De Novo and Recurrent Aneurysms in Pediatric Patients With Cerebral Aneurysms

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Background and Purpose—Long-term angiographic follow-up studies on pediatric aneurysm patients are scarce.

Methods—We gathered long-term clinical and angiographic follow-up data on all pediatric aneurysm patients (≤18 years at diagnosis) treated at the Department of Neurosurgery, Helsinki University Central Hospital, between 1937 and 2009.

Results—Fifty-nine patients with cerebral aneurysms in childhood had long-term clinical and radiological follow-up (median, 34 years; range, 4–56 years). Twenty-four patients (41%) were diagnosed with altogether 25 de novo and 11 recurrent aneurysms, with 9 (25%) of the aneurysms being symptomatic. New subarachnoid hemorrhage occurred in 7 patients; 4 of these patients died. Eight patients (33%) had multiple new aneurysms. The annual rate of hemorrhage was 0.4%, and the annual rate for the development of de novo or recurrent aneurysm was 1.9%. There were no de novo aneurysms in 7 patients with previously unruptured aneurysms. However, 1 recurrent aneurysm was diagnosed. Current and previous smoking (risk ratio, 2.44; 95% confidence interval, 1.07–5.55) was the only statistically significant risk factor for de novo and recurrent aneurysm formation in patients with previous subarachnoid hemorrhage, whereas hypertension, sex, or age at onset had no statistically significant effect. Smoking was also a statistically significant risk factor for new subarachnoid hemorrhage.

Conclusions—Patients with ruptured intracranial aneurysms in childhood have a high risk for new aneurysms and new subarachnoid hemorrhage, especially if they start to smoke as adults. Life-long angiographic follow-up is mandatory. (Stroke. 2013;44:00-00.)

Key Words: cerebral aneurysm ■ children ■ de novo aneurysm ■ recurrent subarachnoid hemorrhage ■ subarachnoid hemorrhage

Patients who survive subarachnoid hemorrhage (SAH) have a higher rate of new SAH than the general population, even after successful treatment of the initial aneurysm, because of de novo and recurrent aneurysms.1–3 Aneurysms in the first 2 decades of life comprise about 1% to 4% of all intracranial aneurysms.4–7 Long-term angiographic follow-up studies in pediatric intracranial aneurysm patients with mean follow-up times of only 4 to 6 years5,8,9 show de novo aneurysm formation rates of 13% to 23%.4,5,9

We gathered data on long-term clinical and angiographic follow-up studies of pediatric aneurysm patients in a single-center consecutive series. We assessed the risk of these patients to harbor de novo and recurrent aneurysms, and the risk factors associated with new angiographic findings in a long follow-up.

Materials and Methods

Patients and Follow-Up

Long-term clinical and angiographic follow-up data on all pediatric patients with cerebral aneurysms (≤18 years at diagnosis) originally admitted to the Department of Neurosurgery, Helsinki University Central Hospital between 1937 and 2009 were gathered. Detailed data on these patients and their later long-term excess mortality have been reported earlier.7,10 The long-term follow-up studies with cerebral angiographies were carried out at 20 referral hospitals in Finland between 1978 and 2012. All medical records of these patients from other hospitals were evaluated. All radiological studies were reanalyzed by a radiologist/neurosurgeon (RK). Death certificates (Statistics Finland) and autopsy reports for 34 deceased patients were reviewed.

Statistical Methods

Statistical analysis was performed using SPSS software (version 19.0; SPSS Inc, Chicago, IL). The Pearson χ² test and Mann-Whitney U test were used when appropriate. Risk ratios and 95% confidence intervals of possible risk factors associated with new aneurysm formation were calculated. Annual rates of hemorrhage and formation of de novo and recurrent aneurysms were calculated by dividing them by the number of patient follow-up years. Cumulative rate of new SAH was estimated using the Kaplan-Meier product-limit method. The relation of age at onset (by dichotomizing the cohort into younger and older groups at median age on admission), sex, current...
or previous smoking, rupture status of the initial aneurysm, and antihypertensive medication with the occurrence of new SAH was tested with Pearson $\chi^2$ test. Probability value <0.05 was considered statistically significant.

Ethical Aspects
Data from referring hospitals were obtained with the permission of the National Institute for Health and Welfare, and death certificates from Statistics Finland. The ethics committee of Helsinki University Central Hospital approved the study protocol (pediatric aneurysms).

