Long-term Excess Mortality in Pediatric Patients With Cerebral Aneurysms

Päivi Koroknay-Pál, MD, PhD; Aki Laakso, MD, PhD; Hanna Lehto, MD; Karri Seppä, MSc; Riku Kivisaari, MD, PhD; Juha Hernesniemi, MD, PhD; Mika Niemelä, MD, PhD

Background and Purpose—Knowledge of the long-term excess mortality in pediatric aneurysm patients is lacking. The aim of this study was to assess the long-term excess mortality of 102 pediatric patients with cerebral aneurysm treated at the department of neurosurgery at Helsinki University Central Hospital between 1937 and 2009.

Methods—Patients were followed from diagnosis until death or the end of the year 2010. Relative survival ratio provided the measure of excess mortality in these patients compared with mortality of the general Finnish population matched by age, sex, and calendar time.

Results—A majority of the patients (n=89) presented with subarachnoid hemorrhage. Aneurysms (n=118) were treated operatively (n=79), endovascularly (n=1), or conservatively (n=36). The mean follow-up time was 26.8 years (range, 0–55.6 years). By the end of follow-up, 34 of the 102 patients had died; 26 of these deaths (76%) were aneurysm-related. There was overall excess mortality of 10% (cumulative relative survival ratio, 0.90; 95% CI, 0.80–0.96) and 19% (cumulative relative survival ratio, 0.81; 95% CI, 0.66–0.91) at 20 and 40 years after the diagnosis among the 1-year subarachnoid hemorrhage survivors, respectively. The excess mortality was particularly high in boys. There was no long-term excess mortality among patients with unruptured aneurysms. Aneurysm-related deaths included rebleedings from open or partially occluded aneurysms, epileptic seizures, de novo and recurrent aneurysms, or sequelae of subarachnoid hemorrhage.

Conclusions—There is long-term excess mortality in pediatric patients with aneurysm even decades after successful treatment of a ruptured aneurysm, especially among boys. The excess mortality is mainly aneurysm-related. (Stroke. 2012;43:2091-2096.)

Key Words: cerebral aneurysm ■ subarachnoid hemorrhage ■ children ■ excess mortality

In adult patients, acquired risk factors for aneurysm growth and rupture are smoking, hypertension, and excessive alcohol consumption, which have an impact on the high role of cardiovascular deaths among patients with ruptured aneurysm in long-term excess mortality. Intracranial aneurysms in children and adolescents are rare and in these patients, connective tissue disorders and congenital heart diseases are known risk factors for intracranial aneurysm formation. Population-based, long-term, follow-up studies among pediatric patients are scarce.

In the present study, we analyzed survival in a consecutive series of 102 cerebral aneurysm patients who were age ≤18 years when treated at the department of neurosurgery at Helsinki University Central Hospital (HUCH), between 1937 and 2009. Survival was compared with the general population matched by age, sex, and historical era using the relative survival ratio (RSR) as a measure of excess mortality among 1-year survivors. In Finland, the treatment of intracranial aneurysms is centralized to public university hospitals with population responsibility. In addition, a high-quality healthcare system and relative stable population together with accessible patient registries enable population-based epidemiological studies.

Methods

Patients and Aneurysms

A retrospective study of patients age ≤18 years at the time of diagnosis of a cerebral aneurysm admitted to the department of neurosurgery, HUCH, during years 1937 to 2009 was performed. Patients with traumatic aneurysms, arteriovenous malformation-related aneurysms, and vein of Galen malformations were excluded. Foreign patients were excluded. Patients’ clinical and radiological data were reviewed. Diagnosis of subarachnoid hemorrhage (SAH) was based on lumbar puncture or computed tomography. Sizes and locations of aneurysms were evaluated from conventional angiograms, computed tomography angiograms, or radiologist reports. Clinical status on admission was expressed using the Hunt and Hess grading. Aneurysm treatment methods were categorized as active (ie, surgical or endovascular) or conservative. Conservatively treated aneurysms were not subject to any surgical or endovascular treat-
ments or treatment attempts during the entire follow-up. Aneurysm was considered partially occluded if there was any filling in the postoperative angiograms. The detailed characteristics of the patients have been reported elsewhere.12

Follow-Up Data
Patients were followed from diagnosis until death or December 31, 2010. The vital status of the patients (deceased or alive) at the end of year 2010 was obtained from the Finnish Population Register Centre, which contains information on all people residing in Finland. Two patients were lost to long-term follow-up because of them moving abroad. Autopsy reports for patients who died during hospitalization were available. Death certificates, including the dates and causes of death for patients deceased later (n=23) were provided by Statistics Finland, which also provided the comparable data on general Finnish population for the expected survival. Death was considered aneurysm-related if it was attributable to the aneurysm or its treatment, or to late sequelae of aneurysm-associated morbidity, such as pneumonia, in a bedridden patient.

