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Characteristics of Unruptured Compared to Ruptured Intracranial Aneurysms: A Multicenter Case–Control Study

BACKGROUND: Only a minority of intracranial aneurysms rupture to cause subarachnoid hemorrhage.
OBJECTIVE: To test the hypothesis that unruptured aneurysms have different characteristics and risk factor profiles compared to ruptured aneurysms.
METHODS: We recruited patients with unruptured aneurysms or aneurysmal subarachnoid hemorrhages at 22 UK hospitals between 2011 and 2014. Demographic, clinical, and imaging data were collected using standardized case report forms. We compared risk factors using multivariable logistic regression.
RESULTS: A total of 2334 patients (1729 with aneurysmal subarachnoid hemorrhage, 605 with unruptured aneurysms) were included (mean age 54.22 yr). In multivariable analyses, the following variables were independently associated with rupture status: black ethnicity (odds ratio [OR] 2.42; 95% confidence interval [CI] 1.29-4.56, compared to white) and aneurysm location (anterior cerebral artery/anterior communicating artery [OR 3.21; 95% CI 2.34-4.40], posterior communicating artery [OR 3.92; 95% CI 2.67-5.74], or posterior circulation [OR 3.12; 95% CI 2.08-4.70], compared to middle cerebral artery). The following variables were inversely associated with rupture status: antihypertensive medication (OR 0.65; 95% CI 0.49-0.84), hypercholesterolemia (0.64 OR; 95% CI 0.48-0.85), aspirin use (OR 0.28; 95% CI 0.20-0.40), internal carotid artery location (OR 0.53; 95% CI 0.38-0.75), and aneurysm size (per mm increase; OR 0.76; 95% CI 0.69-0.84).
CONCLUSION: We show substantial differences in patient and aneurysm characteristics between ruptured and unruptured aneurysms. These findings support the hypothesis that different pathological mechanisms are involved in the formation of ruptured aneurysms and incidentally detected unruptured aneurysms. The potential protective effect of aspirin might justify randomized prevention trials in patients with unruptured aneurysms.

KEY WORDS: Characteristics, Predisposition to rupture, Risk factors, Subarachnoid hemorrhage, Unruptured intracranial aneurysms

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About 3% of the population have an unruptured intracranial aneurysm[1] but only a minority rupture to cause a subarachnoid hemorrhage (SAH); the overall risk of SAH for unruptured intracranial aneurysms is about 1% per year.[2] SAH causes 5% of all strokes,[3] yet, with young age of onset and approximately 50% mortality, it substantially reduces productive life-years[4-6] despite improvements in risk stratification, imaging, surgical, and intensive care treatment. Up to 76% of patients who survive have permanent cognitive deficits, and only 6% to 17% of survivors return to employment.[7] Hence, predicting (and reducing) the risk of rupture of an intracranial aneurysm is an important clinical and socioeconomic need.[8]

ABBREVIATIONS: CI, confidence interval; **GOSH,** Genetic and Observational Subarachnoid Haemorrhage; **ISUIA,** International Study of Unruptured Intracranial Aneurysms; **OR,** odds ratio; **SAH,** subarachnoid hemorrhage; **SD,** standard deviation

Previous studies assumed common causal mechanisms for ruptured and unruptured

aneurysms, but it is also possible that their underlying risk factors and pathophysiological mechanisms are different. For example, several studies report that ruptured aneurysms causing SAH are smaller than unruptured aneurysms, suggesting that they might form rapidly and quickly rupture, potentially due to different underlying mechanisms.[9-14]

Although many potential risk factors are associated with intracranial aneurysms (eg, aneurysm location, aneurysm size, smoking, number of aneurysms, age, female sex, hypertension, hypercholesterolemia, previous history of SAH, heart disease, and aspirin use[2,8,15-28]), most show inconsistent results,[29,30] which might, in part, relate to rupture status. We therefore tested the hypothesis that incidentally detected unruptured aneurysms have different characteristics and risk factor profiles compared to aneurysms that cause SAH.

METHODS

Patients

We collected data from patients with aneurysmal SAH or unruptured aneurysm without previous SAH enrolled in the Genetic and Observational Subarachnoid Haemorrhage (GOSH) study (designed to examine the genetic and clinical characteristics of patients with ruptured and unruptured aneurysms), which recruited at 22 neurosurgical centers in the UK between 2011 and 2014. Written informed consent was obtained from participants, or from a representative in case of lack of capacity. We excluded patients with perimesencephalic SAH (63 patients; defined by the characteristic distribution of blood [ie, mainly or only in the cisterns around the midbrain] and absence of an identified intracranial aneurysm by the local principle investigator)[31-33] and SAH due to trauma or mycotic aneurysms. Recruitment was as inpatient or from outpatient neurovascular clinics following either new diagnosis or previous diagnosis as an inpatient. Standardized case report forms were completed by trained stroke research practitioners. Medical history was obtained from patient self-reporting and/or available medical records. Hypertension, hypercholesterolemia, and diabetes mellitus were defined as present if the patient or medical records indicated hypertension, hypercholesterolemia, or hyperglycemia for which either drug treatment, lifestyle, or other advice had been provided. We defined antihypertensive drug use, statin use, and aspirin use by patient self-reporting or available documentation on regular intake at the time of either admission with aneurysmal SAH or of being diagnosed with an unruptured aneurysm. Recreational drug use was assessed for cocaine, cannabis, amphetamine, and opiates by patient self-reporting or from relatives. Smoking and alcohol use were defined as ongoing use. Family history of aneurysmal SAH and intracranial aneurysm was defined as presence of at least 1 relative with the relevant disorder. Internal carotid artery location was considered as an aneurysm in the cavernous segment of the internal carotid artery and onwards. The study was approved by a Research Ethics committee.

