Aneurysmal Subarachnoid Hemorrhage

Case Study and Commentary, Robert J. Brown, MD, and Rajat Dhar, MD, FRCP(C)

ABSTRACT
• **Objective:** To provide an overview of the diagnosis, complications, and treatment of aneurysmal subarachnoid hemorrhage (SAH).
• **Methods:** Review of the literature in the context of a clinical case.
• **Results:** SAH is a neurologic emergency most commonly presenting as sudden severe (“thunderclap”) headache. All patients with unusual, new, or “worst headache of their life” require thorough evaluation. The diagnosis of SAH is made by head CT or lumbar puncture; a cerebral angiogram is required to evaluate for source of bleeding, most commonly an intracranial aneurysm. Early management centers on the prevention of aneurysmal rebleeding, including surgical or endovascular intervention to “secure” the aneurysm. Physicians should be knowledgeable with regard to the myriad complications that may occur after SAH, ranging from hydrocephalus and vasospasm to hyponatremia and cardiopulmonary dysfunction.
• **Conclusion:** Despite serious neurologic and systemic complications, outcomes for patients with aneurysmal SAH can be significantly improved with an aggressive and informed multidisciplinary approach.

Spontaneous (nontraumatic) subarachnoid hemorrhage (SAH) usually results from the rupture of a cerebral aneurysm. Located at the branching point of proximal intracranial arteries, these aneurysms are not uncommon, found in about 2% of the adult population (and even more frequently in those with a family history or polycystic kidney disease) [1]. While most of these aneurysms never rupture, there are still 30,000 cases of aneurysmal SAH in the United States each year [2]. SAH has a peak incidence in the sixth decade of life and affects women 1.6 times more than men [3]. Risk factors for aneurysm rupture include hypertension, smoking, heavy alcohol use, and cocaine abuse [4–6]. Mortality can be as high as 50%, with 10% to 20% of patients dying within the first 24 hours from cardiac arrhythmias or cerebral herniation [7,8]. Many survivors are left with neurologic deficits and reduced quality of life. In fact, SAH accounts for a disproportionately high number of years of potential life lost, equivalent to that from the much more common ischemic and hemorrhagic strokes [8]. Prompt recognition and proper diagnosis is imperative to minimize poor outcome as is proper management of the myriad neurologic and systemic complications that can occur in the days to weeks following SAH. Advances in medical care and aneurysm therapy have led to significant reductions in SAH morbidity and mortality over the past 30 years [9].

**CASE STUDY**

**Initial Presentation**

A 52-year-old woman presents to the emergency department (ED) with a severe headache. It occurred suddenly while watching television. She describes it as the “worst headache of my life.” She has nausea and mild photophobia. She denies any past medical history (including no prior similar headaches) but has not seen a doctor in many years. She smokes 1 pack per day and has done so for 34 years. On examination, her blood pressure is 195/103 mm Hg. On electrocardiogram shows normal sinus rhythm with left ventricular hypertrophy.

• **What are the possible causes of this patient’s headache?**

The patient is presenting with a sudden-onset of severe headache and a physical examination unremarkable except for hypertension. While most headaches are benign, severe headaches that are unusual for that patient or of sudden onset require urgent attention to rule out life-threatening causes [10]. The differential diagnosis of these sudden severe headaches, referred to as “thunderclap headaches,” is listed in Table 1.

SAH is the most important cause of thunderclap headache to exclude and accounts for 11% to 25% of cases in prospective series [11–13]. Unfortunately, the diagnosis of SAH is often missed or delayed. A study of 482 patients admitted...
for SAH found that 12% had previously been misdiagnosed including 19% of those who presented with normal mental status [14]. Another study found that 5% of 1507 SAH patients had prior visits to the ED where the diagnosis was not made, and this was more common in nonteaching hospitals [15]. An explanation for the frequency of misdiagnosis is that headache is extremely common but few headache patients presenting to the ED or clinic actually have SAH. Furthermore, associated features of SAH, including nausea and photophobia, are also commonly seen with benign causes of headache such as migraine. However, in a study of patients presenting to the ED with severe headache, 70% of patients with SAH had maximal pain within 60 seconds and none had maximal pain peaking over 1 hour or more after onset [13]. These data suggest that all patients presenting with severe headache of sudden onset (usually seconds to minutes till peak severity, ie, thunderclap) require urgent evaluation for SAH. Other red flags that should prompt further evaluation include loss of consciousness at headache onset, progressive or unremitting headache unusual for the patient, mental status changes, visual symptoms or diplopia, and fever or neck stiffness [16].