Statistical Methods
The RSR provided a measure of the excess mortality for children diagnosed with cerebral aneurysm, irrespective of whether the excess mortality was directly or indirectly attributable to the aneurysm itself. The RSR is the ratio of the observed survival proportion of the patients to the expected one in a comparable reference population.13 The expected survival was derived from the mortality rates of the general population of Finland matched to the patients with respect to age, sex, and calendar time using the Hakulinen method.14,15 The estimates of the cumulative RSRs with their 95% CI were calculated from 1 year after admission to department of neurosurgery, HUCH, using R environment for statistical computing and graphics.16 The CIs were constructed on the log cumulative hazard scale, and the variance of the observed survival proportion was estimated using Greenwood’s method.17,18 Statistical analyses between the different patient and aneurysm-characteristics were carried out using Student t test and Pearson’s χ²-test and were performed using a commercial software (IBM SPSS Statistics 19.0, Inc).

Ethical Aspects
The study was approved by the ethical committee of HUCH. The status of the patients was obtained with the permission of Finnish Population Registry. The death certificates with causes of death were obtained with the permission from Statistics Finland.

Results

Patients and Treatments
During the years 1937 to 2009 altogether, 102 pediatric patients with aneurysm were admitted to the department of neurosurgery, HUCH. In addition to these patients, 10 patients with traumatic aneurysms and 2 foreign patients were treated, but excluded. Patient characteristics are described in Table 1. Aneurysms were treated operatively (n=79), endovascularly (n=1), or conservatively (n=36). Two patients died before treatment. Initially, of the 79 surgically treated patients, 54 patients (68%) had completely occluded aneurysms, 8 patients (10%) had partially occluded aneurysms, and 9 patients (11%) had completely open aneurysms. Aneurysm closure status was not available for 8 aneurysms. The only endovascularly treated aneurysm was completely occluded. Most patients with ruptured aneurysms were boys (P<0.05). At the end of follow-up, the incidence of cardiovascular diseases, ie, hypercholesterolemia and hypertension, was no higher in this patient group than it was in the Finnish population overall.12 In our series, no connective tissue disorders were diagnosed and only few patients had a history of hypertension as a result of heart disease. Also, positive family history resembled that of the adults.12

<table>
<thead>
<tr>
<th>Aneurysm location†</th>
<th>Boys</th>
<th>Girls</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICA</td>
<td>29 (40%)</td>
<td>24 (53%)</td>
<td>53 (45%)</td>
</tr>
<tr>
<td>ACA</td>
<td>20 (27%)</td>
<td>11 (24%)</td>
<td>31 (26%)</td>
</tr>
<tr>
<td>ACA</td>
<td>5 (7%)</td>
<td>1 (2%)</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>MCA</td>
<td>11 (15%)</td>
<td>4 (9%)</td>
<td>15 (13%)</td>
</tr>
<tr>
<td>PCA</td>
<td>1 (1%)</td>
<td>1 (2%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>PCoA</td>
<td>2 (3%)</td>
<td>. . .</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Basilar</td>
<td>4 (5%)</td>
<td>2 (4%)</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>Vertebral</td>
<td>. . .</td>
<td>1 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>PICA</td>
<td>1 (1%)</td>
<td>1 (2%)</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>

Hunt and Hess classification at diagnosis

<table>
<thead>
<tr>
<th>Grade</th>
<th>Boys</th>
<th>Girls</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5 (13%)</td>
<td>6 (14%)</td>
<td>11 (11%)</td>
</tr>
<tr>
<td>1</td>
<td>3 (5%)</td>
<td>. . .</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>2</td>
<td>33 (55%)</td>
<td>24 (57%)</td>
<td>57 (56%)</td>
</tr>
<tr>
<td>3</td>
<td>10 (17%)</td>
<td>6 (14%)</td>
<td>16 (16%)</td>
</tr>
<tr>
<td>4</td>
<td>5 (8%)</td>
<td>5 (12%)</td>
<td>10 (10%)</td>
</tr>
<tr>
<td>5</td>
<td>4 (7%)</td>
<td>1 (2%)</td>
<td>5 (5%)</td>
</tr>
</tbody>
</table>