Statistical Analysis

Demographic, clinical, and radiological data were first assessed in univariable analysis comparing patients with aneurysmal SAH to those with unruptured aneurysm (Table 1). Variables for multivariable analysis were chosen based on univariable analysis, as well as previous studies and biological plausibility. We conducted a multivariable backward stepwise logistic regression analysis to identify factors independently associated with aneurysmal SAH. We excluded family history of SAH or unruptured aneurysm and previous history of stroke from the multivariable analysis, due to potential selection bias in the unruptured aneurysm group.[16]. A sensitivity analysis was conducted including these variables. As a further sensitivity analysis, we used multiple imputation for missing data values. The level of statistical significance was set at 5% (P-value = .05). Statistical analysis was performed using STATA 13 (2011, StataCorp, College Station, Texas).

RESULTS

Baseline characteristics are summarized in Table 1. We included 2334 patients: 1729 with ruptured intracranial aneurysms (1215 females [70.3%], 514 males [29.7%], mean age 53.24, 12.70 standard deviation [SD]) and 605 patients with unruptured aneurysms (425 females [70.25%], 180 males [29.75%] mean age 57.03, 12.17 SD).

Associations of Potential Risk Factors With Incidental Intracranial Aneurysms and Aneurysmal SAH

In univariable analysis, factors associated with aneurysmal SAH as opposed to incidentally-detected unruptured aneurysms were as follows: hypertension not treated (odds ratio [OR] 2.54; 1.65-3.93 95% confidence interval [CI]; $P < .001$), ethnicity (black ethnicity [compared to the baseline group (white ethnicity)], OR 2.31; 1.37-3.90 95% CI; $P = .003$), smoking (OR 1.31; 1.09-1.59 95% CI; $P = .005$), recreational drug use (OR 1.73; 1.09-2.90 95% CI; $P = .02$), and aneurysm location (anterior cerebral artery and anterior communicating artery, posterior communicating artery, and posterior circulation [compared to aneurysms of the middle cerebral artery] with location in the anterior cerebral artery or anterior communicating artery having the largest impact [OR 3.50; 2.64-4.64 95% CI]; Table 1). Factors that were inversely associated with aneurysmal SAH (ie, which were apparently protective) were as follows: older age at diagnosis (as a continuous variable OR 0.98; 0.97-0.98 95% CI; $P < .001$; as a categorical variable by every 10-yr increase of age the OR of aneurysm rupture status was 0.21; 0.14-0.26 95% CI), hypertension (OR 0.53; 0.44-0.64 95% CI; $P < .001$), antihypertensive medication use (OR 0.45; 0.37-0.54 95% CI; $P < .001$), hypercholesterolemia (OR 0.45; 0.37-0.55 95% CI; $P < .001$), statin medication use (OR 0.40; 0.33-0.50 95% CI; $P < .001$), diabetes mellitus (OR 0.60; 0.40-0.90 95% CI; $P = .013$), previous stroke (OR 0.18; 0.12-0.26 95% CI; $P < .001$), angina (OR 0.45; 0.27-0.77 95% CI; $P = .002$), heart disease (OR 0.53; 0.35-0.81 95% CI; $P = .003$), use of aspirin (OR 0.22; 0.17-0.28 95% CI; $P < .001$), positive family history of intracranial aneurysm or SAH (OR 0.63; 0.49-0.80 95% CI; $P < .001$ [positive family history of aneurysmal SAH separately (OR 0.79; 0.69-0.90 05% CI; $P = .001$), positive family history of unruptured intracranial aneurysm separately (OR 0.66; 0.54-0.81 95% CI; $P < .001$]), location of aneurysm in the internal carotid artery (OR 0.47; 95% CI 0.35-0.62), and aneurysm size