Patients with SAH may report a history of a recent severe or unusual headache that resolved in the days to weeks prior. This has been termed a “sentinel headache” and may suggest the presence of an unstable aneurysm with either a small hemorrhage or sudden expansion. Many patients will not seek medical attention or are misdiagnosed when they do. This can be devastating as many will suffer a more severe rebleed prior to proper diagnosis. A systematic review found that 10% to 43% of SAH patients report having such sentinel headaches [17]. Proper recognition and evaluation of those presenting with this potential warning sign could lead to early diagnosis of a high-risk aneurysm and a reduction in morbidity and mortality from subsequent rupture.

The funduscopic examination is often overlooked but can be of benefit in patients presenting with unusual headache. A study of 101 patients presenting with SAH reported an abnormal fundus in half [18]. The most common findings were retinal hemorrhages, including subhyaloid hemorrhage, and papilledema (Figure 1). Hemorrhages into the vitreous humor (Terson syndrome) occur less frequently but may result in significant visual impairment for which vitrectomy may be indicated [19]. The presence of acute third cranial nerve palsy (ie, dilated pupil with ptosis and inability to adduct the affected eye) is another classic finding of SAH related to compression of the nerve by an aneurysm in the region of the posterior communicating artery.

Because she described a classic thunderclap headache, despite the absence of other signs or symptoms an urgent evaluation to rule out SAH is indicated.

The primary diagnostic test in the evaluation of patients with thunderclap headache is a noncontrast computed tomography (CT) scan of the head. If performed soon after headache onset, its sensitivity for SAH is almost 100% [20]. However, its sensitivity falls by 10% per day and so it cannot be relied

### Table 1. Differential Diagnosis of Thunderclap Headache

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Clues</th>
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<tr>
<td>Subarachnoid hemorrhage (eg, aneurysmal)</td>
<td>Retinal hemorrhage, neck stiffness</td>
</tr>
<tr>
<td>Sentinel headache (aneurysmal instability)</td>
<td>Visual and oculomotor disturbances</td>
</tr>
<tr>
<td>Pituitary apoplexy</td>
<td>Horner’s syndrome, facial pain</td>
</tr>
<tr>
<td>Cervical artery dissection</td>
<td>Retinal (flame) hemorrhages, blood pressure</td>
</tr>
<tr>
<td>Acute hypertensive crisis</td>
<td>Drug abuse including SSRI</td>
</tr>
<tr>
<td>Reversible cerebral vasoconstriction syndrome (including Call-Fleming syndrome)</td>
<td>Focal neurological deficits</td>
</tr>
<tr>
<td>Stroke – ischemic or hemorrhagic</td>
<td>Orthostatic headache (worse standing)</td>
</tr>
<tr>
<td>Spontaneous intracranial hypotension</td>
<td>Hypercoagulability</td>
</tr>
<tr>
<td>Cerebral venous sinus thrombosis</td>
<td>Postural headache, syncope</td>
</tr>
<tr>
<td>Colloid cyst (intraventricular obstruction)</td>
<td>May be recurrent over days to weeks</td>
</tr>
<tr>
<td>Primary thunderclap headache (including exertional, cough, and sexual headaches)</td>
<td></td>
</tr>
</tbody>
</table>

**Further Evaluation**

Upon further questioning, the patient says her headache peaked instantaneously, as if she were “struck by a baseball bat.” Neurologic examination finds an awake and fully oriented woman with intact language. Her pupils are equal and briskly reactive. Extraocular movements are intact and her smile is symmetric. There is no pronator drift and her strength is full in all limbs. She does not have neck stiffness.