Aneurysm size‡

<table>
<thead>
<tr>
<th>Size</th>
<th>Boys</th>
<th>Girls</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7 mm</td>
<td>26 (39%)</td>
<td>16 (38%)</td>
<td>42 (39%)</td>
</tr>
<tr>
<td>7–14 mm</td>
<td>28 (42%)</td>
<td>18 (43%)</td>
<td>46 (42%)</td>
</tr>
<tr>
<td>15–24 mm</td>
<td>2 (3%)</td>
<td>4 (10%)</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>&gt;25 mm</td>
<td>11 (16%)</td>
<td>4 (10%)</td>
<td>15 (16%)</td>
</tr>
</tbody>
</table>

Single/Multiple

<table>
<thead>
<tr>
<th>Category</th>
<th>Boys</th>
<th>Girls</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single</td>
<td>50 (83%)</td>
<td>39 (93%)</td>
<td>89 (87%)</td>
</tr>
<tr>
<td>Multiple</td>
<td>10 (17%)</td>
<td>3 (7%)</td>
<td>13 (13%)</td>
</tr>
</tbody>
</table>

Follow-up

<table>
<thead>
<tr>
<th>Total person y</th>
<th>Boys</th>
<th>Girls</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1623</td>
<td>51 (52%)</td>
<td>1117 (56%)</td>
<td>2740 (56%)</td>
</tr>
</tbody>
</table>

SAH indicates subarachnoid hemorrhage; ICA, internal carotid artery; ACoA, anterior communicating artery; ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; PCoA, posterior communicating artery; PICA, posterior inferior cerebellar artery.

*Pearson’s χ²-test showed no differences in these variables between boys and girls.
†There were no AICA, SCA, or AChoA aneurysms.
‡Data not available for 9 aneurysms.
Long-Term Mortality in Patients With Ruptured Aneurysms

Overall mortality during the first year after SAH was 13%. Of the 1-year survivors, 8 patients (10%) died from recurrent SAH after a median of 11.0 years (range, 1.5–33.4 years). In 3 patients, death was caused by a bleeding from a de novo aneurysm and in 4 patients from the initially incompletely occluded aneurysm. One patient with totally occluded aneurysm died because of massive SAH 11 years later. This bleeding was assessed as recurrent aneurysmal SAH on death certificate after autopsy; however, no detailed information about the new aneurysm (ie, recurrent versus de novo) was available (Tables 2 and 3).

Table 2. Causes of Death of the 34 Patients Who Died During the Follow-Up Period

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Time From Diagnosis to Death (y)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1</td>
<td>1–5</td>
</tr>
<tr>
<td>Aneurysm-Related</td>
<td>14</td>
<td>2 (67%)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All deaths</td>
<td>14 (43%)</td>
<td>3 (9%)</td>
</tr>
</tbody>
</table>

*Alcohol intoxication.  †Recurrent SAH, recurrent or de novo aneurysm.

Patients With Unruptured Aneurysms

Only 1 death (a 17-year-old patient died because of alcohol intoxication) was observed in patients with unruptured aneurysm after surviving the first year postdiagnosis.

Unknown Deaths

For 3 patients, the actual cause of death was not certain. One patient moved abroad later and died, but no death certificate or autopsy report was available. Another patient was found dead at home and no autopsy was performed. This death was classified as cardiovascular on the death certificate; however, aneurysm-related death cannot be excluded. The third patient died because of massive intracerebral hemotoma and intraventricular bleeding, but no angiography or autopsy was performed to identify etiology of the bleeding. This patient initially had a ruptured aneurysm that was surgically completely occluded 40 years earlier. The causes of deaths of these 3 patients were classified as unknown and aneurysm-unrelated.

Long-Term Excess Mortality

Long-term excess mortality compared with the matched Finnish population was estimated for patients surviving at least 1 year after diagnosis, separately for patients with ruptured and unruptured aneurysms. The overall cumulative RSRs in 1-year survivors with ruptured aneurysms (n=77) were 0.90 (95% CI, 0.80–0.96) and 0.81 (95% CI, 0.66–0.91) at 20 and 40 years after the diagnosis (Table 4, Figure A). Boys (n=48) fared worse, with excess mortality of 15% (95% CI,
Patients with ruptured aneurysm (n=77) had significant excess mortality, in contrast to patients with unruptured aneurysms (n=11). There was comparable excess mortality in patients with both single (n=77) and multiple (n=11) aneurysms (Table 4, Figure B).

