Morbidity and Mortality Associated with Intracranial Aneurysms.
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Abstract: Subarachnoid hemorrhage (SAH) is bleeding into the subarachnoid space. It may result from a rupture of an intracranial aneurysm, bleeding from an arteriovenous malformation, hypertensive intracerebral hemorrhage with extension into the subarachnoid space, hemorrhage from an intracranial tumor, trauma, and hematologic disorders. If trauma is eliminated as a cause of SAH, more than 80% of SAHs are due to rupture of an intracranial aneurysm. This paper will focus on morbidity and mortality associated with ruptured and unruptured intracranial aneurysms.

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Introduction
Most intracranial aneurysms are idiopathic, i.e., the exact cause is unknown. Factors contributing to their evolution include (1) developmental defects of the arterial wall, which may be affected by genetic factors; (2) hypertension or hemodynamic stress; and (3) atherosclerosis. Intracranial aneurysms also occur in some patients with polycystic kidney disease, fibromuscular dysplasia, Ehlers-Danlos syndrome, Marfan syndrome, infection, and trauma. Intracranial aneurysms are usually not detected until SAH occurs. Rarely, an unruptured aneurysm is discovered incidentally during investigation for other brain lesions or as a result of screening tests in individuals known to be at risk for an aneurysm.

Clinical studies estimate that the prevalence of intracranial aneurysms in the general population is between 0.5% and 1.0%. Epidemiologic studies indicate that the age-specific incidence of aneurysmal SAH increases with age. In the Framingham study, for example, the annual incidence of SAH in the 60-69-year and 70-88-year age groups was 37 and 79 per 100,000, respectively. The highest population-based rates for SAH are reported in Japan and Finland.

The diagnosis of SAH is usually made with a computed tomography (CT) scan, with the greatest diagnostic accuracy during the first 24 hours. After the first day, if the CT scan was negative, lumbar puncture is performed to examine the cerebrospinal fluid for the presence of blood. Cerebral angiography is the current standard for confirming that the SAH was due to a ruptured intracranial aneurysm. Approximately 10% to 20% of cerebral angiograms performed for SAH do not find the source of bleeding. Repeat angiography 1 week later will disclose a previously unrecognized aneurysm in an additional 1% to 2% of cases. Whether the additional small yield is worth the cost and morbidity of the second angiogram is a source of controversy. Based on advances in technolo-
gy, it is possible that magnetic resonance angiography will replace conventional angiography as the primary diagnostic modality for intracranial aneurysms.\(^6\)

Historically, carotid ligation was performed prior to 1970 in an attempt to prevent rebleeding. While more effective than conservative management, i.e., bed rest and antihypertensive medications, this surgery has largely been abandoned in favor of direct surgical treatment of the aneurysm. Wrapping or coating of intracranial aneurysms with materials such as muscle or surgical gauze is another obsolete technique that is now reserved for cases in which the aneurysm is otherwise untreatable. In a long-term university study from Genoa and Sassari, Italy, the likelihood of rupture following this form of treatment approximated the risk (1% per year) associated with untreated, unruptured aneurysms.

Direct surgical clipping is the most routine and definitive treatment of an intracranial aneurysm. With this method, the neck of the aneurysm is obliterated by applying a clip that stops blood flow into the aneurysmal dome but preserves the parent artery. Most patients are cured by this procedure. A potential concern is improper clip placement, identified via postoperative angiography in up to 8% of cases.\(^2\) There is a possibility of recurrent hemorrhage in these patients but insufficient studies have been performed to quantify the risk.

In a subset of patients, surgical clipping may be a high risk procedure because of the size or site of the aneurysm, the presence of a wide or calcified aneurysmal neck, or poor condition of the patient. Endovascular treatment may be used in these situations.\(^7\) This technique relies on the placement of intravascular balloons or coils to obliterate the aneurysm. Successful occlusion of the aneurysm has been reported in a number of studies, but early and late rebleeding has been observed with both techniques. As physicians gain more experience, endovascular obliteration will probably replace surgical clipping in most patients.