- **What further physical examination may be helpful and what diagnostic testing is mandatory?**
on to absolutely exclude SAH [21]. For this reason, a lumbar puncture is required in all patients with negative CT scans and a suspicion for SAH. The cerebrospinal fluid (CSF) is analyzed visually or by spectrophotometry for xanthochromia, a yellow discoloration of the CSF (due to presence of heme breakdown products including bilirubin) when centrifuged. Xanthochromia will remain present for up to 2 weeks following SAH with 100% sensitivity and is still present in 40% of cases 4 weeks after the event [22]. For this reason, it is more useful than CT scanning in patients presenting in a delayed fashion after headache onset. Unfortunately, less than 1% of hospitals use spectrophotometry in the analysis of CSF but instead rely on visual inspection; this may be less reliable [23]. A study of 152 patients with thunderclap headache and negative CT scans found that xanthochromia by visual inspection was 93% sensitive with negative predictive value of 99% [24]. Since xanthochromia requires the degradation of red blood cells and the circulation of heme breakdown products from the intracranial subarachnoid space to the lumbar cisterns (which takes 6–12 hours after SAH), lumbar puncture should be deferred for this period to ensure optimal sensitivity [25]. If blood appears in the CSF obtained by lumbar puncture (either visually or if numerous red blood cells are seen in the cell count) it may be difficult to differentiate true SAH from a “traumatic tap.” It is often taught that a decreasing number of red blood cells from the first tube collected to the last tube (especially with clearing of red blood cells by the last tube) suggests a traumatic tap. However, this has not been shown to be a reliable method of excluding SAH [26]. Xanthochromia, which will not be seen with a traumatic tap, remains the mainstay for diagnosing SAH via lumbar puncture. Opening pressure should also be measured during any lumbar puncture for severe headache as finding an elevated CSF pressure should guide further investigation such as magnetic resonance imaging (MRI) (with magnetic resonance venography [MRV]) even if xanthochromia is absent.

While MRI is probably as sensitive as CT in the diagnosis of SAH [27], the time required to perform it as well as its high cost and restricted availability limit its use in the emergency evaluation of headache. However, for the CT and lumbar puncture–negative patient presenting with atypical headache, especially if associated with focal findings or high opening pressure on lumbar puncture, an MRI, and potentially magnetic resonance angiography and MRV, may be useful in ruling out other serious etiologies shown in Table 1.

Examination Results

Funduscopic examination does not show disc swelling or retinal hemorrhage. CT scan of the head is performed and shows high-density fluid in the basal cisterns consistent with SAH (Figure 2).

• What test is indicated to evaluate for the presence and location of an aneurysm or other vascular abnormality?

Once the diagnosis of SAH has been made, the gold standard for determining the etiology of bleeding is the 4-vessel cerebral catheter angiogram. Catheter angiography is not only the most sensitive test for detecting small aneurysms or other vascular abnormalities (including arteriovenous malformations), but it also provides a potential means for simultaneously or subsequently treating the aneurysm (further described below). Many centers now utilize 3-dimensional digital subtraction angiography (DSA) in addition to standard 2-dimensional DSA. This is not only more sensitive in detecting small aneurysms, but can provide a much better picture of the anatomy of the aneurysm and of its relationship to adjacent vasculature and intracranial structures [28]. Despite the sensitivity of catheter angiography, up to 20% of initial angiograms performed for SAH will not reveal a source [29]. Repeat angiography 1 or more weeks later should be performed as up to 10% will eventually be found to have a ruptured aneurysm not seen initially [30]. In these cases, the initial angiogram may have been negative secondary to thrombosis of the aneurysm with lack of contrast filling or failure to fully opacify all cerebral vessels. Those patients whose second angiogram remains negative for an aneurysm likely have another nonaneurysmal cause. The various causes of SAH are listed in Table 2.

