CLINICAL PRACTICE

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Subarachnoid Hemorrhage

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A 17-year-old boy had a sudden headache and briefly lost consciousness while at soccer practice. On arrival at the emergency department, he appeared drowsy and reported having the worst headache he had ever had. His blood pressure was 186/92 mm Hg. The neurologic examination was normal. Computed tomography (CT) of the head without contrast enhancement showed diffuse subarachnoid hemorrhage and enlargement of the temporal horns of the lateral ventricles. How should this patient be further evaluated and treated?

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THE CLINICAL PROBLEM

Subarachnoid hemorrhage without a preceding trauma is caused by the rupture of an intracranial aneurysm in 80% of cases; other causes include vascular malformations and vasculitis. Subarachnoid hemorrhage accounts for 5 to 10% of all strokes in the United States,[1] and affected patients tend to be younger than those affected by other subtypes of stroke, which results in a greater loss of productive life.[2] Among the patients with aneurysmal subarachnoid hemorrhage who survive, half suffer long-term neuropsychological effects and decreased quality of life.[3] Early identification and treatment of the aneurysm can prevent aneurysm rerupture and can address sequelae from the initial rupture. Intervention may be appropriate in cases of subarachnoid hemorrhage that are not caused by aneurysms (e.g., cases involving arteriovenous malformation), but up to 10% of cases of nonaneurysmal subarachnoid hemorrhage involve no vascular abnormality, and surgical or endovascular treatment is not considered to be necessary.[4]

INTRACRANIAL ANEURYSMS

Intracranial aneurysms occur in 1 to 2% of the population.[5] Aneurysms typically form at branch points along intracranial arteries (Fig. 1 and the interactive graphic); hemodynamic stress on the wall between the two exiting branches weakens that region.[6] The risk of intracranial aneurysms is increased among persons with a family history (defined as at least one first-degree relative who has had an intracranial aneurysm, with a greater risk if two or more first-degree relatives have had such an event), among persons with certain connective-tissue disorders (e.g., the Ehlers–Danlos syndrome), and among persons with polycystic kidney disease.[7,8] Factors associated with an increased risk of aneurysm rupture include black race, Hispanic ethnic group, hypertension, current smoking, alcohol abuse, use of sympathomimetic drugs, and an aneurysm larger than 7 mm.[7,9]

KEY CLINICAL POINTS

SUBARACHNOID HEMORRHAGE

- Subarachnoid hemorrhage from a ruptured intracranial aneurysm is a life-threatening stroke that affects younger patients than those affected by other forms of stroke.
- Aneurysmal subarachnoid hemorrhage is diagnosed by confirmation of subarachnoid hemorrhage on a computed tomographic (CT) scan of the head and by confirmation of an aneurysmal source by CT angiography of the head, catheter angiography of the head, or both.
- The prevention of aneurysm rerupture is the first goal of treatment. Randomized, controlled trials suggest that aneurysms that are judged to be treatable by either open surgery or endovascular intervention are better treated by the latter; however, open surgery is preferred in certain cases.
- Vasospasm and delayed cerebral ischemia contribute to the occurrence of complications and death after successful occlusion of an aneurysm and remain the major challenge of aneurysmal subarachnoid hemorrhage.
- Decisions about treatment for aneurysms and about the management of aneurysmal subarachnoid hemorrhage sequelae are best made at high-volume centers by experienced surgeons, interventionalists, and neurologic intensive care experts.

The rate of detection of unruptured intracranial aneurysms has increased as the use of CT and magnetic resonance imaging (MRI) has become more common.[10] The treatment of unruptured intracranial aneurysms remains controversial and is not addressed here.