Results

Patients
During 1937 to 2009, altogether 114 pediatric aneurysm patients were admitted, and of these, 10 patients with traumatic aneurysms and 2 foreign patients were excluded. There were 88 1-year survivors, 59 (67%) of whom had long-term data available (36 men and 23 women, 7 with unruptured aneurysms; Figure 1). These 59 patients had initially 67 aneurysms (6 had multiple aneurysms at onset), and 96% and 39% had a 2-vessel and 4-vessel angiographies initially, respectively. Of these 59 patients, 52 presented with SAH, 3 had symptomatic unruptured aneurysms, and 4 were incidental findings. The median age at presentation was 16.0 years (mean, 14.9 years; range, 1–18 years). Three patients had an aortic coarctation, 1 had polycystic kidney disease, and 1 had tuberous sclerosis. Eleven patients (19%) had at least 1 first-degree relative with cerebral aneurysms.

Angiographic Long-Term Follow-Up
Of the 88 1-year survivors, angiographic follow-up (computed tomography angiography, n=33; magnetic resonance angiography, n=13; and digital subtraction angiography, n=13) was available for 56 (64%) and neuropathological autopsy for 3 (4%); (total, 59 patients [67%]). The median follow-up was 34.0 years (mean, 32.5 years; range, 4–56 years). There were 25 de novo aneurysms and 11 recurrent aneurysms in 24 patients (41%); 8 patients (33%) had multiple new aneurysms (the online-only Data Supplemental Tables S1 and S2). The median time for diagnosis of symptomatic (7 patients with SAH and 2 patients with epileptic seizure) and asymptomatic aneurysms was 13.0 years (mean, 18.3 years; range, 6–33 years) and 36.0 years (mean, 37 years; range, 26–47 years), respectively. Seven (27%) of all de novo/recurrent aneurysms presented with SAH, and these patients had an early case fatality of 57% (the online-only Data Supplemental Figure S1). There were no de novo aneurysms in patients with previously unruptured aneurysms. However, 1 patient had a symptomatic but unruptured recurrent aneurysm. Asymptomatic growth of an untreated aneurysm was diagnosed in 3 patients (5%). Spontaneous thrombosis of the aneurysm was diagnosed in 3 patients (5%), after a mean of 30 years (range, 3 months–50 years).

Thirty-five patients (59%) were current (n=24; 41%) or previous (n=11; 19%) smokers, and 26 (44%) were hypertensive. Six of the 8 patients with multiple aneurysms were current (n=5) or former (n=1) smokers.

Of the de novo aneurysms, 24% were on the side ipsilateral to the initial aneurysm. The median sizes of symptomatic and asymptomatic aneurysms were 15.0 mm (mean, 14.8 mm; range, 6–28 mm) and 3.0 mm (mean, 6.2 mm; range, 1–14 mm), respectively ($P >0.5$). The most common locations for new aneurysms were anterior communicating artery (n=6) and posterior communicating artery (n=6). Five patients had a new aneurysm in the posterior circulation, but only 2 of them had had both carotid and vertebral angiographies initially.

Figure 1. Flow chart of the 88 first-year survivors. Two patients (*) had a new subarachnoid hemorrhage (SAH), and later new aneurysms in screening.
Out of the original 102 patients, 34 had died by the end of the year 2011. Four had died because of SAH from a de novo or recurrent aneurysm.

**Annual Rates and Risk Factors**

During the 1935 person-years of follow-up, the annual rate of hemorrhage (n=7) was 0.4% and development of new aneurysms (n=36) was 1.9%. In patients with previous SAH (1766 person-years of follow-up), the corresponding rates were 0.5% and 2%. Separate annual rates for de novo (n=25) and recurrent (n=11) aneurysms were 1.3% and 0.6% for all patients, respectively. Current or previous smoking had a marginally statistical significant relationship with de novo or recurrent aneurysm formation (18 of 35 smokers [51%] had new aneurysms, compared with 6 of 24 nonsmokers [25%; risk ratio, 2.06; 95% confidence interval, 0.96–4.42; Figure 2). In patients with ruptured aneurysm in childhood, smoking increased the risk slightly more: risk ratio 2.44 (95% confidence interval, 1.07–5.55). All 7 patients with new SAH were current or previous smokers (P=0.020, Pearson χ² test); none of the other studied factors were significant risk factors for new SAH. Cumulative risk of new SAH 40 years after the initial diagnosis was 15% (95% confidence interval, 5% to 25%).

**Discussion**

Our study with almost 2000 person-years of follow-up shows that >40% of patients with aneurysms in childhood develop new aneurysms in adulthood, with smoking being a statistically significant independent risk factor, especially in patients with SAH during childhood. Smoking was also a statistically significant risk factor for new SAH.

**Annual Rates and Risk Factors for New Aneurysm**

Annual rates of up to 2.6% for de novo aneurysms and 3.5% for recurrent aneurysms among pediatric patients have been reported. This is somewhat higher than in our study (1.3% and 0.6%, respectively); our series is more consistent with adult series with rates of 1.8% to 4% and 0.06 to 0.5%, respectively.