Noninvasive vascular imaging with CT angiography or MRA has been increasingly used in the workup of SAH. Both are less sensitive for aneurysms under 5 mm in size, and therefore a negative result would not preclude a catheter an-
However, many institutions do not have 24-hour availability of catheter angiography. In these situations, CT angiography may be used as the initial test once the diagnosis of SAH is made. This is not only a quick and noninvasive means to prove the presence of an aneurysm, but it is also useful in elucidating the aneurysm’s relationship to bony structures, which may be useful if surgery is planned [32]. In cases when the aneurysm is amenable to surgical clipping, catheter angiography may be avoided altogether (unless intraoperative angiography is performed).

One cause of nonaneurysmal SAH worth discussing in more detail is the perimesencephalic hemorrhage. As its name implies, blood is localized anterior to the midbrain and/or pons with only restricted extension into the suprasellar cistern or Sylvian fissures and without frank intraventricular or parenchymal extension (Figure 3). Angiography must still be performed in these cases as 5% of patients with this radiographic pattern will harbor a posterior circulation aneurysm [33]. However, the diagnosis can be made with the classic radiographic appearance and negative (CT or catheter) angiography; repeat angiography may not be required in these cases. These account for 10% of spontaneous SAH and are associated with a significantly better outcome [34,35]. The bleeding is thought to be of venous origin and recurrence or rebleeding is rare.

A diagnostic algorithm for the evaluation of SAH is shown in Figure 4.

**Continuing Course**

The patient is admitted to the neurosciences intensive care unit. A cerebral angiogram is arranged for the morning.

- **What is the incidence of early aneurysmal rebleeding and how can it be minimized?**

Rebleeding from the aneurysm is the leading cause of early death in those who survive the initial hemorrhage. Therefore, the initial management of aneurysmal SAH is directed at stabilizing the patient and preventing rebleeding. The risk of rebleeding is as high as 13.6% in the first 24 hours, but falls to 1% to 2% per day over the next 14 days [36,37]. The most definitive way to prevent rebleeding is to secure the aneurysm, excluding it from the circulation. Historically, the practice was to delay treatment of the aneurysm to allow the brain to recover from the initial insult. However, given over 50% mortality from aneurysmal rebleeding, current practice has shifted to securing the aneurysm as soon as feasible (usually within 24 hours of presentation).
American Heart Association guidelines for the management of SAH recommend control of hypertension prior to aneurysm treatment [38]. This is based on retrospective studies that show an association of elevated systolic blood pressure with a higher risk of rebleeding [37,39]. Controlled lowering of blood pressure in the acute period carries minimal risks as long as cerebral perfusion pressure is maintained. Antihypertensive agents can be administered above blood pressure thresholds, which in the absence of clear evidence-based guidelines, can be set at a systolic pressure of 160 mm Hg or a mean arterial pressure (MAP) of 110 mm Hg. While as needed intravenous labetalol and/or hydralazine are commonly used, for significantly hypertensive patients an infusion of nicardipine may be efficacious. These blood pressure targets can be relaxed once the aneurysm has been secured, allowing for permissive hypertension to ensure adequate cerebral perfusion.

The most promising method of preventing rebleeding prior to surgery is the administration of antifibrinolytic therapy, such as tranexamic acid. Initial studies of antifibrinolytics confirmed a reduction in the risk of rebleeding, but this benefit was offset by an increase in cerebral infarction with no overall improvement in outcome [40,41]. These studies were performed in the era of delayed aneurysm treatment, which necessitated the use of antifibrinolytics for a prolonged period, including when risk of vasospasm was greatest. With contemporary management in which the aneurysm is treated early, use of antifibrinolytics is only required for the brief period before the risk of ischemia rises. A contemporary study found a significant reduction in rebleeding without an increase in cerebral ischemia in 505 patients in whom antifibrinolytics were continued until the aneurysm was secured but for no longer than 72 hours [42]. The study was underpowered to demonstrate a difference in outcomes between the 2 groups. Pending the results of larger trials, antifibrinolytics should be considered to reduce the risk of rebleeding in patients presenting to a hospital without the ability to immediately treat the aneurysm or if any delay to treatment is expected.

**Continuing Course**

The patient is placed on a nicardipine infusion to keep her MAP less than 110 mm Hg. Tranexamic acid (1 g every 6 hours) is administered given that definitive treatment will be delayed. She remains stable overnight and a cerebral angiogram is performed the next morning. This demonstrates a 7-mm aneurysm arising from the anterior communicating artery (Figure 5).

