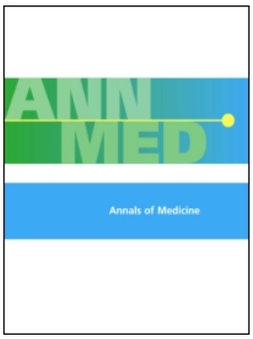

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ORIGINAL ARTICLE

Hypertension predisposes to the formation of saccular intracranial aneurysms in 467 unruptured and 1053 ruptured patients in Eastern Finland

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Objective. **Hypertension associates with subarachnoid hemorrhage from saccular intracranial aneurysm (sIA-SAH) when compared to matched controls or general population. Few series compare hypertension in unruptured sIA versus sIA-SAH, so its impact on the sIA disease remains uncertain.**

Methods. **Kuopio sIA Database (www.uef.fi/ns) contains all cases of unruptured and ruptured sIAs admitted to Kuopio University Hospital from its Eastern Finnish catchment population. We compared the age-adjusted incidence of drug-treated hypertension in 467 unruptured and 1053 ruptured sIA patients admitted to Kuopio University Hospital from 1995 to 2007, using the national registry of prescribed medicines.**

Results. **Antihypertensive medication was more frequent in the unruptured (73% versus 62%) with higher age-adjusted incidence. At sIA diagnosis, the sIA-SAH group had more often untreated hypertension (29% versus 23%). The size of unruptured sIAs increased with age at sIA diagnosis, independently of hypertension. Multiple sIAs, familial sIA, and sIA-SAH were not associated with hypertension in multivariate analysis. Results indicate that drug-treated hypertension associates with the formation of sIAs rather than their growth or rupture.**

Conclusion. **Hypertension is highly prevalent in the carriers of unruptured sIAs when compared to those with ruptured sIA. Hypertension may associate with the sIA formation, and may predispose to the rupture of sIA if untreated.**

Key words: Hypertension, intracranial aneurysm, subarachnoid hemorrhage

Key messages

- Hypertension is highly prevalent in carriers of unruptured sIAs.
- Hypertension may associate with the formation of sIA.
- Untreated hypertension may predispose to the rupture of sIA.

Introduction

About 3% of the general population develops saccular intracranial aneurysms (sIAs) during life at the forks of intracranial extracerebral arteries (1,2). Most do not rupture and are too small to cause neurological symptoms by compression. If diagnosed during life, most unruptured sIAs are incidental findings in neuroimaging for other causes or screening for familial sIAs. The course of the sIA disease involves formation (3–5), further growth (4–7), and rupture (8) of the sIA pouch. About 95% of aneurysmal subarachnoid hemorrhages are caused by the rupture of the sIA wall (sIA-SAH), a devastating form of stroke that affects the working age population (9). The annual incidence of SAH is 4–7 per 100,000 worldwide (10) but over twice as high in Finland and in Japan (10). The sIA disease is a complex trait, affected by age, female sex, smoking, hypertension, and excess drinking (11), and by genomic factors (12,13) with at least 10% of ruptured sIA-SAH patients having a family history (14,15).

Hypertension, a complex trait that also affects the arterial wall (16), is a strong risk factor for brain infarction and intracerebral hemorrhage (17). Antihypertensive medication is essential in their primary and secondary prevention (18). Hypertension is significant in the formation and growth of sIAs in animal models (19) as well as in small clinical series (3–5). Hypertension strongly associates with angiographically verified sIA-SAH when compared to matched controls or the general population (Table I) (20–25). Few series compare hypertension in unruptured sIA carriers against sIA-SAH cases or unaffected controls (20,26–28).

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Table I. Previous studies on the association of hypertension and angiographically verified saccular intracranial aneurysms since 2000.

