those of control group. Significant differences between cases and controls were found in serum total cholesterol ($p=0.02$), triglyceride ($p=0.01$), current smoking ($p<0.01$), use of statin ($p<0.01$) and antihypertensive drugs ($p<0.01$). Statin was used in 9.4% of cases and 26.0% of controls in any quantity by at least one prescription. No significant difference was observed in aspirin use ($p=0.39$) and use of other lipid-lowering drugs ($p=0.79$).

Table 2 shows multivariable adjusted odds ratios of aneurysm rupture. The model includes 6 other potential confounders in addition to statin use. Use of any statin was associated with an independently and significantly lower risk of rupture (adjusted odds ratio: 0.30, 95% CI: 0.14-0.66). Even if we used low-density lipoprotein cholesterol as a potential confounder instead of serum total cholesterol, the similar result was obtained (adjusted odds ratio: 0.30, 95% CI: 0.12-0.65). Higher serum total cholesterol was related to a significantly lower risk of rupture, independently from other confounders including statin use.

Table 3 shows the results of their relationships stratified by serum total cholesterol level. Levels of serum total cholesterol were stratified into three categories: less than 130mg/dl, 130 mg/dl to 219 mg/dl, and 220 mg/dl or greater. Of these categories, statin use was significantly associated with a lower risk of rupture in participants with 130 to 219 mg/dl (adjusted odds ratio: 0.20, 95% CI:0.07-0.56) and those with 220mg/dl or greater (adjusted odds ratio: 0.32, 95% CI: 0.04-2.28).

Discussion

To the best of our knowledge, this is the first case-control study that has examined the relationship between statin use and the risk of cerebral aneurysm rupture. Our results showed that ever-use of any statin was associated with a 70% decrease in rupture risk in unruptured aneurysm patients. This suggests that statin played an important role in reducing the risk of cerebral aneurysm rupture.

In the study, serum total cholesterol was significantly higher in the control group than those of case group, and there is a possibility that higher cholesterol levels are associated

with decreased rupture risk. We conducted a stratified analysis by serum total cholesterol level to evaluate whether serum total cholesterol itself has any influence on cerebral aneurysm rupture. We observed that statin use was associated with a decreased rupture risk regardless of serum cholesterol level in participants with 130 to 219 mg/dl and 220mg/dl or more. We cannot assess in participants with less than130mg/dl because few patients with low cholesterol levels were included in this study.

Statins are frequently prescribed in clinical practice to lower serum cholesterol for the prevention of stroke and cardiovascular diseases. In addition to their cholesterol-lowering effect, statins have an anti-inflammatory effect on vascular walls known as a pleiotropic effect.[9] Several reports have showed that some statins are effective in experimental cerebral aneurysm models. Aoki et al. reported that the administration of simvastatin and pitavastatin reduced the incidence of cerebral aneurysms in rats.[6,7]

On the contrary, Tada et al showed that pravastatin and simvastatin induced the growth of cerebral aneurysms in estrogen-deficient rats.[10] They also reported the risk of rupture increased in high-dose pravastatin. The differences in the results of experimental aneurysmal models may depend on the differences in the models and doses used. Recently, Marbacher S et al reported no significant relationship between statin use and incidence of cerebral aneurysms.[11] They conducted a single-center case-control study, and found no overall association between statin use and incidence of cerebral aneurysm formation even when

dichotomized into hydrophilic and lipophilic user, or between short (≤12-month) and long (≥36-month) duration of intake, although hypertension and smoking significantly increased the risk of cerebral aneurysm development. However, they did not examine the association between statin use and cerebral aneurysm rupture risk.

Recently, it has been reported that statin use prevents clinical worsening in patients with abdominal aortic aneurysms (AAAs), and the administration of statins in patients with small AAAs is recommended.[12] Statins also have been the focus of controversy in relation to clinical practice regarding cerebral hemorrhage. In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, there was a 16% reduction in stroke outcomes favoring atorvastatin therapy.[13] However, in a post hoc analysis, there was an excess risk of hemorrhagic stroke (hazard ratio, 1.66) associated with atorvastatin administration.[14] A recent systematic review of cohort studies suggested no association between statin administration and intracerebral hemorrhage.[15] There has been no paper which shows statin use may influence cerebral aneurysm rupture.

Unlike the arteriosclerosis or the aortic aneurysm, hyperlipidemia is not a risk factor for rupture of cerebral aneurysms. Several reports have shown that hyperlipidemia appears to reduce the risk of subarachnoid hemorrhage.[16,17] Our study also showed that higher cholesterol levels are protective against cerebral aneurysm rupture, and that statins appears to be protective against cerebral aneurysm rupture in higher and normal cholesterol level groups,

although the effect of statins in lower cholesterol group is unknown. It is not proved whether protective effects shown by this study are based on the action of cholesterol-lowering effect or pleiotrophic effect. Moreover, proper doses of statins to prevent cerebral aneurysm rupture in each level of cholesterol are not determined yet. We must be careful when statin treatment is applied in patients with cerebral aneurysms considering the possible risk of cerebral hemorrhage, and further studies are mandatory before determining mechanisms of protective effects of statins on cerebral aneurysm and proper doses of statins to prevent cerebral aneurysm rupture.

There are several limitations of this study. First, as usually occurred in case–control studies, our results may be influenced by selection bias and recall bias. To minimized selection bias, both cases and controls were obtained from many hospitals throughout Japan. We also conducted multivariable logistic regression analyses to exclude the effects of several confounding factors. As a result, two factors, statin use and smoking status had significant effects in risk reduction of SAH. Since smoking status has shown to influence the occurrence of SAH,[4] the protective effect of statin use seems to be plausible. Secondly, we did not analyze serum lipids before and after statin administration to verify the effects of statins. In this case-control study, total serum cholesterol measurement was not available before statin administration, and we could not directly analyze the relationship between cholesterol-lowering effects of statin use and the ruptured of cerebral aneurysm. Since

pleiotrophic effects of statins without lowering serum cholesterol are supposed to modify inflammatory process, [9] the values of serum cholesterol may not exert as significant factors to reduce the risk of SAH. In fact, regardless of serum cholesterol levels, statin use seems to be protective in the occurrence of rupture in this study. Thirdly, there is a possibility that patients in case group might not consult a medical institution because of no medical check or no chance of statin use compared with patients in control group who might be more interested in their health. Participants in the control group could take other drugs such as anti-hypertensive drugs, anti-inflammatory drugs, other lipid-lowerig drugs more frequently than the case group but there were no significant differeces between groups except statins. Interestingly, a recent paper showed that frequent aspirin use might have a protective effect for risk of intracranial aneurysm rupture in a case control study using a prospective untreated cohort of the International Study of Unruptured Intracranial Aneurysms .[18] The differences in patients' background, dosage of aspirin, study designs may cause the discrepancy between this study and ours, and further clinical studies are needed to prove the protective effects of medical treatments for cerebral aneurysms.

Conclusions

We showed in this paper for the first time the preventive effects of statin use on rupture of cerebral aneurysms. However, we did not prove prospectively direct effects of statin use on

patients with cerebral aneurysms, and it remains uncertain whether statins are beneficial for the prevention of SAH in human population, and whether there are any differences in the effect of statin use by the kinds and the dosage of statins.

Further and larger studies, particularly prospective randomized trial studies, are necessary to confirm our findings and safety of statins in SAH prevention and treatment of cerebral aneurysms.

Acknowledgments

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Disclosures

None.

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