Despite advances in diagnostic, medical and surgical technologies, overall mortality due to aneurysmal SAH has not decreased substantially during the past 30 years. This is because many patients either die before receiving medical care or have already suffered severe brain injury by the time they reach the hospital.\(^1\) Among patients who survive to reach the hospital, mortality rates following nontraumatic SAH average 25% and significant morbidity occurs in 50% of survivors.\(^2\) Patients who survive a first SAH often experience a second hemorrhage before the aneurysm can be clipped, with a case-fatality rate of 70% for patients who rebleed. The risk of rebleeding is 3% to 4% in the first 24 hours, 1% to 2% per day during the first month, and 3% per year after 3 months.\(^2\)

RUPTURED ANEURYSMS
Natural History
Occasionally a ruptured aneurysm is not repaired because of its size, inaccessibility, or the patient’s age or physical condition. These individuals are at risk of sudden death due to rebleeding.

A life table analysis reported the long-term prognosis of 266 British patients with aneurysmal SAH who were treated nonsurgically.\(^8\) The study spanned the years 1944 to the mid-1970s, and was limited to subjects with a single intracranial aneurysm confirmed by angiography who survived a minimum of 6 months after the hemorrhage. Mean follow-up was 9 years (range 6 months to 22 years). Expected deaths were based on English Life Table No. 12. Thirty-four patients had a nonfatal rebleed and were withdrawn from the study. There were 84 deaths: 51 fatal rebleeds and 33 deaths due to other causes. During the first 10 years, rebleeding occurred at a rate of 3.5% per year.
Overall relative mortality was 316%. Relative mortality decreased with duration since SAH: 6 months to 5 years- 413%; 5 to 10 years- 263%; 10 years and longer- 211%. Decreasing relative mortality was also observed with age: 40 to 49 years- 739%; 50 to 59 years- 421%; and 60 years and older- 166%.

A second life table analysis reported the outcome of 568 American patients who experienced a ruptured intracranial aneurysm between 1958 and 1965. All subjects were treated conservatively (bedrest and antihypertensive medications), and follow-up was obtained on 96% of patients at 5 years, 94% at 10 years, 79% at 15 years, and 68% at 20 years. Mortality ratios were calculated for patients who survived more than 6 months after the hemorrhage. Expected deaths were determined from 1970-74 group life insurance experience. The relative mortality for aneurysms of all sites combined over the period 6 months to 20 years post-SAH was approximately 300%. Relative mortality generally decreased with time elapsed: 6 months to 5 years- 400%; 5 to 10 years- 270%; and 10 to 20 years- about 200%. SAH of unknown origin was associated with a relative mortality of 140%.

Subarachnoid Hemorrhage Of Unknown Origin
Subarachnoid hemorrhage of unknown origin refers to a situation in which angiographic evaluation and other neuroimaging tests fail to find a cause for the hemorrhage. This circumstance occurs in as many as 20% of patients with SAH. These patients generally have a favorable prognosis (as evidenced by the life table data reported by Lew et al) although large series report rebleed rates of 2% to 10%, usually in the first few years after the initial SAH.

Most cases of angiogram negative SAH are due to one of two causes:

- Perimesencephalic hemorrhage- These hemorrhages are due to rupture of a small superficial artery which arises directly from the Circle of Willis or the basilar artery. It is thought this type of hemorrhage obliterates the source of bleeding, and that there is very little risk of recurrence.

- Nonvisualized aneurysm- Proposed mechanisms to explain the failure of angiography to detect these aneurysms include thrombosis of the aneurysm, local vasospasm, and obliteration of the aneurysm by rupture. In each of these circumstances, the patients remain at risk for re-rupture due to resumption of filling of the vascular defect by arterial blood.

A cooperative study from the Netherlands reported the outcome of patients with SAH and negative angiography according to the pattern of hemorrhage on third-generation computed tomography. Follow-up averaged 45 months (range 6 to 96 months). Hemorrhage was classified as perimesencephalic (confined to an area near the midbrain of the brainstem) or aneurysmal (characteristic of CT scans in patients with proven aneurysms). None of the 77 patients with a perimesencephalic CT pattern had a rebleed or reported sudden bouts of headache reminiscent of their prior hemorrhage. In contrast, 4 of 36 subjects with an aneurysmal CT pattern had a second SAH. The authors concluded that use of the term “angiogram-negative subarachnoid hemorrhage” was no longer justified, and recommended that these patients be classified for prognostic purposes according to the pattern of hemorrhage on computed tomography.