- What are the options for treating her aneurysm?

Treatment of ruptured cerebral aneurysms has evolved from carotid ligation (a practice associated with significant morbidity and little efficacy) to delayed surgical wrapping or clipping and now to the modern era of either early surgical clipping or endovascular coiling. Surgery is no longer delayed as studies have demonstrated that early cranioto-
Subarachnoid Hemorrhage

Figure 4. Diagnostic algorithm for the evaluation of subarachnoid hemorrhage (SAH). *Not required for perimesencephalic hemorrhage.

my is not associated with excess surgical risk but reduces the risk of rebleeding [43]. Endovascular coiling involves the placement of platinum coils into the aneurysm. These coils induce thrombosis which obliterates the aneurysm and excludes it from the circulation [44]. Early aneurysmal treatment also allows for vasospasm to be aggressively treated without concern for rupture during induced hypertension [45].

Whether an aneurysm is clipped or coiled depends on several factors, including aneurysm location, morphology, and the experience of the institution and operators. Aneurysms at the bifurcation of the middle cerebral artery (MCA) have a more peripheral location within the Sylvian fissure and so are more accessible to surgical clipping and less easy to access by endovascular approaches. Most posterior circulation aneurysms as well as proximal internal carotid aneurysms are difficult to approach surgically and are therefore most frequently coiled. For the 2 most common aneurysms, the anterior communicating artery and the posterior communicating artery aneurysm, either option is usually viable. Clipping is preferred if the aneurysm has a wide neck or if a compressive cranial neuropathy is present. However, the choice varies greatly between institutions with some institutions relying almost entirely on one method or the other. The experience with endovascular treatment and advances in techniques and technologies (use of stents, newer coils, etc.) has progressed significantly, allowing more aneurysms to be treated by this less invasive approach [46–48].

Studies have shown that endovascular coiling is associated with lower periprocedural morbidity, but surgical clipping may be more effective in preventing aneurysm recurrence and rebleeding over time. The International Subarachnoid Aneurysm Trial (ISAT) randomized 2143 patients whose aneurysms were felt to be amenable to either coiling or surgery to receive one or the other [49]. Endovascular coiling resulted in an absolute risk reduction for death or dependency of 7.4% at 1 year compared with
surgical clipping. However, it is important to note that patients whose aneurysms were felt to be better treated with one option over the other were not included in this trial (for example, most MCA aneurysms were treated surgically and most posterior circulation aneurysms were treated by endovascular means, outside of the trial) and so results cannot be generalized to the full breadth of SAH patients. An important variable to consider is the patient’s age, as surgery may offer greater durability with benefits exceeding the short-term procedural risks over time [50]. Ultimately, the decision to clip or coil a ruptured aneurysm should be discussed with the patient in concert with an experienced neurosurgeon and endovascular specialist.

**Procedure**

Given the experience of the center in the endovascular treatment of aneurysms and the aneurysm’s narrow base, the patient undergoes coiling with successful obliteration of the aneurysm.

The patient is drowsier after aneurysm coiling. Repeat head CT (Figure 6) reveals enlarged temporal horns of the lateral ventricles consistent with hydrocephalus. She undergoes placement of an external ventriculostomy drain. She is started on levetiracetam 1000 mg twice daily on admission, which is discontinued on day 4 without occurrence of seizures.

- **What other complications may occur in the hospital course of this patient with SAH?**

Once the aneurysm is successfully secured, the risk of rebleeding is markedly reduced and subsequent management is directed at the prevention and treatment of complications of the SAH, both neurologic and systemic. These include hydrocephalus, seizures, hyponatremia, cardiopulmonary dysfunction, and vasospasm with delayed cerebral ischemia.