The type of treatment, ie, active (n=66) versus conservative (n=22), did not affect the long-term excess mortality by itself, but the completeness of aneurysm occlusion was a significant factor (Table 4, Figure D). Patients treated during the early years had a higher long-term excess mortality than did those treated later, correlating directly with incompleteness of aneurysm closure (P<0.005). Younger patients (age ≤14 years) tended to have greater long-term excess mortality than did patients ≥15 years at the time of diagnosis (Table 4, Figure C). Location or size of the aneurysm did not affect the long-term excess mortality. There was no difference between saccular (n=73) and fusiform (n=4) aneurysms in the survival; however, the number of fusiform aneurysms was low in this cohort. There were no aneurysm-related deaths among patients with unruptured aneurysms in the long-term follow-up after surviving the first year postdiagnosis. Cumulative survival ratios and corresponding 95% CIs, stratified by age, sex, number, location and size of the aneurysms; treatment type; and completeness of aneurysm closure are presented in Table 4.

### Discussion

A single-center, long-term excess mortality study was performed in 102 consecutive pediatric patients with aneurysm treated at our institution during the last 70 years, with a mean follow-up of 25 years. Among 1-year SAH survivors, there was excess mortality of almost 20% at 40 years after diagnosis. The excess mortality was most notable in boys. In our series, ruptured aneurysms were also significantly more prevalent in boys. However, because of a relatively small sample size, no multivariate analysis can be meaningfully carried out to investigate further the difference in survival between sexes. There was no excess mortality in patients with unruptured aneurysms surviving up to 1 year after diagnosis. There was more excess mortality in patients treated in the earlier years than in the recent decades in concordance with the fact their aneurysms were more often incompletely occluded. From the early years, the aneurysm treatment has improved considerably, and in modern practice, incomplete occlusion is exceptional. However, among 1-year survivors
Long-Term Mortality

Aneurysm-related deaths were the major causes of death throughout the follow-up. During the first 10 years after diagnosis, patients died because of rebleedings either during conservative treatment of previously ruptured aneurysm or after insufficient treatment with totally or partially open aneurysms. Among complex vertebrobasilar aneurysms with residual neck, the rebleeding rate has been reported to be 10% in a long-term follow-up. The first lethal de novo aneurysm bleeding occurred 11 years after and the other 2 bleedings over 30 years after treatment of the index aneurysms. All the lethal de novo aneurysm bleedings occurred in patients with previously ruptured aneurysms. There was only 1 suspected death from a recurrent aneurysm, which occurred 11 years after treatment of the index aneurysm.

Epilepsy caused 10% of the aneurysm-related deaths in our series. The incidence of epilepsy after SAH has been reported to be 12% to 19%. Pneumonia as a late sequela of SAH was the cause of death in 2 bedridden patients.

Long-Term Excess Mortality

Previously, SAH patients who recovered well after the treatment of a ruptured aneurysm were believed to attain the life expectancy of the general population. In a study focused on distal anterior cerebral artery aneurysms, no excess mortality was found in patients surviving more than 3 years. However, evidence for excess mortality even after successful treatment of a ruptured aneurysm has been reported, independent risk factors being male sex, high age at SAH, and aneurysm location at basilar tip. In a study by Ronkainen et al., the excess mortality was not explained by the new SAH events; instead, systemic cardiovascular diseases were the most important causes of death in the long run.

Pediatric patients with aneurysm appear to be a special group. The majority of the aneurysms in our series had anterior locations, especially in internal carotid artery and anterior communicating artery, differing from that of adults (middle cerebral artery in >30% in Finnish patients). The excess mortality in them was clearly caused by de novo aneurysms and SAH-related causes. Even though the mean follow-up time in the present study was over 25 years, the mean age of the patients at the end of follow-up is still quite young at 50 years. Only 1 cardiovascular death was diagnosed.

Summary

There was a significant long-term excess mortality in pediatric patients with aneurysm even decades after successful treatment of a ruptured aneurysm, being most significant in boys. However, there was no increased long-term excess mortality in patients with unruptured aneurysms after surviving 1 year postdiagnosis. The causes of death were mainly aneurysm-related, ie, rebleedings from incompletely treated aneurysms, seizures, and de novo and recurrent aneurysms. Our results emphasize the importance of angiographically verified complete occlusion of aneurysms followed by lifelong follow-up of pediatric patients with cerebral aneurysm.

Acknowledgments

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Disclosures

None.
References
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