An earlier report from University Hospital in Lund, Sweden provides an indication of the prognosis of patients with SAH of unknown origin when third-generation computed tomography scans are not performed. The authors followed a cohort of 127 patients with SAH in whom no cause of bleeding could be found despite pan-angiographic evaluation (bilateral carotid angiography and
uni- or bilateral vertebral angiography). The SAHs occurred between 1968 and 1978, and follow-up averaged 5.4 years (range 1 to 12 years). Most subjects were between 40 and 70 years of age. Patients were excluded from the study if there was any suspicion of intracerebral hemorrhage or if cerebral angiography was technically defective.

Of the 119 patients who survived the 2nd week, 94% (n=112) returned to at least part-time work, and 82% (n=98) returned to full activity. Persistent symptoms such as fatigue, frequent headaches, and dizziness were reported by 22% of patients who returned to full activity. After the first week post-SAH, there were only 3 recurrent bleeds. In 2 patients, the second SAH occurred 2 and 5 years, respectively, after the first. Repeat angiography demonstrated an intracranial aneurysm in each patient; these were surgically clipped. A third patient rebled 1 month after the first SAH; repeat cerebral angiography was normal and recovery was complete.

Subarachnoid Hemorrhage In The Elderly

Historically, ruptured intracranial aneurysm was treated less aggressively at the older ages because of poorer morbidity and mortality following surgery. This pattern has changed with improvements in medical and surgical management. For example, the Shimane Prefectural Central Hospital, Izumo, Japan reported the outcome of elderly patients who were treated for SAH between 1980 and 1985 as compared to 1986 to 1990. They observed a 26% improvement in 5-year survival in patients aged 70 to 79 years who were treated surgically.

The Department of Clinical Neurosciences in Edinburgh, Scotland audited the experience of all patients aged 60 years or older with a confirmed diagnosis of SAH (n=186) or symptomatic unruptured intracranial aneurysm (n=13) who were admitted between 1982 and 1990. 43.8% of patients were in the 60-64-year age group, 32.2% were in the 65-69-year group, and 24% were aged 70 years or older. 70% were females. Median duration of follow-up after hospital discharge was 40 months (range 3 to 120 months). Four patients were lost to follow-up.

The following data were reported in patients who were discharged after making a good recovery (n=113) or who were moderately disabled (n=14). A subsequent diagnosis of stroke referred to ischemic stroke or intracerebral hemorrhage rather than SAH.

- Surgically treated (n=73)- Causes of death included fatal stroke (n=3), gradual neurologic deterioration (n=1), and unrelated illness (n=6). Two patients suffered a nondisabling stroke.

- Angiogram negative (n=32)- One patient suffered a fatal stroke, 4 died from unrelated illnesses, and 1 patient had a nondisabling stroke. Since four-vessel angiography was performed in only 16% of patients, it is likely that some of the subjects in this group had intracranial aneurysms that would have been detected with a more detailed medical evaluation.

- No angiogram (n=14)- One fatal stroke occurred and three other patients died from unrelated causes. Two patients suffered a nondisabling stroke.

- Angiogram positive, no operation (n=8)- This group included subjects with a ruptured intracranial aneurysm that was not surgically repaired. One patient had a confirmed fatal SAH 3 months after discharge. Three additional deaths were due to unrelated illness.

Outcome was less favorable in the 17 subjects who were severely disabled when discharged from the hospital. Seven patients died, 3 showed varying degrees of improvement, and the others remained the same.

A final group consisted of 11 patients who were discharged in good condition with a known intracranial aneurysm that had never ruptured.
Median duration of follow-up was 34 months (range 3 to 119 months). Two deaths were observed; 1 patient died 3 months later due to SAH, and another died from renal failure.