The reported incidence of aneurysmal subarachnoid hemorrhage varies widely across the world, from 2.0 cases per 100,000 persons in China to 22.5 cases per 100,000 persons in Finland[11]; variation may in part reflect differences in the rates of detection across countries.[12,13] The 2003 Nationwide Inpatient Sample estimated 14.5 hospitalizations for aneurysmal subarachnoid hemorrhage per 100,000 U.S. adults per year.[14] Aneurysmal subarachnoid hemorrhage is more common among women than among men, and the incidence increases with age to a peak among persons in their 50s.[14]

An interactive graphic showing management of subarachnoid hemorrhage is available at NEJM.org

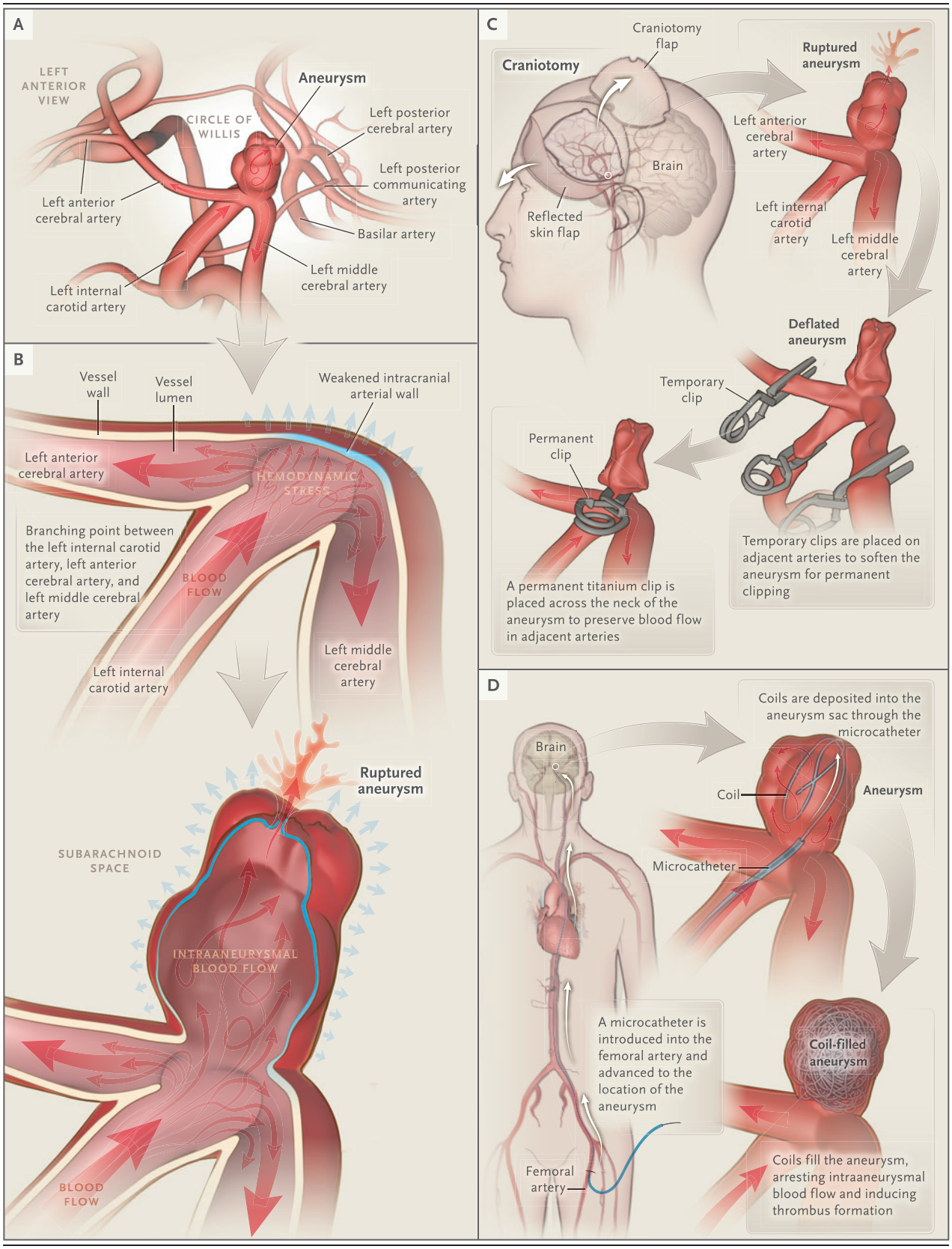
When an aneurysm ruptures, it is an intracranial catastrophe. Blood pushes into the subarachnoid space at arterial pressure until the intracranial pressure equalizes across the rupture site and stops the bleeding, with thrombus formation at the bleeding site. The reported case fatality rate is 25 to 50%,[15] owing to consequences of either the original bleeding or rerupture; this estimate does not fully account for patients who die before receiving medical attention.[16]