TABLE 1. Characteristics of the Cohort and Results of Univariable Analysis

Variable	Ruptured aneurysm	Unruptured aneurysm	OR; 95% CI	*P* value
Age, (mean) yr	53.2 (12.7 SD)	57.0 (12.2 SD)	0.98; 0.97-0.98	<.001
Gender			1.0; 0.82-1.22	.99
Male	514 (29.7%)	180 (29.8%)		
Female	1215 (70.3%)	425 (70.3%)		
Ethnicity				.002
White	1484 (87.91)	551 (93.39%)		
Mixed	26 (1.54%)	5 (0.85%)	1.93; 0.74-5.05	
Asian	72 (4.27%)	17 (2.88%)	1.57; 0.92-2.69	
Black	106 (6.28%)	17 (2.88%)	2.32; 1.37-3.90	
Family history				
Positive family history SAH/UIA	213 (12.3%)	111 (18.4%)	0.63; 0.49-0.80	<.001
Positive family history of SAH	191 (11.1%)	98 (16.2%)	0.79; 0.69-0.90	.001
Positive family history of UIA	25 (1.5%)	19 (3.1%)	0.66; 0.54-0.81	<.001
Smoker	765 (44.3%)	228 (37.7%)	1.31; 1.09-1.59	.005
Drinker	1168 (67.6%)	392 (64.8%)	1.13; 0.93-1.37	.215
Recreational drug use	99 (5.7%)	20 (3.3%)	1.78; 1.09-2.90	.02
Medical history				
Hypertension	542 (31.4%)	281 (46.5%)	0.53; 0.44-0.64	<.001
Hypertension not treated	123 (80.9%)	29 (19.1%)	2.54; 1.65-3.93	<.001
Antihypertensive medication	425 (24.6%)	255 (42.2%)	0.45; 0.37-0.54	<.001
Hypercholesterolemia	350 (20.2%)	218 (36.0%)	0.45; 0.37-0.55	<.001
Statin medication	273 (15.8%)	192 (31.7%)	0.40; 0.33-0.50	<.001
Diabetes mellitus	69 (4.0%)	39 (6.5%)	0.60; 0.40-0.90	.013
Previous stroke	40 (2.3%)	72 (11.9%)	0.18; 0.12-0.26	<.001
Previous ICH	9 (0.5%)	4 (0.7%)	0.79; 0.24-2.56	.75
History of myocardial infarction	41 (2.4%)	19 (3.1%)	0.75; 0.43-1.30	.304
Coronary artery disease (angina)	33 (1.9%)	25 (4.13%)	0.45; 0.27-0.77	.002
Cardiac disease (myocardial infarction and angina)	58 (3.4%)	37 (6.1%)	0.53; 0.35-0.81	.003
Peripheral vascular disease	25 (1.5%)	15 (2.5%)	0.58; 0.30-1.10	.09
Aspirin	120 (6.94%)	154 (25.45%)	0.22; 0.17-0.28	<.001
Aneurysm location				<.001
MCA	341 (21.04%)	194 (34.34%)		
ICA	135 (8.33%)	164 (29.03%)	0.47; 0.35-0.62	
ACA/Acom	572 (35.29%)	93 (16.46%)	3.50; 2.64-4.64	
Pcom	359 (22.15%)	63 (11.15%)	3.24; 2.35-4.47	
Posterior circulation	214 (13.20%)	51 (9.03%)	2.39; 1.68-3.40	
Aneurysm size (mean), mm	6.6 (4.16 SD)	9.0 (6.3 SD)	0.91; 0.90-0.93	<.001
Multiple aneurysms	447 (25.9%)	161 (26.6%)	0.96; 0.78-1.19	.714

SD = standard deviation; ICH = intracerebral hemorrhage; MCA = middle cerebral artery; ICA = internal carotid artery; ACA = anterior cerebral artery; Acom = anterior communicating artery; Pcom = posterior communicating artery; SAH = subarachnoid hemorrhage; UIA = unruptured intracranial aneurysm.
For aneurysm location, there were 40 missing values in the ruptured and 108 in the unruptured group.
For aneurysm size, there were 345 missing values in the ruptured and 61 in the unruptured group.

(OR 0.91; 0.90-0.93 95% CI; $P < .001$; 406 missing values). For the univariable analysis, we also analyzed aneurysm size as a categorical variable dividing it into 5 mm step categories, which also showed that larger aneurysms are independently associated with a decreased risk of aneurysmal SAH (coefficient –0.089; –0.11-[–0.07] 95% CI; $P < .001$).

Most aneurysms were smaller than 7.0 mm. Unruptured aneurysms tended to be larger (mean aneurysm size 9.0 mm, SD 6.3 mm; median 7.0 mm) compared to ruptured aneurysms (mean aneurysm size 6.6 mm, 4.2 mm SD; median 5.7 mm). The mean duration of antihypertensive treatment was 8.12 yr (7.81 SD; median 5); however, this was not associated with aneurysmal SAH in the univariable analysis (OR 1.00; 0.98-1.02 95% CI; $P = .977$).

Of 119 patients with recreational drug use, 93 reported consumption of cannabis, 30 cocaine, 17 ecstasy, and 5 opiates. Forty-one patients had consumed multiple drugs.

In the multivariable regression analysis, following factors were independently associated with aneurysmal SAH in the final adjusted model (Table 2): black ethnicity compared to white ethnicity (OR 2.42; 1.29-4.56 95% CI; $P = .013$ overall categorical variable) and aneurysm location (location in the

TABLE 2. Multivariable Analysis Model Evaluating Differences Between Unruptured and Ruptured Intracranial Aneurysms

	Odds ratio	95% CI	*P* value
Age	1.0	0.98-1.01	.365
Sex (male vs female)	0.86	0.66-1.11	.242
Ethnicity			.013
White (reference)			
Black	2.42	1.29-4.56	
Asian	2.00	0.98-4.08	
Mixed	1.26	0.45-3.53	
Smoker	1.22	0.96-1.56	.104
Use of antihypertensive medication	0.65	0.49-0.84	.001
Hypercholesterolemia	0.64	0.48-0.85	.002
Aspirin use	0.28	0.20-0.40	<.001
Aneurysm location			
MCA (reference)			
ICA	0.53	0.38-0.75	
ACA/Acom	3.21	2.34-4.40	
Pcom	3.92	2.67-5.74	
Posterior circulation	3.12	2.08-4.70	
Aneurysm size	0.76	0.69-0.84	<.001

MCA = middle cerebral artery; ICA = internal carotid artery; ACA = anterior cerebral artery; Acom = anterior communicating artery; Pcom = posterior communicating artery.