Reference (year)	Country	Type of study	Cases/controls	Matching of controls	Mean age ± SD (y), cases/controls	Hypertension, cases/controls	Multivariate analysis	Diagnosis of hypertension[a]
aSAH versus matched controls								
Shiue et al. (2012)	Australia	Case-control, multicenter, prospective	432 aSAH/473 controls	Age, sex, city-matched community controls	56.5 ± 16.8	189 (47%)/161 (34%)	OR 1.79 (1.29–2.50); $P = 0.0007$	Medical records and interview
Inagawa (2010)	Japan	Case-control, single center, prospective	798 aSAH/798 controls	Age, sex-matched from Izumo-Hikawa district	64 ± 12	431 (54%)/241 (30%)	OR 3.19 (2.51–4.05); $P < 0.001$	Medical records
Ruiz-Sandoval et al. (2009)	Mexico	Case-control, multicenter, retrospective	231 aSAH/231 controls	Age, sex-matched community controls	52	96 (42%)/67 (29%)	OR 2.46 (1.59–3.81); $P < 0.005$	Medical records, BP on admission
Okamoto et al. (2007)	Japan	Case-control, single center, prospective	201 aSAH/402 controls	Age, sex-matched community controls	59.1	47.8%/24.8%	OR 4.6 (2.8–7.8); $P < 0.05$	Antihypertensive therapy by interview
Ohkuma et al. (2003)	Japan	Case-control, multicenter, prospective	390 aSAH/390 controls	Age, sex-matched hospital controls	58 ± 13	181 (46%)/117 (30%)	OR 2.29 (1.66–3.16); $P < 0.05$	Interview
Kubota et al. (2001)	Japan	Case-control, multicenter, prospective	127 aSAH/127 controls	Age, sex-matched hospital controls	52 ± 10	52 (40%)/26 (20%)	OR 2.35 (1.57–3.53); $P = 0.034$	Structured questionnaire
aSAH versus unruptured sIA patients								
Vlak et al. (2013)	Netherlands	Case-control, retrospective, single center	250 aSAH/206 unruptured sIAs	Age matched	54.7 ± 12.5/54.6 ± 11.6	61 (24.6%)/77 (38.1%)	n.s.	Medical records
You et al. (2008)	Korea	Case control, single center, prospective	167 aSAH/123 unruptured sIAs	Age, sex- et al. matched	53.5 ± 13.1/57.9 ± 10.1	59 (35.3%)/63 (51.2%)	OR 1.55 (0.86–2.79); $P = 0.143$	Medical records
Unruptured sIA patients versus matched controls								
Vlak et al. (2013)	Netherlands	Case-control, retrospective, single center	206 unruptured sIAs/574 controls	Age and sex-matched	54.6/54.8	77 (38.1%)/104 (19%)	OR 2.9 (1.9–4.6); $P < 0.05$	Medical records
Inagawa (2010)	Japan	Case-control, single center, prospective	266 unruptured sIAs/798 controls	Age, sex-matched from Izumo-Hikawa district	66 ± 11	154 (58%)/241 (30%)	OR 3.26 (2.39–4.46); $P < 0.001$	Medical records
Unruptured sIA patients								
UCAS Japan (2012)	Japan	Prospective, multicenter	5720 patients with 6697 unruptured sIAs		62.5 ± 10.3	2480 (43.4%)		Interview
Guresir et al. (2013)	Germany	Prospective, single center	263 patients with 384 unruptured sIAs		55 ± 12	112 (42.6%)		Interview

[a]In all cohorts, the diagnosis of hypertension was made before the diagnosis of unruptured sIA disease or the time of aSAH.
aSAH = aneurysmal subarachnoid hemorrhage; IA = intracranial aneurysm; sIA = saccular intracranial aneurysm; BP = blood pressure; OR = odds ratio in multivariate analysis; n.s. = not significant.

Kuopio sIA Database (www.uef.fi/ns) contains all cases of unruptured and ruptured sIAs admitted to the Kuopio University Hospital (KUH) from a defined Eastern Finnish catchment population since 1980 (15). We have studied the phenotype (15), familial form (14,15), outcome (29), concomitant diseases (30,31), and genomics of the sIA disease (12,13). Here we compare the incidence of drug-treated hypertension in 467 unruptured and 1053 ruptured sIA patients with first diagnosis between 1995 and 2007. We analyze whether hypertension associates with the formation or further growth of sIA rather than rupture.

Materials and methods

Catchment population of Kuopio University Hospital

During the study period from 1995 to 2007, only Neurosurgery of KUH provided full-time acute and elective neurosurgical services for the KUH catchment population in Eastern Finland (31).

The KUH area contains four central hospitals with neurological units of their own. From 1995 to 2007, the geographic area remained the same, but the population decreased from 880,914 to 851,066. The median age increased from 38 to 42 years in males and from 41 to 45 years in females, and the proportion of males remained unchanged at 49%.

Kuopio Intracranial Aneurysm Database (www.uef.fi/ns)

All cases of SAH diagnosed by spinal tap or CT in the KUH catchment area have been acutely admitted to KUH for angiography and treatment if not moribund or very aged. Cases with unruptured intracranial aneurysms (IAs) and no SAH have also had neurosurgical consultation for elective occlusion. They were detected as incidental findings in neuroimaging for other causes, as symptomatic or by screening sIA family members (Table II). The findings were confirmed by four-vessel catheter angiography, magnetic resonance angiography (MRA), or computed tomography angiography (CTA). The exact numbers of rejected cases are not available. KUH Neurosurgery maintains a database of all cases of unruptured and ruptured intracranial aneurysms admitted to the KUH since 1980. The database has been prospective since 1990. The database is run by a full-time nurse, who interviews new cases and codes variables with detailed information, including family history. The criterion for sIA family is at least two affected first-degree relatives (15). Clinical data from the hospital periods and follow-up visits are entered. The purchases of medications prescribed to these patients from 1995 to 2008, as well as cancers and other diagnosed diseases, and causes of death have been entered from national registries.