SIGNS AND SYMPTOMS

The hallmark presenting symptom of aneurysmal subarachnoid hemorrhage is "the worst headache of my life."[17] The onset of the headache is sudden, and the headache is severe and reaches maximal intensity in seconds (known as a thunderclap headache). In 10 to 40% of patients, this headache is preceded by a warning leak or "sentinel"

Figure 1 (facing page). Repair of Aneurysms That Have Caused Subarachnoid Hemorrhage.

The anatomy of the subarachnoid space and the circle of Willis is shown in Panel A. A major artery (the internal carotid artery) enters the skull from below and then follows a course through the subarachnoid space, giving off perforating branches that supply the parenchyma. High pulsatile pressure at branching points of the proximal artery (arrow, Panel B) soon after the arterial wall sheds much of its supporting adventitia can promote the formation of saccular aneurysms in susceptible persons. In such cases, an aneurysm forms at the branch point of an artery, where the arterial pulsation stress is maximal. Most lesions remain silent until rupture occurs, at which time blood is rapidly released into the subarachnoid space, leading to early effects such as intracranial pressure elevation, parenchymal irritation, edema, and hydrocephalus and delayed effects, such as vasospasm and delayed cerebral ischemia. Open surgical repair of such an aneurysm (Panel C) involves exposing the aneurysm and the adjacent normal arteries so that the surgeon can apply a titanium clip on the neck of the aneurysm, which effectively excludes it from arterial circulation. Removal of portions of the skull base provides improved access and operative exposure for the surgeon without the need for substantial brain retraction. The aneurysm is then collapsed and the field inspected to make sure that no branches are compromised by the clip placement. The inner walls of the aneurysm base are approximated by the clip, which generally provides a lifelong cure of the lesion. Endovascular repair of such an aneurysm (Panel D) involves the navigation of an intraarterial catheter through the circulation under fluoroscopic guidance until the catheter tip is in the lumen of the aneurysm. With the use of the catheter, platinum coils are delivered and packed into the lumen of the aneurysm, which slows or prevents blood flow into the aneurysm and leads to thrombus formation, effectively blocking arterial blood from entering the aneurysm. Angiographic examination of the result confirms flow through the normal arterial branches. Not all aneurysms can be treated with endovascular repair (some will have to be treated with surgery), but endovascular repair can treat many aneurysms without a visible scar.



headache,[18] which typically occurs within 2 to 8 weeks before overt subarachnoid hemorrhage.[9,10] Although hemorrhage can occur during physical or psychological stress, it occurs more commonly during activities of daily living.[19] Associated symptoms or signs include nausea, vomiting, or both; photophobia; neck stiffness; focal neurologic deficits; and a brief loss of consciousness.[20] More severely affected patients present with altered mental status, from mild lethargy to profound coma; the degree of encephalopathy at presentation is the major determinant of the prognosis.

Aneurysmal subarachnoid hemorrhage accounts for only 1% of all headaches evaluated in the emergency department.[21] Consequently, a sentinel headache may be dismissed as a migraine headache or other headache without further evaluation; the likelihood of death or disability is four times as high among patients in whom a sentinel headache is misdiagnosed as it is among patients in whom a sentinel headache is correctly diagnosed.[22] Therefore, a high index of suspicion for aneurysmal subarachnoid hemorrhage from the patient's history is warranted and potentially lifesaving.

STRATEGIES AND EVIDENCE

EVALUATION

Initial Stabilization

If a patient survives the initial rupture of the aneurysm and reaches medical attention, management of the aneurysmal subarachnoid hemorrhage is directed at reversing or stabilizing acute life-threatening sequelae, particularly in the case of comatose patients. Establishing a secure airway, normalizing cardiovascular function, and treating seizures are common first steps before diagnostic studies are pursued.