TABLE 3. Multivariable Analysis Model, Sensitivity Analysis Including Positive Family History of SAH or Unruptured Intracranial Aneurysm and Previous History of Stroke

	Odds ratio	95% CI	*P* value
Age	1.0	0.98-1.01	.392
Sex	0.83	0.64-1.08	.171
Ethnicity			.012
White (reference)			
Black	2.41	1.27-4.56	
Asian	2.13	1.02-4.46	
Mixed	1.20	0.43-3.38	
Antihypertensive medication	0.69	0.52-0.90	.007
Hypercholesterolemia	0.69	0.52-0.92	.011
Aspirin use	0.32	0.22-0.45	<.001
Aneurysm location			<.001
MCA (reference)			
ICA	0.533	0.38-0.75	
ACA/Acom	3.23	2.34-4.44	
Pcom	4.07	2.75-6.01	
Posterior circulation	3.12	2.06-4.72	
Aneurysm size	0.76	0.69-0.84	<.001
Positive family history	0.61	0.44-0.85	<.001
Previous stroke	0.24	0.14-0.41	<.001

MCA = middle cerebral artery; ICA = internal carotid artery; ACA = anterior cerebral artery; Acom = anterior communicating artery; Pcom = posterior communicating artery.

posterior communicating artery had the largest influence [OR 3.92; 2.67-5.74 95% CI]; $P < .001$ overall categorical variable; internal carotid artery location was inversely associated with aneurysmal SAH status). Independent factors inversely associated with aneurysmal SAH status were as follows: treatment with antihypertensive medication (OR 0.65; 0.49-0.84 95% CI; $P = .001$), hypercholesterolemia (OR 0.64; 0.48-0.85 95% CI; $P = .002$), aspirin use (OR 0.28; 0.20-0.40 95% CI; $P < .001$), increasing aneurysm size (OR 0.76, 0.69-0.84 95% CI; $P < .001$), and internal carotid artery location (OR 0.53; 0.38-0.75 95% CI).

In a sensitivity analysis including family history of aneurysm and previous history of stroke in the final model, the associations with aneurysmal SAH did not significantly change; Asian ethnicity became a significant predictor for aneurysmal SAH (OR 2.13; 1.02-4.46 95% CI; $P = .012$, overall categorical variable), and the model's prediction increased (likelihood ratio test $P < .001$, Pseudo R2 increasing from 0.18 to 0.20; Table 3). A further sensitivity analysis using multiple imputation for missing data in the variables aneurysm size (406 missing values) and aneurysm location (148 missing values) showed no change in OR (data not shown).

DISCUSSION

In this large observational study, we show patients with incidentally detected unruptured intracranial aneurysms have different patient and aneurysm characteristics and potential risk factors compared to patients with ruptured aneurysms. Certain aneurysm locations (anterior cerebral artery and anterior communication artery, posterior communicating artery, and posterior circulation) and black ethnicity were independently associated with aneurysmal SAH, compared to patients with an unruptured aneurysm. In addition, we found that location in the internal carotid artery is inversely associated with aneurysmal SAH. We also demonstrated that antihypertensive medication use, aspirin use, hypercholesterolemia, and larger aneurysm size are independently associated with a decreased risk of aneurysmal SAH compared to the population of incidental intracranial aneurysms.

In our cohort, incidentally detected unruptured aneurysms were larger compared to those with aneurysmal SAH. Our findings are consistent with other studies that show the majority of ruptured aneurysms are less than 10 mm.[12,14,34,35] Indeed, in our study the size of unruptured aneurysms was larger than that reported in a previous meta-analysis.[1] This could indicate selection bias, a limitation of any hospital-based study. However, an important strength is that we have data on unruptured aneurysm size in 544 patients (90%); in the meta-analysis, this was only available in 368 patients (25%).[1]