Table II. Indications for diagnostic neuroimaging in 467 unruptured sIA patients in 1995–2007 from Eastern Finland.

	No AHTM in follow-up ($n = 124$)	AHTM started before or after sIA diagnosis ($n = 343$)
Incidental sIA	100 (81%)	283 (83%)
Median size (mm) (quartiles)	5 (3–8)	6 (4–9)
Headache	19	50
Brain infarction or TIA	4	37
Vertigo	8	27
Amnesia	3	15
Trauma	6	14
Other	55	115
Unknown	4	25
Screening for familial sIA	15 (12%)	30 (9%)
Median size (mm) (quartiles)	5 (3–6)	4 (3–6)
Symptomatic sIA	9 (7%)	30 (9%)
Median size (mm) (quartiles)	14 (7–30)	17 (9–28)
Vision defect	3	12
Epileptic seizure	0	5
Hemiparesis	2	8
Other	4	5

AHTM = antihypertensive medication; sIA = saccular intracranial aneurysm; TIA = transient ischemic attack.

Study population

The cohort consisted of 467 unruptured and 1053 ruptured consecutive sIA patients, fulfilling the following criteria: 1) a citizen of Finland and resident of the KUH catchment area at first diagnosis of sIA disease between 1 January 1995 and 31 December 2007; 2) admission alive to KUH; 3) verification of sIAs by angiography; 4) other intracranial vascular malformations (fusiform, traumatic, or mycotic aneurysm, moyamoya disease, arteriovenous malformation) excluded by angiography; and 5) autosomal polycystic kidney disease and Marfan's syndrome excluded.

Antihypertensive medication

The diagnosis of hypertension was made based on purchased antihypertensive drugs. The Social Insurance Institution of Finland maintains a nationwide registry of all prescribed medicines purchased since 1994. Purchases by the 1520 sIA patients between 1 January 1994 and 31 December 2008 were obtained from the registry and linked to the database. The patient recruitment period from 1 January 1995 to 31 December 2007 allows data on the purchased drugs for at least 1 year before and after the sIA diagnosis. Antihypertensive as well as antidiabetic and statin medications were classified according to the anatomic therapeutic chemical (ATC) classification system. In Finland, these drug groups are sold by prescription only.

Variables

The variables used in the analyses were (Table III):

For all sIA patients:

1. sIA disease carrier (gender; age at first sIA diagnosis; sporadic versus familial sIA patient; use and starting age of antihypertensive, antidiabetic, and statin medications; current or former smoking versus none, missing in 1 unruptured and 288 sIA-SAH patients)
2. sIA disease (location and diameter of the primary sIA; one versus two or more sIAs)
3. occlusive therapy (microsurgical versus endovascular versus other versus none)

For sIA-SAH patients only:

4. condition on admission to KUH (Hunt and Hess Scale; intracerebral hemorrhage; intraventricular hemorrhage; acute hydrocephalus)
5. outcome at 12 months (Glasgow Outcome Scale)

Review of relevant literature

A PubMed search on 27 November 2013 for articles published in English after 1 January 2001 with the terms (subarachnoid* hemorrhage) AND (hypertension OR "blood pressure") gave 825 hits. Only the following were included: 1) case-control studies with 2) angiographically verified IAs, 3) age- and sex-matched controls, and 4) multivariate analysis of risk factors. Another search with the terms aneurysm* AND (intracranial OR cerebral) AND unruptured AND (risk factor* OR etiology OR hypertension OR "blood pressure") gave 530 hits. Only

Table III. Clinical characteristics of 1520 sIA patients in 1995–2007 from Eastern Finland.