Grading Systems Used for Patients with Subarachnoid Hemorrhage

A variety of grading systems correlate the clinical status of the patient at the time of presentation with the long-term neurologic outcome. The two most commonly used grading systems are the Hunt–Hess classification and the World Federation of Neurosurgical Societies classification (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[23,24] In both systems, the severity of encephalopathy is the major determinant of grade. Aneurysm rupture produces immediate widespread brain dysfunction and "late" events days after the rupture, both of which affect the outcome through mechanisms that are only partially understood.[25,26]

Imaging

CT of the head without contrast enhancement is the first essential step in the diagnosis of subarachnoid hemorrhage (Fig. 2).[20,27] In the first 3 days after the onset of symptoms, the sensitivity of the CT scan is close to 100%, but it subsequently declines to 50% by 5 to 7 days after the onset of symptoms.[28,29] CT of the head may also show a space-occupying hematoma or acute hydrocephalus — consequences of aneurysm rupture for which patients are considered to require immediate surgical attention. If the CT of the head is negative but clinical suspicion is high, additional tests are indicated.

Lumbar puncture has been used to detect blood or xanthochromia in cerebrospinal fluid,[30] but lumbar puncture performed after a negative CT of the head is now of debated value owing to the low prevalence of subarachnoid hemorrhage and the difficulty in distinguishing between subarachnoid hemorrhage and trauma related to the lumbar puncture.[29] MRI, with fluid-attenuated inversion recovery, proton density, and gradient-echo sequences, is exquisitely sensitive to heme in the cerebrospinal fluid.[31] CT angiography, which is now commonly performed at the time of the initial CT, can show that an aneurysm is present and can provide the essential information in the case of patients who present in extremis with a large intraparenchymal clot that is thought to require immediate surgical evacuation.[32] CT angiography can now reliably detect aneurysms as small as 2 mm, but tiny blister aneurysms or aneurysms filled with thrombi may be missed.

Digital subtraction angiography remains the standard for diagnosing an aneurysm and for defining relevant anatomy for treatment (Fig. 3).[32] The combination of three-dimensional angiography reconstructions with two-dimensional angiography in digital subtraction angiography is more sensitive for detecting aneurysms and provides more detailed anatomical data than digital subtraction angiography alone and also helps in planning treatment.

MEDICAL INTERVENTIONS TO REDUCE THE RISK OF RERUPTURE

Patients in whom aneurysm rerupture occurs have a much higher risk of death and neurologic injury than patients who have a single aneurysm rupture.[33] The risk of rerupture is 4 to 14% in the first 24 hours after aneurysmal subarachnoid hemorrhage,[34,35] but the risk remains elevated for 30 days after the initial rupture if the aneurysm is not treated.

Hypertension can increase the risk of rerupture, but the goals of treatment remain poorly defined, with few trial data available to support specific blood-pressure targets.[36] Antifibrinolytic therapy may stabilize the initial thrombus at the bleeding site. In a randomized, controlled trial, the incidence of aneurysm rerupture was 2% among the patients who received antifibrinolytic therapy as compared with 11% among patients who did not receive such therapy.[37] Although antifibrinolytic therapy may have benefit when aneurysm treatment is delayed (e.g., when a patient is transferred to another facility), its use did not improve overall outcomes and is associated with an increased risk of deep venous thrombosis and delayed cerebral ischemia.[38] Seizures occur in up to 20% of patients, especially in patients with intraparenchymal bleeding, and can cause hemodynamic instability that precipitates aneurysm rerupture[39]; however, data are lacking from randomized trials to support routine administration of antiseizure medication, and routine prophylaxis is not recommended.

TREATMENT OF RUPTURED CEREBRAL ANEURYSMS

Clinical experience and randomized trials have shown that treatment for ruptured aneurysms is safe and eliminates the immediate risk of aneurysm rerupture.[40-43] Treatment can be achieved by means of open surgical clipping or endovascular aneurysm obliteration; both treatments should be provided by specialized, experienced practitioners at high-volume centers.[44]

Surgical clipping of a ruptured aneurysm requires opening the skull (craniotomy). With the use of the operating microscope, the subarachnoid spaces around the cerebral arteries are opened at the base of the skull to mobilize delicate brain tissue without injury (Figs. 1 and 3). Once the aneurysm is exposed, a titanium clip is placed across the neck of the aneurysm to mechanically close the sac at its neck while preserving blood flow through the adjacent normal arteries.