Also in line with our data is the International Study of Unruptured Intracranial Aneurysms (ISUIA), in which a lower risk of rupture was reported in intracranial aneurysms with a diameter of less than 10 mm; this observation that small unruptured aneurysms are at lower risk of future rupture than large

unruptured aneurysms has been convincingly shown in other large prospective studies.[20,36,37] One explanation for this apparent inconsistency is that aneurysms that rupture to cause SAH and incidentally detected unruptured aneurysms have different pathological mechanisms making them behave differently.[38] Most intracranial aneurysms are considered to form over days to weeks, at which point they either rupture or stabilize due to remodeling of the arterial wall.[10,11] Whether early rupture or stabilization occurs might be because of different underlying pathological hemodynamic and inflammatory mechanisms.[39] Indeed, differences have been described in the histology of ruptured compared to unruptured aneurysms.[9,10] Our data are consistent with this hypothesis, in which rapidly developing aneurysms that rupture are expected to be small. By contrast, the majority of stable unruptured aneurysms would be expected to have low rupture rates, even if rupture rate is higher in larger aneurysm compared to smaller aneurysms.[1,3,39,40] Nevertheless, patients whose unruptured aneurysms increase in size during follow-up are at high risk of rupture and warrant further treatment.[41,42] An alternate explanation is that our results are due to selection bias. One could hypothesize that larger ruptured aneurysms were excluded due to prehospital death if they suffered more severe hemorrhages, while smaller unruptured aneurysms were excluded as they may not have been referred to tertiary care. Therefore, only tentative conclusions can be drawn from this result and its meaning must be considered carefully. This could only be resolved in a longitudinal prospective large trial. However, a population of patients with unruptured aneurysms as in ISUIA and other studies would not suffice and it would require a healthy population with no prior diagnosis of an aneurysm. Due to the relatively low incidence of aneurysms and particularly SAH, these would be logistically challenging.

The large sample size allowed us to investigate not only risk factors but also their treatments. A previous study has found a linear relationship between increase in systemic arterial pressure and pressure in the aneurysm sac.[43] This finding supports the hypothesis that a rapid increase in blood pressure rather than a chronic increased blood pressure lead to aneurysm rupture. Patients with untreated hypertension had a higher OR for rupture. Furthermore, treatment, rather than duration of treatment, appears to be associated with a decrease in aneurysmal SAH. These findings are most consistent with a rapid benefit from antihypertensive treatment, rather than a long-term remodeling of the aneurysm wall. The potentially protective effect of treatment is consistent with the hypothesis that a sudden rise in blood pressure might trigger the rapid formation of aneurysms that are prone to rupture early. Different antihypertensive drugs with different mechanisms of action might have differing influences on aneurysm formation and rupture other than purely through blood pressure control.[44] However, we did not have data on specific antihypertensive agents, which should ideally be addressed in further prospective studies.

We found that regular aspirin use was significantly less common in patients with SAH than in patients with unruptured aneurysms even after fully adjusting for potential confounders (ischemic heart disease, peripheral vascular disease, and diabetes; OR 0.28; 95% CI 0.20-0.40; $P < .001$). This could mean that aspirin use protects against SAH in patients with unruptured aneurysms. Although it is possible that the use of aspirin results in more severe SAH, which might be excluded from our study (eg, if patients die before reaching hospital), we did not find any association between aspirin use and severity of SAH (data not shown). Thus, this seems an unlikely explanation for the higher proportion of patients taking aspirin in the unruptured aneurysm group (25.45% vs 6.94% in the aneurysmal SAH group). A recent study also showed no association of aspirin or anticoagulation with mortality or complications; on the contrary, aspirin was associated with a shorter hospital stay;[45] other studies showed a potential decrease in ischemic events after SAH and increase in asymptomatic survival.[46,47] However, further studies suggest that aspirin given preventively might increase the risk of intracerebral hemorrhage and rebleeding after SAH.[46,48,49] Furthermore, our findings are in keeping with prospective data from the ISUIA and other studies, which showed a protective effect for regular aspirin use on intracranial aneurysm rupture.[25,47] Aspirin could potentially reduce the risk of aneurysm rupture by inhibiting inflammatory mediators (eg, matrix metalloproteinases and tumor necrosis factor alpha).[50] Our findings suggest that unruptured aneurysms are not a contraindication to antiplatelet therapy for patients with a clear indication. Due to lack of definitive strong evidence, neither for a protective effect nor harmful effect, this requires further research. Indeed, our data strengthen the case for randomized trials testing the benefit of regular aspirin use on aneurysm rupture. We cannot fully explain the reason for aspirin use being higher in the unruptured aneurysm group; apart from a true biological effect, another possibility is that patients found to have an unruptured aneurysm are investigated for additional diseases that lead to aspirin prescription (eg, hypertension, hypercholesterolemia, or previous stroke).

Our study also suggests that hypercholesterolemia could have a protective effect on aneurysm rupture (OR 0.64; 95% CI 0.48-0.85; $P = .002$). Previous smaller studies found a similar relationship, but were unable to determine whether this finding might be due to statin treatment rather than the underlying hypercholesterolemia.[16,51] We were able to adjust for use of statins, and showed that hypercholesterolemia was a protective factor for aneurysmal SAH, independent of the use of statin medications. The mechanism remains unclear. We suggest that part of the effect could emerge through stabilization of the aneurysm wall and so preventing newly formed aneurysm from early rupture.