	Unruptured sIA patients $n = 467$			Ruptured sIA (sIA-SAH) patients $n = 1053$		
	No AHTM in follow-up, $n = 124$ (26%)	AHTM started before sIA diagnosis, $n = 237$ (51%)	AHTM started after sIA diagnosis, $n = 106$ (23%)	No AHTM in follow-up, $n = 404$ (38%)	AHTM started before sIA diagnosis, $n = 348$ (33%)	AHTM started after sIA diagnosis, $n = 301$ (29%)
Males	56/195 (29%)	101/195 (52%)	38/195 (19%)	201/449 (45%)	117/449 (26%)	131/449 (29%)
Females	68/272 (25%)	136/272 (50%)	68/272 (25%)	203/604 (34%)	231/604 (38%)	170/608 (28%)
sIA disease diagnosis						
Median age (quartiles)	49 (43–56)	58 (50–68)	54 (46–64)	51 (43–61)	60 (51–69)	51 (43–61)
Females	50 (43–57)	59 (51–70)	54 (47–65)	53 (44–66)	60 (51–70)	55 (46–65)
Familial sIA disease	38 (31%)	51 (22%)	38 (36%)	49 (12%)	46 (13%)	49 (16%)
Multiple sIAs (≥ 2)	30 (24%)	63 (27%)	30 (28%)	100 (25%)	110 (32%)	83 (28%)
Characteristics of sIAs						
Median size of sIA (mm) (quartiles)	5 (3–7)	5 (3–8)	5 (3–8)	7 (5–10)	7 (4–10)	6 (4–9)
Location of sIAs	171 sIAs	337 sIAs	151 sIAs	404 sIAs	347 sIAs	301 sIAs
ACoA	17 (10%)	49 (15%)	15 (10%)	115 (28%)	91 (26%)	102 (34%)
Mbif	82 (48%)	131 (39%)	59 (39%)	113 (28%)	92 (27%)	94 (31%)
ICA	37 (22%)	88 (26%)	44 (29%)	104 (26%)	71 (21%)	55 (18%)
BAbif	6 (4%)	22 (7%)	9 (6%)	15 (4%)	29 (8%)	8 (3%)
Others	29 (17%)	47 (14%)	24 (16%)	57 (14%)	64 (18%)	42 (14%)
Antihypertensive medication	124 (26%)	237 (51%)	106 (23%)	404 (38%)	348 (33%)	301 (29%)
Median starting age (quartiles)		53 (47–63)	56 (50–68)		55 (47–65)	54 (46–65)
Females		54 (46–65)	56 (50–70)		56 (48–65)	57 (49–68)
Statin medication	26 (21%)	138 (58%)	26 (25%)	43 (11%)	131 (38%)	125 (42%)
Median starting age (quartiles)	56 (50–66)	61 (52–68)	57 (50–64)	57 (50–62)	62 (56–70)	58 (51–66)
Antidiabetic medication	4 (3%)	32 (14%)	8 (6%)	14 (3%)	44 (13%)	34 (11%)
Median starting age (quartiles)	53 (41–62)	66 (58–71)	62 (57–69)	56 (53–63)	63 (57–69)	62 (51–72)
Smoking						
Current	47 (38%)	80 (34%)	47 (38%)	149 (37%)	73 (21%)	131 (44%)
Former	11 (9%)	25 (11%)	11 (9%)	29 (7%)	30 (9%)	31 (10%)
No	66 (53%)	131 (55%)	66 (53%)	85 (21%)	130 (37%)	104 (35%)
Unknown smoking status	0 (%)	1 (%)	0 (%)	141 (35%)	115 (33%)	35 (12%)
Condition on admission for sIA-SAH						
Hunt and Hess Scale						
I Asymptomatic				58 (14%)	37 (11%)	31 (10%)
II Moderate to severe headache				108 (27%)	123 (35%)	157 (51%)
III Drowsiness/confusion				87 (22%)	79 (23%)	73 (25%)
IV Stupor				80 (20%)	58 (17%)	36 (13%)
V Decerebrate posturing				71 (18%)	51 (14%)	4 (2%)
Intracerebral hemorrhage				126 (31%)	88 (25%)	74 (25%)
Intraventricular hemorrhage				129 (32%)	108 (31%)	60 (20%)
Acute hydrocephalus				198 (49%)	174 (50%)	110 (37%)
Occlusive therapy of sIA						
Clipping	60 (48%)	104 (44%)	52 (49%)	235 (58%)	170 (49%)	194 (65%)
Embolization	12 (10%)	28 (12%)	16 (15%)	102 (25%)	121 (35%)	102 (34%)
None	52 (42%)	105 (44%)	38 (36%)	67 (17%)	57 (16%)	5 (2%)
Glasgow Outcome Scale at 12 months						
5 Good recovery				179 (44%)	159 (46%)	226 (75%)
4 Moderate disability				47 (12%)	51 (15%)	59 (20%)
3 Severe disability				22 (5%)	18 (5%)	14 (5%)
2 Persistent vegetative state				2 (%)	4 (1%)	1 (%)
1 Death	4 (3%)	14 (6%)	0	154 (38%)	116 (33%)	1 (%)

ACoA = anterior communicating artery; AHTM = antihypertensive medication; BAbif = basilar artery bifurcation; ICA = internal carotid artery; Mbif = middle cerebral artery bifurcation; sIA = saccular intracranial aneurysm; sIA-SAH = subarachnoid hemorrhage from ruptured sIA.

studies with angiographically verified IAs were included. The reference lists of relevant articles were checked for further relevant publications. The most recent study was included from a single cohort (Table I).