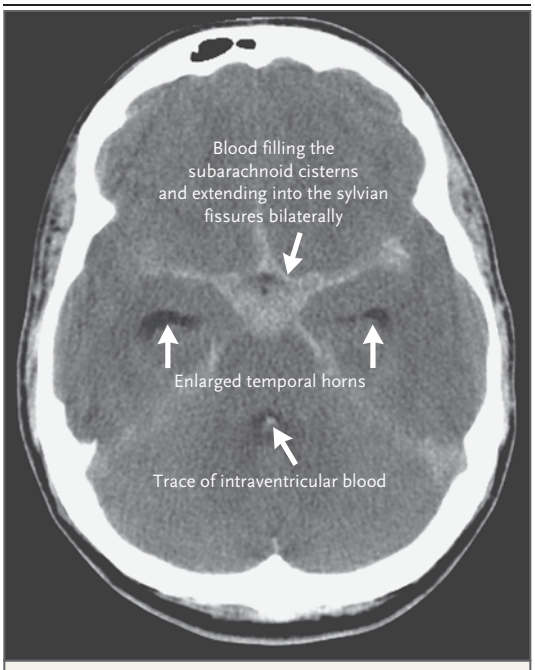


Figure 2. CT Scan of the Head Showing Evidence of Subarachnoid Hemorrhage.

Subarachnoid hemorrhage, as seen on axial CT, varies from none detected, to diffuse deposition of a thin layer of blood (<1 mm thick) in the cerebrospinal fluid–filled cisterns at the base of the brain, to a thick blood clot (≥1 mm thick) in the cerebrospinal fluid–filled cisterns around the circle of Willis, as seen in this patient from the vignette. Subarachnoid hemorrhage can extend beyond the basal cisterns into the sylvian fissures or into the ventricles or brain parenchyma. The distribution of blood offers clues to the location of the aneurysm. The greater amount of blood in the left basal cisterns than in the right points to a likely location of the aneurysm on the left side of the cerebral circulation. The enlarged temporal horns are evidence of hydrocephalus; in most patients (and especially in younger patients) the temporal horns should not be visible.

Endovascular treatment of a ruptured aneurysm involves navigating a catheter under fluoroscopic guidance from an entry point in the arterial circulation (typically the femoral artery in the groin) up to the parent artery of the aneurysm (Figs. 1 and 3). A microcatheter is then advanced into the aneurysm sac and metal coils are deposited into the aneurysm lumen through the microcatheter, a process that arrests intraaneurysmal blood flow and induces thrombus