We found black ethnicity to be independently associated with aneurysmal SAH, but whether this is due to genetic or environmental factors remains uncertain. Greater risk of aneurysmal SAH in black patients compared to white patients has been described

before.[52] Another study found that patients who underwent treatment for unruptured aneurysms generally had higher socioeconomic status and were more likely to be white, female, or insured, suggesting the findings to be due to social implemented reasons rather than based on genetic differences.[53]

Our study has important strengths. We included a large sample from multiple neurosurgical centers throughout the UK. The participants with aneurysmal SAH and unruptured aneurysms were recruited from the same hospitals over the same time period using standardized inclusion criteria and report questionnaire with standardized definitions of all risk factors. Moreover, the unruptured aneurysm group is free of the disease (aneurysmal SAH). Our large sample size allowed us to undertake a multivariable analysis including many clinical and anatomical factors in our model.

Limitations

Our study also has limitations. Selection bias toward patients with unruptured intracranial aneurysms with a family history of intracranial aneurysm or aneurysmal SAH or with a previous stroke has been suggested (as these patients will be more likely to undergo brain imaging).[16] Indeed, common reasons for intracranial aneurysm screening were positive family history for aneurysmal SAH or unruptured aneurysm, or a previous history of stroke; 18.35% of the unruptured aneurysm patients had a positive family history of SAH or intracranial aneurysms compared to 12.32% with aneurysmal SAH ($P < .001$). Of the patients with unruptured aneurysms, 11.9% had a previous history of stroke compared to 2.3% of those with aneurysmal SAH ($P < .001$). Nevertheless, a sensitivity analysis controlling for these variables did not affect our findings (Table 3). As the aim of our study was not to compare "risk factors" between 2 groups with the same underlying disease but to evaluate for differing characteristics and potential risk factors in 2 different diseases, selection bias should be negligible. The study was designed to examine the different genetic and clinical characteristics of patients with ruptured and unruptured aneurysms; we are here presenting the large amount of clinical data collected to explore clinical differences between these cohorts. Another limitation arises from the fact that patients who are diagnosed with an unruptured intracranial aneurysm might not be seen by a neurologist or neurosurgeon due to their advanced age or significant comorbidities. These patients could not be included in our study.

We did not explicitly collect the information about why unruptured intracranial aneurysms were diagnosed, apart from the small symptomatic number (9 patients). The study has also potential for bias toward aneurysmal SAH survivors; patients who died before they could be recruited, or in whom no informant could provide consent, were excluded from our study. Another potential limitation of our study is the case–control design preventing any direct inferences on causality. However, an observational natural history study in a similar population of untreated intracranial aneurysms is unlikely to be either feasible or ethically acceptable; not all diagnosed unruptured aneurysms can be left untreated and be followed up, which also introduces selection bias. Although it would be highly desirable that diagnosed unruptured aneurysms result from random screening of the population, this is unlikely to happen without large-scale intracranial imaging studies, which are likely to be logistically, financially, and ethically challenging.

CONCLUSION

We found that patients with aneurysmal SAH most likely have a different risk factor profile in comparison to patients with incidentally detected unruptured aneurysms. Aneurysm location and black ethnicity are associated with aneurysmal SAH in comparison to incidentally detected unruptured aneurysms. Antihypertensive medication, aspirin use, hypercholesterolemia, aneurysm location on the internal carotid artery, and aneurysm size are associated with unruptured intracranial aneurysms compared to aneurysmal SAH. These findings support the hypothesis that risk factors for the type of aneurysm that ruptures early are different to unruptured aneurysms or to those that rupture later. The large potentially protective effect of aspirin use justifies randomized clinical trials to prevent SAH in patients with unruptured aneurysms offering an alternative treatment option in small aneurysms, where the decision for invasive treatment is difficult. This would also hopefully resolve the controversial evidence on protective or harmful effects of aspirin.

Disclosures

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UK; Dr Kari Saastamoinen, The Royal London Hospital, London, UK; Mr Umang Patel, Sheffield Teaching Hospitals NHS Trust, Sheffield, UK; Dr Enas Lawrance, Mayday Hospital, Croydon, UK; Dr Subha Vandabona, Mount Gould Hospital, Plymouth, UK; Prof David Mendelow, Newcastle University Hospital NHS Trust, Gosforth, UK; Ms Rachael Teal, Oxford Radcliffe Infirmary, Oxford, UK.

COMMENTS

From 2011 to 2014, the authors enrolled patients with unruptured and ruptured aneurysms in a multicenter study involving 22 UK hospitals. A total of 2334 patients were recruited for this case-control study aimed at identifying differences between ruptured and unruptured aneurysms. The authors report several associations which should hopefully stimulate discussion on variables that contribute to, and conversely may protect from, aneurysm rupture. Many of their observations were congruent with earlier studies of characteristic of patients with aneurysms, which provides further support of our clinical risk stratification for aneurysm rupture in patients and assists in our patient counseling.

Among the interesting findings they report, they found acetylsalicylate therapy was protective for aneurysm rupture (OR 0.22; 0.17-0.28 95% CI; $P < .001$), providing more evidence to support randomized trials looking into this variable. They also found that treatment of hypertension was protective against aneurysm rupture (OR 0.45; 0.37-0.54 95% CI; $P < .001$) irrespective of duration of treatment, which they hypothesized may mean that it is an acute, rapid increase in blood pressure that stresses an aneurysm wall into rupturing, rather than a chronically elevated blood pressure. Unfortunately, they did not have data on which antihypertensive medications patients were on, which could provide important guidance on possible pharmacologic interventions that might alter an aneurysm's natural history.