Statistical analysis

Univariate analyses were performed using the Mann–Whitney *U* test or the chi-square test. Multivariate analyses were performed using linear regression (Figure 2) and binomial logistic regression (Table III). $P < 0.05$ was considered significant. In the analyses relating the sIA diameter to the age at diagnosis, cases with missing sIA diameter or smoking status as well as symptomatic unruptured sIAs were excluded (Figure 2). To account for differences of ages at sIA diagnosis between the unruptured and ruptured groups, age was standardized to the joint age distribution of both age groups. Standardized rates and confidence intervals were calculated according to Fay and Feuer (32). The incidences of hypertension in the unruptured and ruptured groups were calculated for 10-year age intervals, and the confidence intervals in each age group were calculated as exact central Poisson confidence intervals (33). Age standardization was done using R statistical computing environment, and other analyses were made using SPSS 19 for Mac.

Ethical aspects

The study was approved by the Ethics Committee of the KUH. Data fusion from the national registries was performed with the approval from the Ministry of Social Affairs and Health of Finland.

Results

Study cohort

The entire cohort consisted of 1520 consecutive sIA patients, first diagnosed between 1995 and 2007 (Table III). There were 467 unruptured sIA cases (25% familial) and 1053 sIA-SAH cases (11% familial), with total follow-up times of 3074 and 6130 years, respectively. Of the 467 unruptured sIA cases, 92% were incidental findings (median 6 mm) in neuroimaging, while 8% caused neurological symptoms mainly by their size (median 16 mm) (Table II). The cumulative mortality rate at 12 months was 3.9% for the unruptured cases and 8.5% for the sIA-SAH cases in good condition on admission (Hunt and Hess Scale 1–2) but 42.5% for the sIA-SAH cases in poor condition (Hunt and Hess Scale 3–5).

Hypertension in unruptured versus sIA-SAH patients

During the observation period for drug use (1994 to 2008), antihypertensive medication was used by 73% of the unruptured sIA patients in contrast to 62% of the sIA-SAH patients (Table III). The medication was started before the sIA diagnosis more often in the unruptured group (57% versus 33%) (Table III). The age-adjusted incidence of hypertension was higher in the unruptured group, 94.5 (95% CI 87.6–102) versus 72.5 (95% CI 68.5–76.8) per 1000 follow-up years (Figure 1). The incidence was calculated separately for the sIA-SAH cases with poor condition on admission (Hunt and Hess Scale 3–5) because their high mortality reduced the percentage of antihypertensive medications started after the rupture (Table III, Figure 1). Antihypertensive treatment was started after the sIA diagnosis in 23% of the unruptured and 29% of the sIA-SAH patients ($P < 0.05$).

Smoking by unruptured versus sIA-SAH patients

Current or former smokers until sIA diagnosis were identified in 45% of the unruptured sIA cases (62% males, 32% females) and in 42% of the sIA-SAH cases (55% males, 32% females; data missing in 27%) (Table III).

Hypertension and smoking versus familial sIA disease

Familial sIA disease was carried by 25% of the unruptured group (23% males, 26% females) and by 11% of the sIA-SAH group (16% males, 12% females) (Table III). In multivariate analysis, hypertension or smoking was not associated with the familial sIA disease in either group (data not shown).

Hypertension and smoking versus multiple sIAs

Multiple sIAs (two or more) were diagnosed in 25% of the unruptured group (26% males, 25% females) and in 28% of the sIA-SAH group (25% males, 30% females) (Table III). In multivariate analysis, hypertension or smoking was not associated with multiple sIAs (data not shown).

Hypertension and smoking versus size of sIA at first diagnosis

The size at diagnosis of the incidentally found unruptured sIAs in 428 patients (Table II) increased with age (Figure 2), independently of gender, familial sIA disease, hypertension, or smoking in multivariate analysis (0.10 mm/year; 95% CI 0.048–0.154; $P < 0.001$). In comparison, the size of the ruptured sIAs did not increase significantly with the age at first diagnosis (0.03 mm/year; 95% CI –0.001 to 0.054; $P = 0.06$).