Morbidity
Many patients suffer long-term physical, cognitive, or emotional disabilities after rupture of an intracranial aneurysm. Data from multiple studies indicate that only 30% to 46% of patients completely recover, and 25% to 75% experience emotional or psychological disturbances in daily living.15

Investigators at Hôpital Neurologique, Lyon, France found that successful surgical repair of a ruptured intracranial aneurysm did not always predict a return to previous activities.14170 patients were followed for periods ranging from 1 to 14 years (mean 3.6 years) after surgery. Patient status was classified as either good (little or no post-SAH sequelae- 154 patients) or fair (mild sequelae, e.g., mild hemiparesis or minor psycho-intellectual impairment- 18 patients). Approximately one-third of the group did not resume previous activities or resumed activities at a lesser level. Explanations included (1) work that was either physical or involved a great deal of responsibility, (2) older age, i.e., patients chose early retirement, and (3) psychological, emotional or intellectual difficulties (this factor was found most frequently). The poor correlation between neurologic condition and functional status was also observed in a study from Technical University in Aachen, Germany.15 Many patients with a favorable neurologic outcome after clipping of a ruptured intracranial aneurysm did not return to their prior level of activity because of persistent neuropsychological deficits.

A study from Brook General Hospital, London, reported much more favorable results. Investigators followed 70 patients who survived a SAH (ruptured aneurysm- 59; arteriovenous malformation- 7; unknown cause- 4), 60 of whom were treated surgically.16 None of the participants had any neurologic deficit at time of discharge but mild cognitive impairment was observed in some cases. At 3 months post-discharge, almost everyone was functioning at or near their premorbid level and most patients felt they were back to normal except for tiring more easily than usual. Minimal cognitive difficulties were noted in a few subjects. By 1 year, the only common residual symptom was fatigue and most people considered that the experience of the SAH was behind them. None of the subjects showed evidence of cognitive deficit. Many patients had problems related to their quality of life, but these were rarely attributable to the effects of the SAH. Most previously employed people returned to work 3 months after their illness, initially part time, with most working full time within weeks. Many patients chose early retirement, and a few decided to leave an occupation in which they had long been unhappy. For most people, returning to work at the earliest possible moment was one of the most therapeutic steps in their recovery. There was little benefit in extending their convalescence beyond 3 months.

UNRUPTURED ANEURYSMS
Natural History
The natural history of unruptured intracranial aneurysms was reported in a study from Okayama University Medical School, Okayama, Japan.17 Fifty-four patients with 72 unruptured aneurysms were followed for an average of 43.7 months (range 2 days to 116 months). The aneurysms were not clipped because of patient choice or physical condition. Subjects were initially identified for a variety of reasons including symptoms caused by an unruptured aneurysm; multiple aneurysms in patients who had experienced a SAH (the ruptured aneurysm was clipped); and rare instances in which aneurysms were discovered incidentally during investigation for other intracranial lesions or as a result of screening tests in healthy individuals (e.g., magnetic resonance angiography).

Aneurysmal rupture was observed in 11 of the 54 patients. Ten of the 11 ruptured aneurysms
resulted in death. The greatest likelihood of rupture was in patients with an aneurysm that had previously caused symptoms. Rupture occurred in 4 of 22 patients under 59 years, 7 of 20 patients between 60 and 69 years, and none of the 12 patients over 70 years of age. Ruptured aneurysm was the cause of death in 83.3% of subjects under 59 years, 55.6% of those between 60 and 69 years, and 0% of those over 70 years of age. The mean annual bleeding rate was 1.92% per year. Risk of bleeding was significantly greater for aneurysms with a diameter between 10 and 19 mm, and for aneurysms that were multilobed rather than unilobed.

Predictors Of Future SAH
Intracranial aneurysms that have never bled are reported to rupture at a rate of 1% to 1.4% per year. Given the catastrophic outcome of this event, it is important to identify factors that correlate with future bleeding. These factors are summarized below.

Size
The size of an aneurysm is determined by the largest diameter of the dome. This parameter is believed to be the most important factor for predicting subsequent bleeding. Various authors who have tried to determine the critical size for rupture have specified sizes ranging from 5 to 8 mm. From a histopathologic perspective, a portion of the wall becomes extremely thin once the aneurysm reaches a size of 4 or 5 mm. This area is thought to be the point of subsequent rupture. Based on clinical and pathological studies, it is reasonable to believe that the critical size for SAH from an intracranial aneurysm begins at 4 or 5 mm in diameter, and that it is hazardous to leave aneurysms of more than 10 mm untreated. This conclusion is supported by combined data from 3 studies indicating a long-term risk of rupture of 3.8% for aneurysms 9 mm in diameter or smaller; 29.6% for those 10 to 19 mm in size; and 35.5% for aneurysms 20 mm or larger. Some authors recommend clipping aneurysms that are larger than 5 to 7 mm if the patient is an acceptable surgical risk.