One finding inconsistent with several prior studies is that the larger aneurysms in this study were associated with a decreased risk of rupture (OR 0.91; 0.90-0.93 95% CI; $P < .001$). The majority of ruptured aneurysms in this data set were less than 10 mm. The authors provide 2 hypotheses for this finding. The first is that rapidly growing, newly formed aneurysms are more likely to burst as it is the rate of growth that constitutes an increased risk for rupture, rather than overall size. A previous study by Villablanca et al[1] found that growth of unruptured aneurysms was associated with a 12-fold higher risk of hemorrhage. The second is that selection bias accounts for this finding, as larger ruptured aneurysms may not survive long enough to be enrolled in the study. The tertiary referral center that enrolled patients in this study may never have evaluated a statistically meaningful subset of ruptured aneurysms due to death either in the field, or prior to transfer. A combination of both factors likely contributes to their findings.

This paper suffers from the flaws of any case-control study in that selection bias is inherent and unavoidable, but this does not invalidate the findings as long as the reader acknowledges the shortcomings and views the results through the proper lens.

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[1] Villablanca JP, Duckwiler GR, Jahan R, et al. Natural history of asymptomatic unruptured cerebral aneurysms evaluated at CT angiography: growth and rupture incidence and correlation with epidemiologic risk factors. *Radiology*. 2013;269:258-265.

The authors collected data from patients with aneurysmal SAH or unruptured aneurysm without previous SAH enrolled in the Genetic and Observational Subarachnoid Haemorrhage (GOSH) study. Patients were recruited from 22 neurosurgical centers in the UK between 2011–2014. This is a cross-sectional, association study comparing SAH to unruptured aneurysm patients.

Their results showed: A) aneurysms originating from anterior cerebral artery, anterior communication artery, posterior communicating artery, and posterior circulation had higher risk of rupture; B) Black ethnicity was independently associated with aneurysmal SAH, compared to patients with an unruptured aneurysm; C) Internal carotid artery aneurysms had less risk of aneurysm rupture when compared to middle cerebral artery aneurysms (used as a reference); and D) Use of antihypertensive medication and aspirin decreased the risk of aneurysm rupture significantly.

Of great surprise, larger aneurysm size was independently associated with a decreased risk of aneurysmal SAH compared to the population of incidental intracranial aneurysms. This finding is unique to this study and warrants further studies in the future to either validate or challenge it.

As for the finding of the protective effect of aspirin in decreasing risk of aneurysm rupture, this was consistent with several studies in human and murine models of cerebral aneurysms published in the literature. In these studies, cause and effect were investigated and showed that aspirin confers its protection via COX2/mPGES-1/PGE_2 pathway.[1,2]

Also these studies showed that there is a gender differential response to aspirin in decreasing risk of aneurysm rupture.[1] These studies revealed that aspirin decreased the risk of aneurysm rupture significantly more in males than in females.[1] The enzyme 15-PGDH was identified to be responsible for this effect, and when its activity was medically manipulated, the observed response was reversed.[1] As for the safety of chronic use of aspirin when a cerebral aneurysm ruptures, several studies have shown0 that daily aspirin use did not worsen neurological outcome following SAH.[3,4]

As for the fact that one study showed that short-term (<3 months) use of aspirin was associated with increased risk of aneurysmal SAH (aSAH), whereas there was no significant difference found in terms of risk of aSAH for 3 to 12 months, 1 to 3 years, and >3 years duration of use, this finding is most consistent with observational bias. The reason for that is if aspirin was truly a causal risk factor for aSAH, one should see an increased risk for all time periods, not only limited to the first 3 months.

In summary, we strongly agree with the authors that a phase 3, multi-center, double-blinded, placebo-controlled trial is warranted to delineate the potential protective effect of acetylsalicylic acid in decreasing aneurysm rupture and/or growth.

To that effect, a clinical trial called Aneurysm Rupture Reduction and Expansion Stabilization Trial (ARREST) is designed and currently being reviewed by the NIH/NINDS. The hypothesis of the trial is that daily acetylsalicylic acid (325 mg p.o.) use will result in decreased growth and rupture of small unruptured intracranial aneurysms (3–7 mm in diameter) by at least 45% over 4 years of follow-up when compared to placebo. Strict blood pressure control (systolic blood pressure < 140), smoking cessation, and control of hypercholesterolemia are background treatment for this trial.

If aspirin therapy is shown to be effective, it could offer an innovative, inexpensive, easily accessible management option for small unruptured intracranial aneurysms, and would be the first pharmaceutical treatment

shown to reduce the risk of small unruptured aneurysms rupture and/or growth.

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The authors should be congratulated for their extensive and time consuming work of collecting and analyzing their data on this important topic. As in all medical studies there are concerns that should be taken into account when the results are interpreted in practice.

High case fatality after aneurysmal subarachnoid hemorrhage (SAH) is the main reason why unruptured intracranial aneurysms (UIAs) are treated when found.[1,2] Because of the increasing use of magnetic resonance imaging (MRI), MR angiography (MRA), and CT angiography (CTA) for examining symptoms unrelated to UIAs (chronic headache, dizziness, nausea, visual disorders, etc), asymptomatic UIAs are being detected more frequently. As SAH incidence is decreasing[3,4] and discovery of UIAs is increasing, indication of UIA treatment is becoming more challenging. Today even more UIAs than ruptured aneurysms are treated in large neurosurgical centers.