**Hydrocephalus**

Acute hydrocephalus occurs in 30% of patients over the first 24 to 48 hours of SAH [51]. Both the amount of blood and its location increase the likelihood of obstruction to CSF flow. Clinical signs of hydrocephalus include worsening headache, mental status changes, nausea/vomiting, and diplopia. Diagnosis is confirmed by a CT scan showing enlarged
ventricular size, especially the temporal horns of the lateral ventricles which should normally be slit-like. Symptomatic obstructive hydrocephalus requires prompt placement of an external ventriculostomy drain allowing for drainage of CSF and blood, as well as monitoring of intracranial pressure. Over time, the drain may be weaned and removed as blood resorbs and CSF is able to circulate freely. However, as many as one-quarter of patients require long-term CSF diversion, most commonly via placement of a ventriculoperitoneal shunt [52]. Some patients may develop a communicating hydrocephalus later in life.

Seizures

Epileptic seizures may occur in the acute period after SAH with an incidence as high as 18% [53]. These most often occur prior to hospital admission, especially at ictus when it may be hard to differentiate witnessed accounts of loss of consciousness from a seizure. The use of prophylactic antiepileptic drugs (AEDs) is common after SAH but has never been demonstrated to be efficacious or to have a favorable risk-benefit profile. The theoretical benefit is that seizures prior to securing the aneurysm may increase the risk of rebleeding. However, a study found that greater exposure to phenytoin was associated with a worse cognitive function in survivors of SAH [54]. For these reasons, there has been a move towards minimizing the duration of AED use. This strategy was supported by a study comparing 79 SAH patients receiving phenytoin until discharge with 370 patients receiving a 3-day course that found no difference in the frequency of seizures [55]; the shorter course was associated with less AED-related complications. Many practitioners now use levetiracetam instead of phenytoin due to fewer drug interactions and adverse effects [56]. In patients that do have in-hospital seizures, AEDs are generally continued for longer periods, although the appropriate duration is not well established. The overall long-term risk of developing epilepsy (defined as 2 or more unprovoked seizures) after SAH was 7% in a study of 247 patients and 17% in those with in-hospital seizures [57]. Subclinical seizures can occur in patients comatose with severe SAH, and EEG monitoring should be considered in patients not waking up or subsequently deteriorating in the ICU [58].

Vasospasm and Delayed Cerebral Ischemia

A majority of patients will develop some degree of narrowing of the intracranial arteries around the circle of Willis, peaking around 7 to 10 days after SAH [59]. This phenomenon, termed “vasospasm,” is most likely related to the effect of blood breakdown products and the inflammatory cascade they induce [60,61]. There may be an increase in blood pressure around this period which serves as a compensatory mechanism to maintain cerebral blood flow (CBF) in the face of vasospasm. Despite this, 20% to 40% of patients will develop symptoms of delayed cerebral ischemia (ie, focal neurologic deficits and/or alteration in cognitive functioning or deterioration in mental status) in association with vasospasm and reduced flow through cerebral vessels [62]. Ischemia may lead to cerebral infarction and permanent neurologic deficits [63]. In fact, cerebral infarction is the major contributor to neurologic morbidity and mortality in those surviving the first few days after aneurysmal rupture [64]. Therefore, the prevention and treatment of cerebral vasospasm has significant potential to impact outcomes of SAH patients and has been the focus of extensive research and a number of clinical trials. Being able to predict those at highest risk of vasospasm may be useful in directing aggressive monitoring and interventional strategies at a targeted population.

- What is the risk of vasospasm in our patient?

The risk of vasospasm increases with greater amount and thickness of blood in the cisterns of the brain and in the ventricles. Several scales have been developed to help estimate this risk, including the Fisher [65] and recently modified Fisher scales [66]. Both grade the admission CT scan based on whether thick or only thin layers of blood are present in the basal cisterns and whether intraventricular hemorrhage is present. However, the modified Fisher scale more linearly predicts risk of vasospasm and is now preferred [67] (Table 3).

Modified Fisher Grade

The patient is assigned a modified Fisher grade 3 based on her admission head CT, which estimates her risk of vasospasm to be 35%.

- What screening should be employed to monitor her for the development of vasospasm?