The majority of our patients were current or previous smokers, and half of them had hypertension. However, the only statistically significant factor for recurrent or de novo aneurysm formation was smoking (with almost a 2.5-fold risk in patients with previously ruptured aneurysm). One possible reason for the lack of other statistical risk factors is obviously the relatively small cohort size (as compared with adult SAH population studies).

In our study, the original angiographies were up to 50 years old, and for some patients, only the neuroradiologist’s report was available. Possibly, some of the new aneurysms might be, in fact, undiagnosed old ones. As pointed out by Bruneau et al, in studies where true retrospective analysis of old images has been performed, a lower incidence of de novo aneurysms has emerged. One study showed that only one third of aneurysms were true de novo aneurysms and the rest were initially missed. We had 3 patients with de novo aneurysms in posterior circulation, with only carotid angiographies performed originally. Two of these patients had de novo aneurysms in both anterior and posterior circulation.

**Annual Rates for New SAH**

In our series, the annual rupture rate (0.4%) is in concordance with previously reported pediatric studies (0.6%), even though in Finnish patients, the risk of an aneurysm rupture is 2- to 3-fold than that of other populations, excluding the Japanese, for undefined reasons. The early case fatality from a ruptured new aneurysm was high (57%) relative to recent literature.

We had 2 patients with previous internal carotid artery ligation, and one of them had a ruptured de novo anterior communicating artery aneurysm, a known late complication of internal carotid artery ligation.

**Risk Factors for New SAH**

Smoking was a statistically significant risk factor for new SAH, as well as new aneurysm formation. None of the other known risk factors had a statistically significant role in new SAH in our patients, probably because of the relatively small absolute number of patients with recurrent SAH.

**When and Whom to Follow-Up**

Most of the angiographic follow-up studies among pediatric aneurysm patients recommend strict surveillance, tailored depending on the chosen treatment modality. In our series, the earliest symptomatic recurrent aneurysm (with epileptic seizure) was found 6 years after the initial treatment, and the first de novo aneurysms (with SAH) at 11 years after SAH in concordance with reported adult series. One pediatric series of 26 patients with angiographic follow-up reported the earliest recurrent and de novo aneurysms at a short-term interval of 5 months, whereas another at 5 years.
Among adult series, a short-term angiographic follow-up at 3- to 5-year intervals was recommended in patients aged <50 years with hypertension, whereas another study suggested imaging for female patients at 10 years after the initial aneurysm treatment.

Our study suggests that all pediatric aneurysm patients should have follow-up imaging, preferably with magnetic resonance angiography, at 3- to 5-year intervals, regardless of possible risk factors.

Summary
Patients with cerebral aneurysms in childhood have a high risk for developing new and recurrent aneurysms—up to 41% in our series. Cumulative risk of new SAH 40 years after the initial diagnosis was 15%. Current and previous smoking are risk factors for de novo and recurrent aneurysm formation, as well as new SAH in adulthood, especially in patients with a previously ruptured aneurysm. A life-long angiographic follow-up at 3- to 5-year intervals is advisable for all pediatric patients with cerebral aneurysms.

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Disclosures
A.L. has received consulting fees from Orion Pharma, Espoo, Finland.

References
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**Supplemental Figures and Tables.**

**Figure S1(A-D).** A 12-year-old boy presented with SAH, and DSA showed a left-sided ICA bifurcation aneurysm. There were no aneurysms on the right side (A). The aneurysm was clipped and completely occluded (B). The patient made a full recovery with no neurological deficits. Eleven years later, the patient had a new SAH with GCS 3 on admission (C). CTA showed a right-sided PCoA *de novo* aneurysm (arrow) (D). The patient died and autopsy results confirmed the angiographic finding. No residual or recurrent aneurysms were present at the initial aneurysm site.
Table 1. Patients with a symptomatic new aneurysm.

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<th>Nro</th>
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Patient Nro 1 had initially an unruptured aneurysm. ACA=Anterior cerebral artery, ACoA=Anterior communicating artery, ICA b=Internal carotid artery bifurcation, ICA o=Internal carotid artery oftalmic, MCA=Middle cerebral artery, PCoA=Posterior communicating artery, SAH=subarachnoid hemorrhage, SZ=seizure.
Table 2. Patients with an asymptomatic new aneurysm.

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All patients had initially ruptured aneurysms. ACA=Anterior cerebral artery, ACoA=Anterior communicating artery, ICA b=Internal carotid artery bifurcation, ICA o = Internal carotid artery oftalmic, MCA=Middle cerebral artery, PCoA=Posterior communicating artery, PICA=Posterior inferior cerebellar artery, SCA=Superior cerebellar artery.