There are only few prospective UIA studies on the risk and risk factors for subsequent aneurysm rupture.[5] In meta-analysis there were significant differences and heterogeneity between study populations for patient selection. Only aneurysm size and locations were convergent risk factors for aneurysm rupture between studies. Age, sex, smoking, hypertension, geographical region, aneurysm multiplicity, and prior SAH as risk factors differed between studies. One must remember that in most prospective studies higher risk UIAs (large or growing UIAs as well as UIAs in younger age groups and smokers) were treated more likely without any follow-up than other ones.[5] In meta-analysis, there was only 1 true natural history follow-up study of UIAs which were diagnosed before the era when UIAs were not treated.[5,6] In the International Study of Unruptured Intracranial Aneurysms (ISUIA), 58% were excluded from follow-up at baseline because higher risk UIAs were occluded and additional 32% were treated during follow-up of few years before a possible rupture.[5,7] If 71% of patients with UIAs are excluded totally or after a short-term follow-up, the remaining patients (older patients with smaller UIAs, higher prevalence of cardio- and cerebrovascular diseases, more common use of preventive antiplatelet and anticoagulant treatments, and a shorter life expectancy) are not such a subgroup whose results can be generalized to all patients with UIA. Such concern is dealt with several post hoc studies published from that cohort.

Because of uncertainty of risk and risk factors for UIA rupture several case-control studies have been published wherein patients with ruptured aneurysms have been compared to those with UIAs supposing that differences between the groups are risk factors for aneurysm rupture. These studies are always retrospective since variables of patients with ruptured aneurysms are collected after end-point event (aneurysm rupture). Recently, in this journal, we have shown that morphology measurement parameters of aneurysms measured after aneurysm rupture have no value in prediction of future rupture of diagnosed UIA.[8]

The present study consists of 2334 patients with a mean age of 54.2 years (1729 patients with aneurysmal SAH and 605 with UIAs) were recruited from 22 UK tertiary care centers within 4 years (approximately 26 patients annually per center). There were several potential factors (aneurysm location, ethnicity, smoking and recreational drug use, hypertension, and inversely patient age, hypercholesterolemia, previous stroke, diabetes mellitus, coronary heart disease, use of aspirin, antihypertensive and statin medications, and family history of aneurysms) associating with ruptured aneurysms compared to UIAs. Since this was a cross-sectional retrospective study, the differences do not necessarily mean causal relationships. In retrospective studies selection of cases is the most important source of study bias. Use of multivariable analysis or increase in sample size does not abolish study bias.

The most important difference between the results of this and previous studies is for size of aneurysms. Previous studies have shown that aneurysm size is directly associated with rupture risk,[1,5–8] while the situation suggests the opposite in this study. The mean size of UIAs in this study was 9 mm and that of ruptured ones 6.6 mm. Since the patients were diagnosed in tertiary care centers, at least 25% of SAH patients of corresponding populations were excluded because of deaths before hospital admission or in emergency rooms.[4] These excluded patients are older, have larger aneurysms, higher systolic blood pressure values, long-term hypertension, and possibly more likely space-occupying intracerebral hematomas due to middle cerebral artery aneurysm ruptures.[9] So, true sizes of ruptured aneurysm were likely underestimated. Correspondingly, UIAs were larger than in previous studies. According to a review,[10] the prevalence of UIAs in adult populations is approximately 3%, and 93% of these are <10 mm in diameter and 66% <5 mm. In prospective UIA follow-up studies, mean sizes ranged from 4 to 6 mm.[5–8] So in these patients, particularly younger persons and smaller UIAs were likely missed. Since the proportion of UIAs in this study was low compared with ruptured ones as well as proportion of cardiovascular diseases, risk factors, and medications was higher than in general populations, UIAs can better be considered side findings of investigations for these diseases than true incidental ones from otherwise generally heathy populations. Thus, it is difficult to believe that larger aneurysms have a smaller rupture risk. I partly agree with authors that UIA size is not of crucial importance for rupture risk because most ruptured aneurysms are <10 mm in diameter. For aneurysm rupture modifiable risk factors seem to be more important than the size.[11]

Inflammation of aneurysm wall as cause of rupture is also based on case-control studies where the effect of rupture event itself and post-rupture reactive changes cannot be ruled out. Similarly, the finding that aspirin has been assumed to reduce rupture risk of UIA is based on post hoc study of the ISUIA where low rupture risk UIAs after treatment selection of cases were followed (see above). Association of aspirin with lower rupture risk may be due to proxy of several other factors associating with aspirin use (Berkson's bias) and to a short follow-up of patients with vascular diseases. It may be challenging to complete a placebo-controlled randomized trial to see whether aspirin prevents aneurysm rupture since patients with elevated SAH risk unlikely want to participate in the trial. Annual rupture of low risk UIAs (<0.5%) is such

that compliance of study medicine intake for years or even decades may be low.

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