There are numerous proposed means of monitoring the brain for development of ischemia after SAH. However, detection of new or worsening neurologic deficits remains the gold standard of bedside monitoring. Typical signs range from alterations in mental status, including agitation, confusion, and lethargy, to focal deficits such as aphasia and hemiparesis [68]. Unfortunately, these signs only occur once cerebral ischemia has already developed. To detect vasospasm before the onset of ischemia, several screening tests have been employed. These include transcran-
nial doppler ultrasonography (TCD), EEG, and radiographic measures of cerebral perfusion and vasculature such as CT angiography/CT perfusion or MRA with perfusion imaging [69–73]. Invasive probes measuring brain tissue oxygen tension and flow are also being studied [74,75].

TCD is the most commonly used screening test for vasospasm, measuring blood flow velocity in the proximal intracranial arteries rather than vessel diameter directly. This assumes that as a vessel narrows, velocity within it will increase. Visualization of all vessels is often incomplete, and in up to 20% of patients no measurements can be made at all (due to lack of proper bone windows) [76]. Furthermore, using vessel velocities alone may be an inaccurate marker of vasospasm as velocity also correlates with systemic blood pressure and other factors. For this reason, TCD velocities cannot be used to monitor response to induced hypertensive therapy [77]. The Lindegaard ratio, the ratio of the velocity in the intracranial vessel being studied to the reference extracranial internal carotid artery, may partially account for these limitations [78]. Ratios above 3 have been associated with moderate vasospasm, while ratios above 6 are associated with severe spasm with improved specificity [79].

A meta-analysis of the accuracy of TCD for vasospasm included 7 studies comparing TCD to angiography [80]. This found that TCD has a specificity of 99% and a positive predictive value of 97% for vasospasm in the middle cerebral artery (MCA), but its sensitivity was only 67%. For the anterior cerebral artery (ACA) or other potentially important vessels, neither sensitivity nor specificity was high enough to support its use. Despite these limitations, given its noninvasive nature and relatively low cost, many institutions routinely use daily TCD as an adjunct to the clinical examination for detecting vascular changes. When TCD reveals rising velocities or higher Lindegaard ratios, angiography may be performed to confirm the diagnosis.

Follow-up

On day 5 of her admission, the patient is noted to have difficulty standing while moving to the bedside chair. Neurologic examination reveals reduced strength in the left leg. She also appears more confused and restless. TCD velocities are elevated in the MCA but normal in the visualized ACA segments. Head CT shows no new lesions.

Table 3. Fisher Scales

<table>
<thead>
<tr>
<th>Grade</th>
<th>Modified Fisher</th>
<th>Fisher</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>No blood</td>
<td>n/a</td>
</tr>
<tr>
<td>1</td>
<td>Thin blood, without IVH</td>
<td>24%</td>
</tr>
<tr>
<td>2</td>
<td>Thin blood, with IVH</td>
<td>33%</td>
</tr>
<tr>
<td>3</td>
<td>Thick blood, without IVH</td>
<td>33%</td>
</tr>
<tr>
<td>4</td>
<td>Thick blood, with IVH</td>
<td>40%</td>
</tr>
</tbody>
</table>

ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage.

This patient is in the window of risk for vasospasm after SAH (starting as early as 3–4 days after hemorrhage). She has developed new focal neurologic deficits and worsening mental status concerning for ischemia. However, a number of other complications that can occur after SAH may mimic vasospasm and should be excluded. Important confounders include hyponatremia (discussed below), fever, infections, seizures, cerebral edema, and rebleeding. Treatment to reverse deficits associated with suspected cerebral ischemia should be instituted concurrent with evaluation of other causes and confirmation of vasospasm by angiography. This ensures that delays are avoided in which ischemia could progress to irreversible infarction.

The focus of treating ischemic deficits centers on restoring adequate CBF to ischemic brain regions. The mainstay of ICU treatment has been hemodynamic augmentation (previously termed “Triple H” therapy, referring to hypertension-hypervolemia-hemodilution) [81]. The central component of hemodynamic therapy for vasospasm is induced hypertension [82]. While increases in systemic blood pressure will not increase CBF in the normal brain within the limits of cerebral autoregulation (typically between MAPs of 50 and 150 mm Hg), this process may be impaired in patients after SAH [83]. In this case, raising MAP will result in commensurate and potentially beneficial improvements in CBF. There has been a shift away from hemodilution and hypervolemia based on recent studies demonstrating little benefit of either of these interventions on CBF [84].