Discussion

Essential findings

We studied the incidence of hypertension in 467 unruptured sIA patients as compared to 1053 sIA-SAH patients, first diagnosed between 1995 and 2007 and admitted to KUH, which solely serves a defined Eastern Finnish catchment population. Only 10% of the unruptured group did not present with hypertension, smoking, or familial sIA disease, independent risk factors for the sIA disease (11). In total, 73% of the unruptured sIA patients and

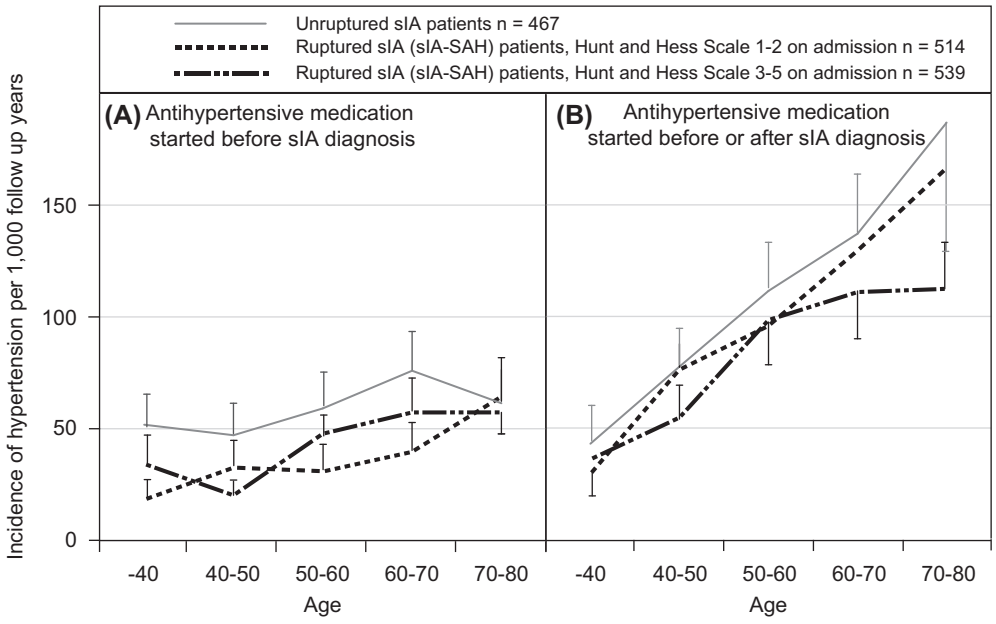

Figure 1. Incidence of hypertension in 467 unruptured saccular intracranial aneurysm (sIA) patients and 1053 ruptured ones (sIA-SAH) by the 10-year age groups and their 95% confidence intervals. A: Patients with antihypertensive medication started before the sIA diagnosis. Follow-up time ends at the start of antihypertensive medication or the time of sIA diagnosis. B: Patients with antihypertensive medication started before or after the sIA diagnosis. Follow-up time ends at the start of antihypertensive medication, death, or 31 December 2008.