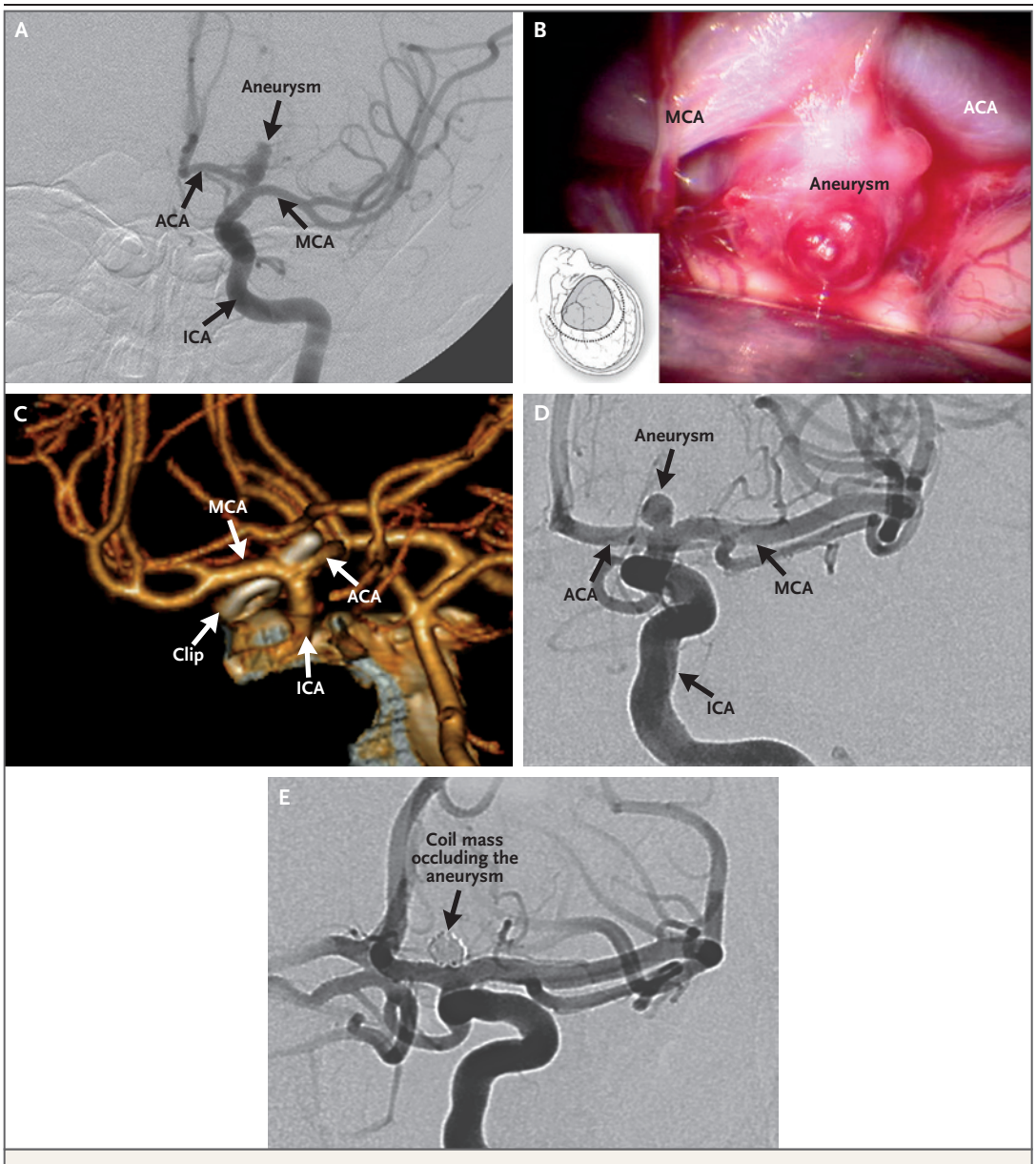


Figure 3. Angiogram Showing Internal Carotid Artery Aneurysms before and after Treatment.

An angiogram obtained in the patient in the vignette shows an aneurysm in the left internal carotid artery (ICA). The aneurysm originates at the point where the ICA bifurcates into the arterial cerebral artery (ACA) and the middle cerebral artery (MCA) (Panel A). At the time of surgery, the aneurysm was exposed and was shown to be multilobulated, very thin-walled, and with friable daughter lobules (Panel B; the inset shows the location of the aneurysm in the patient's brain). CT angiography shows the placement of a surgical clip and complete obliteration of the aneurysm (Panel C). An angiogram obtained in a different patient shows a similarly located ICA aneurysm (Panel D) and the results obtained with endovascular treatment (Panel E).

formation, thereby occluding the aneurysm and eliminating the immediate risk of rerupture.

Two randomized trials have compared endovascular treatment with open-surgical treatment for ruptured intracranial aneurysms: the International Subarachnoid Aneurysm Trial (ISAT) and the Barrow Ruptured Aneurysm Trial (BRAT).[40-43] Despite a significantly higher rate of obliteration and greater durability with open-surgical treatment than with endovascular treatment, both tri-

als showed better functional outcomes at 1 year with endovascular treatment than with open-surgical treatment (Table S2 in the Supplementary Appendix).