Symptoms
Approximately 10% of aneurysms cause symptoms (pain, cranial nerve palsy, visual field deficits, etc.) due to pressure on adjacent structures. The distinction between symptomatic and asymptomatic has prognostic implications since the rate of rupture is much higher with symptomatic aneurysms, perhaps because of their large size. In a 5-year cooperative study of aneurysmal hemorrhage, 26% of patients with symptomatic unruptured aneurysms died of SAH, in comparison with 2.6% of those with asymptomatic aneurysms. The current standard of medical care calls for immediate surgical intervention in patients with symptomatic unruptured aneurysms.

Hypertension
A number of studies have concluded that the risk of SAH in patients with unruptured intracranial aneurysms is higher in patients with hypertension. Certain combinations (e.g., hypertension plus large size) were particularly unfavorable.

Location
Although unruptured cerebral aneurysms are relatively uncommon in the posterior circulation, the risk of bleeding is greater for aneurysms of the vertebrobasilar and posterior cerebral arteries as compared to those in the anterior circulation.

Increasing size
Few studies have considered the significance of aneurysms that increase in size over time. The importance of this parameter will be clarified with further improvements in non-invasive tests such as magnetic resonance angiography.

Shape
The few studies that have addressed aneurysm shape have found an increased risk of rupture with multilobed as compared to unilobed aneurysms.

Age
A statistical analysis from Tufts-New England
Medical Center in Boston estimated the lifetime risk of rupture of an asymptomatic intracranial aneurysm. As expected, the likelihood of eventual rupture was greater if the aneurysm was discovered at a younger age. Lifetime risks of rupture by age were as follows: age 20-16.6%; age 30-16.1%; age 40-14.4%; age 50-10.3%; and age 60-4.68%.

Multiple Intracranial Aneurysms
Multiple aneurysms occur in 20% of patients who have an intracranial aneurysm. There is no significant difference in the risk of rupture of multiple as compared to single aneurysms.

Gender
Unruptured intracranial aneurysms are more common in women than in men, but few studies have addressed gender differences in outcome. The study by Asari et al observed a similar prognosis in males and females.

UNDERWRITING CONSIDERATIONS

Treatment
• Most patients are cured after the aneurysm is clipped.

• Endovascular forms of treatment are becoming more common. With improvements in technique, cure rates may approach those achieved by clipping.

• There is a significant risk of rebleeding with older surgical procedures such as carotid ligation and wrapping or coating of the aneurysm.

Ruptured Aneurysms That Are Not Repaired
• If a ruptured aneurysm is not repaired, the risk of rebleeding averages 3% per year after the first 3 months post-SAH.

• Excess mortality persists for at least 20 years after the hemorrhage.

• Relative mortality decreases with longer durations since SAH and with increasing age.

Subarachnoid Hemorrhage Of Unknown Origin
• Advances in therapy have resulted in significant improvement in survival of elderly patients.

• Older aged insurance applicants with a history of ruptured intracranial aneurysm can be evaluated with the same underwriting parameters that are used for younger individuals.

Morbidity
• Some patients do not return to their previous activities and/or experience persistent psychological, emotional or intellectual difficulties in spite of successful surgical treatment and neurologic recovery.

• A favorable outcome is likely if patients are functioning at or near their premorbid level at 3 months post-hospital discharge.

• For most people, returning to work at the earliest possible moment is one of the most therapeutic steps in their recovery. There is little benefit in extending convalescence beyond 3 months.

Unruptured Intracranial Aneurysms
• Size is the most important factor for predicting future bleeding. The critical size for SAH begins at 4 or 5 mm, and risk increases dramatically for aneurysms of 10 mm or larger.

• Risk of rupture is very high if the aneurysm causes symptoms.

• Other factors which increase the likelihood of rupture include hypertension, aneurysms of the vertebrobasilar and posterior cerebral arteries, and multilobed aneurysms.

• The likelihood of eventual rupture is greater if the aneurysm was discovered at a younger age.

• The importance of increasing size of an aneurysm has not been determined.
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