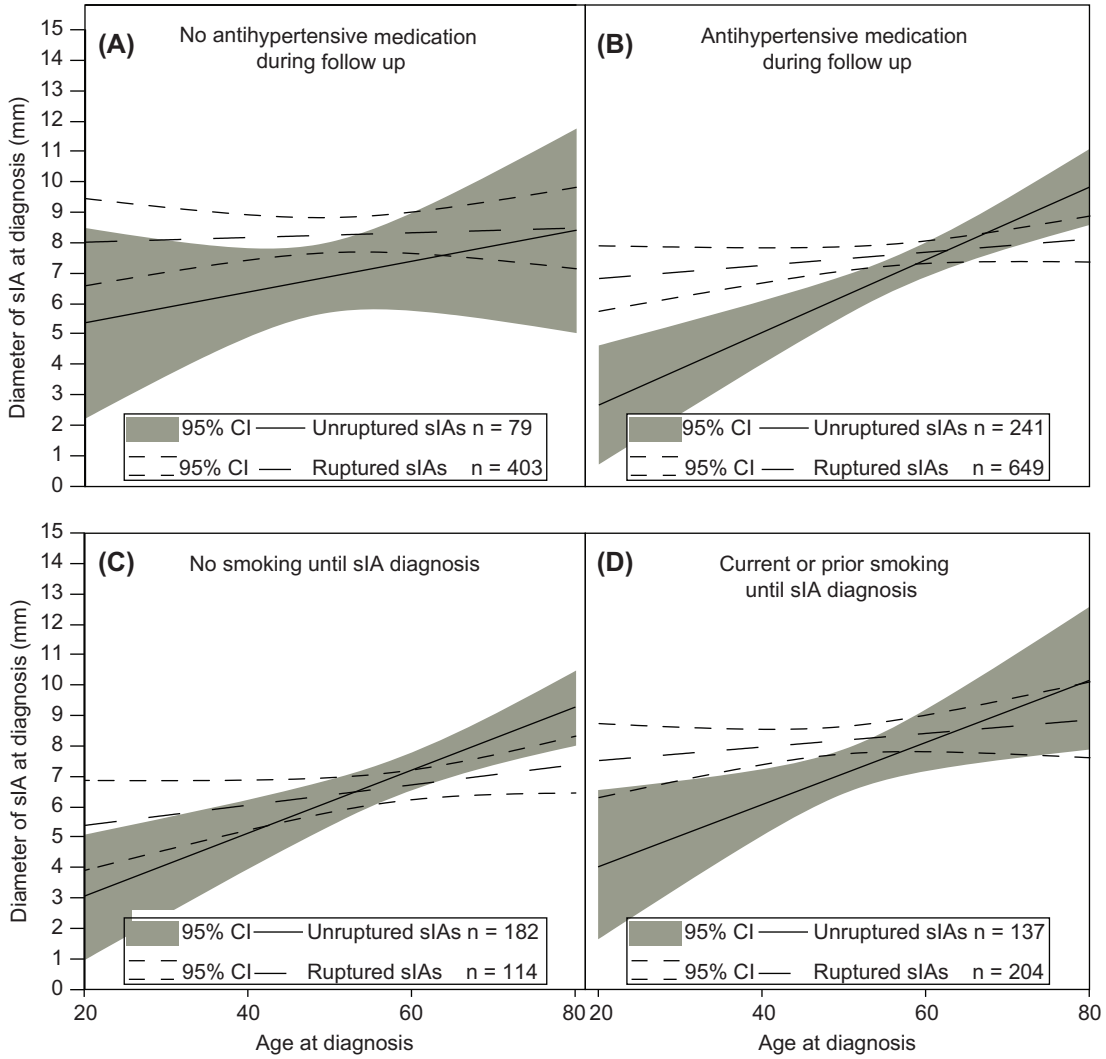

Figure 2. Correlation of the age at diagnosis with the diameter of unruptured saccular intracranial aneurysms (sIAs) and ruptured ones (sIA-SAH). Regression lines and 95% confidence intervals (CIs) are shown for unruptured (continuous lines) and ruptured (dotted lines) patients. A and B: The patients without (A) versus with (B) antihypertensive medication during follow-up. The sIA diameter data were available for 320 unruptured sIA patients and 1052 ruptured sIA patients. C and D: The patients without (C) versus with (D) history of smoking (former or current) until the sIA diagnosis. The sIA diameter data and smoking data were available for 319 (182 in C and 137 in D) unruptured sIA patients and 318 (114 in C and 204 in D) ruptured sIA patients. The unruptured sIAs that caused symptoms were removed from the analysis.

62% of the sIA-SAH patients had purchased antihypertensive medication between 1994 and 2008 (31), at least 1 year before or after the sIA diagnosis. The lower overall percentage of hypertension in sIA-SAH patients may partially relate to their higher 12-month mortality. The age-adjusted incidence of hypertension was higher in the unruptured sIA group than in the sIA-SAH group (Figure 1). The size of unruptured sIAs increased with the age at sIA diagnosis (Figure 2), independently of hypertension. Multiple sIAs, familial sIA disease, or sIA-SAH were not associated with hypertension in multivariate analysis either. Firstly, our findings indicate that hypertension is strongly associated with the formation of sIA. Secondly, untreated hypertension may predispose to the rupture of the sIA wall (27), because at the time of sIA diagnosis the sIA-SAH patients had significantly more often untreated hypertension (see the columns 'AHTM started after sIA diagnosis' in Table III).

Hypertension and sIA disease

One would expect that independent risk factors of the sIA disease would predispose to younger age, and larger size and multiple sIAs at diagnosis. Smoking predisposes to SAH (11,34), even showing synergy with hypertension (35), and smoking is a risk factor for *de novo* sIA formation verified angiographically (3–5). The mechanisms by which hypertension would affect the formation, further growth, or rupture of the sIA pouch have remained uncertain. In previous angiographically verified sIA series, hypertension has strongly associated with sIA-SAH when compared to matched controls or general population (Table I), suggesting that hypertension would predispose the sIA wall to rupture. However, few series have compared unruptured sIA patients to controls or to sIA-SAH patients (Table I). In a case–control study of 250 aneurysmal SAH patients (25% hypertensive) and 206 unruptured IA patients (38% hypertensive), hypertension was not a significant risk factor for rupture (27). In a Japanese case–control study, 53% of the 858 ruptured and 58% of the 285 unruptured sIA patients had a history of hypertension until the sIA diagnosis as compared to 30% in 798 controls (20). The author concluded that hypertension associates with the formation of sIAs rather than their rupture.