In ISAT, a multicenter trial involving patients whose aneurysms were considered to be suitable for either open-surgical treatment or endovascular treatment, rates of dependency or death at the 1-year follow-up were 23.5% in the endovascular-coil group and 30.9% in the open-surgery group (absolute difference, 7.4 percentage points; 95% confidence interval, 3.6 to 11.2). In addition, the endovascular-coil group had a lower mortality rate and a lower risk of seizures through the 7-year follow-up than did the open-surgery group; rebleeding, although infrequent, was more common in the endovascular-coil group than in the open-surgery group. BRAT, a single-center trial, showed a similar benefit of endovascular treatment as compared with open-surgical treatment with respect to functional outcomes at 1 year, although the differences between the two groups were no longer significant at year 3 or year 6. Unlike ISAT, BRAT did not include as an entry criterion the need for the anatomy of the aneurysm to be suitable for either procedure, and more than a third of the patients who were randomly assigned to receive endovascular treatment crossed over to the open-surgery group, the majority owing to the anatomy of the aneurysm or to the surgeon's preference for open-surgical treatment over endovascular treatment.

The results of ISAT, combined with the fact that patients tend to prefer a minimally invasive approach to treatment, have resulted in a dramatic shift toward endovascular treatment of ruptured aneurysms. However, open-surgical treatment may be preferred for patients who have increased intracranial pressure or focal neurologic deficits caused by intracerebral hematoma, for patients whose aneurysms are difficult to visualize angiographically or for whom revascularization with a bypass is deemed to be necessary, and for patients younger than 40 years of age who have anterior circulation aneurysms and good neurologic status, given the greater durability and the lower risk of aneurysm rebleeding with open-surgical treatment than with endovascular treatment.[45] Consequently, patients should be treated at high-volume cerebrovascular centers where surgeons who are experienced and skilled in both open-surgical and endovascular procedures are present.

TREATMENT OF COMPLICATIONS ARISING FROM SUBARACHNOID HEMORRHAGE AND ANEURYSM TREATMENT

Vasospasm and Delayed Cerebral Ischemia

Narrowing of angiographically visible cerebral arteries after aneurysmal subarachnoid hemorrhage (vasospasm) occurs in 70% of patients; the process generally starts 3 to 4 days after aneurysm rupture, peaks at 7 to 10 days, and resolves by 14 to 21 days.[46] Delayed cerebral ischemia is a clinical syndrome of focal neurologic deficits that develops in one third of patients, typically 4 to 14 days after aneurysm rupture,[25] and is a major cause of death and disability after subarachnoid hemorrhage has occurred.[47]

Despite a general belief that vasospasm causes delayed cerebral ischemia, recent evidence suggests that a variety of vascular and neural changes that take place after subarachnoid hemorrhage may contribute to its pathogenesis.[48] Delayed cerebral ischemia develops in fewer than one half of patients with angiographic vasospasm, and ischemia does not occur consistently in the territory supplied by the vessel undergoing spasm. The calcium-channel blocker nimodipine, the only drug known to reduce the risk of delayed cerebral ischemia and improve neurologic outcome after subarachnoid hemorrhage (discussed further below), does not alter the incidence or severity of vasospasm. In clinical trials of a drug that significantly reduced the risk of angiographic vasospasm, no measurable effect was observed on the development of delayed cerebral ischemia or on clinical outcomes.[25,26] Consequently, possible sequelae of subarachnoid hemorrhage other than vasospasm are being explored as mediators of poor outcome after aneurysm rupture and as potential targets for therapy.[25,48,49]

Currently, it is recommended that nimodipine be administered orally to all patients from the time of presentation to 21 days after the occurrence of subarachnoid hemorrhage. A Cochrane review of randomized trials indicated that nimodipine reduced the risk of poor outcomes in patients with subarachnoid hemorrhage by one third.[50] The maintenance of normal circulating blood volume and normal hemoglobin level is associated with a reduced risk of delayed cerebral ischemia, but prophylactic hypervolemia and balloon angioplasty to treat angiographic vasospasm (in the absence of clinical or radiograph-

ic evidence of delayed cerebral ischemia) is discouraged.[51,52]

The clinical examination may not detect delayed cerebral ischemia in an obtunded or comatose patient. Transcranial Doppler ultrasonography is widely used as a noninvasive test to detect vasospasm after subarachnoid hemorrhage, but its usefulness remains debated. Perfusion CT can be used to identify regions of possible brain ischemia in patients who have a new neurologic deficit. If clinically significant delayed cerebral ischemia, with or without vasospasm, is suspected, induced hypervolemia and hypertension (double "H" therapy with intravenous administration of fluid and alpha-adrenergic agents) is recommended to improve cerebral perfusion. If delayed cerebral ischemia occurs in the territory of a major cerebral artery in spasm, cerebral angioplasty, selective intraarterial vasodilator therapy, or both can be considered in cases in which no clinical improvement is observed with induced hypertension.[27]

Hydrocephalus

Hydrocephalus may develop soon after subarachnoid hemorrhage, owing to the presence of extravasated blood blocking normal cerebrospinal fluid circulation through the subarachnoid cisterns that surround major arteries at the base of the brain. Estimates of the incidence of hydrocephalus range from 15 to 85%[27]; most cases are not clinically significant. In cases in which hydrocephalus causes encephalopathy, management of the hydrocephalus typically involves placement of an external ventricular drain, a procedure that generally results in neurologic improvement. Alternatively, lumbar drainage can be used to treat acute hydrocephalus and is associated with a reduced risk of vasospasm; however, obstructive hydrocephalus and intraparenchymal hematoma, which cause increased intracranial pressure, are contraindications to lumbar drainage. Chronic symptomatic hydrocephalus occurs in up to one third of patients in whom acute hydrocephalus develops and is treated with a ventriculoperitoneal shunt for permanent diversion of cerebrospinal fluid. Hydrocephalus may develop days to weeks after subarachnoid hemorrhage and should be suspected in patients who have a good initial recovery followed by a plateau or decline in their condition.

Medical Complications

Patients who have had aneurysm rupture are at risk for multiple medical complications that are common with critical illness, and they should be treated in an intensive care unit, preferably one that specializes in neurocritical care.[53] A detailed discussion of general medical management is beyond the scope of this article, but the goals include euvolemia, normothermia, avoidance of hypoglycemia or marked hyperglycemia, electrolyte balance, and adequate ventilation (for comatose patients) that avoids exacerbating elevated intracranial pressure. Because deep venous thrombosis is relatively common after subarachnoid hemorrhage, especially among immobilized patients, routine prophylaxis is recommended, with intermittent pneumatic compression at all times and with unfractionated heparin starting 24 hours after the ruptured aneurysm has been treated and continuing until patients are mobilized. However, there is a risk associated with anticoagulation for prevention of deep venous thrombosis in cases in which patients may have to undergo multiple invasive procedures.[54]

AREAS OF UNCERTAINTY

The goals for blood pressure and volume status after intervention and the appropriate management of delayed cerebral ischemia remain uncertain. There are few data from randomized, controlled trials to guide strategies for reducing the risk of subarachnoid hemorrhage. Screening protocols designed to identify cases of asymptomatic deep venous thrombosis are of unclear value. Subarachnoid hemorrhage has effects on thyroid and adrenal function, but data are lacking to show a clear benefit of intervention.

Adjuncts to endovascular treatment, including balloon-tipped microcatheters, stents, and flow-diverting stents, have been developed to manage wide-necked and fusiform aneurysms, but these adjuncts often require treatment with antiplatelet therapy, with an attendant risk of bleeding. These adjuncts are evolving rapidly, and more data are needed regarding their risks and benefits.

GUIDELINES

A writing group of the American Heart Association and American Stroke Association published

updated guidelines in 2012 for the management of aneurysmal subarachnoid hemorrhage.[27] The recommendations in this article are generally consistent with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette has clinical and radiographic findings that are consistent with subarachnoid hemorrhage. Catheter angiography is indicated to identify the source of his bleeding. An aneurysm is the most common cause and, if identified, is associated with a very high risk of rerupture during the next 30 days; thus, we would recommend immediate treatment. Data from randomized trials have shown better functional outcomes overall with endovascular treatment than with open-surgical treatment. However, open-surgical treatment (surgical clipping) may be preferred on the basis of certain features of the aneurysm (e.g., morphologic characteristics of the aneurysm and an associated large hematoma) or in younger patients, given the greater durability of the open-surgical treatment in the randomized trials.[55] Given this patient's age, his otherwise healthy status, and the location of the aneurysm in the anterior circulation, we would recommend open-surgical treatment by a specialized, experienced surgeon. If a surgeon with expertise in open-surgical technique is not available at the center, endovascular treatment could be provided instead to eliminate the immediate risk of rerupture.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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