Hypertension in unruptured sIA patients

In the UCAS study, 43.4% of the 5720 unruptured sIA patients (91% incidental; mean age 62.5 years; 68% women; no previous SAH) had a history of hypertension before the angiographic sIA diagnosis (36). Hypertension did not significantly associate with subsequent rupture of the sIAs (HR 1.41; 95% CI 0.96–2.07). In the ISUIA study, 41% of the 4060 angiographically verified unruptured sIA patients had a history of hypertension before the angiographic diagnosis (37). Hypertension was not a significant risk factor for the sIA rupture either. In a recent study of 206 unruptured IA patients and 574 controls, 38% and 19% had a history of hypertension, respectively. Hypertension was a significant risk factor for unruptured sIA in multivariate analysis (OR 2.9; 1–4.6) (28). In a recent study of 263 patients with 384 conservatively treated small anterior circulation sIAs, hypertension was significantly associated with subsequent sIA rupture in follow-up ($P < 0.001$; HR, 2.6; 95% CI 2.1–3.3) (38). In our study, hypertension was detected in 52% before the sIA diagnosis, tallying with previous studies. Hypertension was detected in further 23% after the sIA diagnosis, a trend unnoticed previously. In the national FINRISK study, only 56.2% to 74.5% of participants in the KUH catchment area were aware of their hypertension (39).

Hypertension and unruptured sIA growth

In animal models, hypertension is essential both in the formation and further growth of sIAs (19). Few clinical series have correlated hypertension to the growth of unruptured sIAs between two angiographies. Hypertension was significantly associated with growth in a retrospective series of 53 sIAs (5), but not in a retrospective series of 165 patients (7) and a prospective series of 87 patients (4). The size of unruptured sIAs increases with the age at diagnosis (15), probably due to longer exposure to modifiable risk factors. In our study, the size of unruptured sIAs increased with age at diagnosis, irrespective of hypertension or smoking.

Hypertension and familial sIA disease

The sIA disease is a complex trait, and at least 10% of cases are familial (14,15), 25% of the unruptured and 11% of the ruptured patients in the present series. Possible genomic or epigenomic mechanisms behind the familial form are unknown. A putative sIA risk locus at 5q26 associates with high systolic blood pressure, but leading hypertension risk loci did not associate with the sIA disease in Finland (13). In the Nordic Twin Cohort, the concordance for SAH diagnoses from national hospital discharge registers was only 3.1% in monozygotic twins, but data for unruptured cases was unavailable (40). Korja et al. suggested that familial clustering of modifiable risk factors, e.g. smoking, high blood pressure, and heavy alcohol consumption, significantly contribute to familial SAH (40). In our series, hypertension or smoking were not associated with familial sIA among the unruptured or ruptured patients.

Hypertension and multiple sIAs

Hypertension was significantly associated with the presence of multiple (two or more) intracranial aneurysms in 392 ruptured patients (OR 1.9, 95% CI 1.5–3.5) (41), but not in 298 ruptured and 121 unruptured patients (42), nor in 266 ruptured patients (43). In our study, hypertension or smoking were not associated with multiple sIAs.

Weaknesses and strengths of the present study

In the present study, blood pressure was not monitored prospectively, but the hypertension diagnosis was based on the purchase of prescribed antihypertensive medicines. Higher 12-month mortality of sIA-SAH patients may have reduced the incidence of hypertension detectable after sIA-SAH. Of the unruptured sIA cases, 92% seemed incidental findings, but hypertension may have affected indications for neuroimaging.

There are several strengths that derive from the Scandinavian health care system. Finland is divided into exclusive catchment areas for the five university hospitals, allowing cohorts that are unselected and minimally biased. Accurate population statistics and stable populations ensure that few patients are lost to follow-up. Our series contains angiographically verified sIA cases only, while several series have included other forms of intracranial aneurysms and non-aneurysmal cases of SAH, or were based on archival ICD codes only. We carefully analyzed the reasons for diagnostic imaging in unruptured cases. In Finland, antihypertensive medications are sold by prescription only, and the purchases are available in the national registry. In previous studies, hypertension diagnosis was often made based on previous history or interview, and the hypertension status was not updated during follow-up after the initial sIA diagnosis.

Suggested further research

Saccular intracranial aneurysms form during life at the branching sites of intracranial extracerebral arteries, in the so-called medial raphe (44), the seal between the medial arterial walls of the two daughter branches when they originate from the mother branch. Fetal development of branching tubular trees in various organs, branching morphogenesis, has not been elucidated in intracranial extracerebral arteries.

Two obvious clinical questions arise. Firstly, can the formation of sIAs be prevented by antihypertensive medication? Hardly, if hypertension is an inborn complex trait that affects the arterial walls and the medial raphe area, in particular, long before the rise of measured blood pressure values that finally triggers the start of medication. Possibly, if the sIA pouch formation is actually caused by elevated blood pressure, but even then it is demanding to design reliable population-based studies, and none exist, so far. Unruptured sIAs are in most cases incidental findings in neuroimaging for other reasons. Secondly, is it reasonable, cost-effective, and ethically sound to screen unruptured sIAs by MRA or CTA after fresh diagnoses of hypertension?

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