A randomized trial of hypervolemia found that maintaining higher central venous pressure with albumin boluses did not improve CBF, prevent vasospasm, or improve outcomes.
but exposed patients to higher risk of pulmonary edema [85]. In contrast to hemodilution, some studies have found an association between higher hemoglobin level and better outcomes including less cerebral infarction [86–88]. Ongoing research is evaluating the effects of blood transfusion on cerebral oxygen delivery and investigating the optimal hemoglobin target for patients at risk for ischemia [89]. It may be reasonable to consider transfusion in anemic patients with active cerebral ischemia.

To treat deficits associated with vasospasm, the general practice is to increase MAP above the patient’s current baseline. This can be done stepwise (10%–20% at first) until deficits are reversed, side effects have occurred, or the therapy is considered to have failed (30% or more rise without benefit). An initial fluid bolus of 1 to 2 L may be given to ensure adequate cardiac filling while vasopressors are initiated. Noninvasive cardiac monitoring has largely replaced the use of pulmonary artery catheters to optimize hemodynamics and minimize cardiopulmonary complications that may result from aggressive hemodynamic augmentation [90]. Angiography should be ordered as soon as possible, especially if deficits do not promptly reverse, as not only will this confirm the suspected diagnosis of associated vasospasm, but may allow focused therapies.

Follow-up

Figure 7. Cerebral angiogram (right carotid injection) with severe narrowing of the A1 segment of the right ACA (arrow) as well as moderate narrowing of the MCA. Coiled aneurysm is also seen.

The patient’s MAP is currently 98 mm Hg. She is given a bolus of 1 L 0.9% saline and phenylephrine is started to raise MAP to a target of 110 to 120 mm Hg. A cerebral angiogram is obtained which shows severe narrowing of the A1 segment of the right ACA along with moderately severe narrowing of the MCA (Figure 7). 10 mg of verapamil is injected into the ACA with some improvement in narrowing and distal flow.

• What are endovascular options for treating vasospasm?
  Are there any interventions capable of preventing morbidity from vasospasm?

Endovascular Treatment

Angiographic vasospasm may also be treated by endovascular means, including intra-arterial injection of vasodilators as well as angioplasty of narrowed proximal vessel segments. While the opium alkaloid papaverine had been used in the past as a vasodilator, its short half-life and potential for neurotoxicity has limited its use [91]. Calcium channel blockers such as verapamil and nicardipine are currently used with the most frequency, but their effect is also transient and repeat treatments may be required if cerebral ischemia recurs. Angioplasty provides durable reversal of vasospasm but is only possible in accessible proximal vessels (eg, distal internal carotid artery and proximal MCA) and carries a risk of vessel perforation.

Prevention of Vasospasm

Calcium channel blockers, with their vasodilatory properties, have been studied in a number of trials for the prevention of vasospasm. The largest trial studied nimodipine in 554 patients who received 60 mg every 4 hours of nimodipine for 21 days or placebo. There was a significant improvement in outcome as well as a reduction in cerebral infarction with the use of nimodipine [92]. A meta-analysis of all 7 trials involving a total of 1202 patients showed an odds ratio of 1.86 for good outcome if nimodipine was administered [93]. The odds for cerebral infarction were also reduced to 0.58 compared with controls. Interestingly, while it seemed to improve outcome and prevent infarcts, it did not reduce the angiographic occurrence of vasospasm. This highlights the poor association between visible large vessel narrowing and cerebral ischemia and suggests the possibility that nimodipine has neuroprotective properties. Although the prevention of vasospasm in SAH is a subject of considerable interest and investigation, no therapeutic interventions have yet been shown to be definitively effective.
Follow-up
Following the angiogram, the patient is continued on phenylephrine to maintain MAP between 110 and 120 mm Hg with resolution of her focal deficits and improved mental status. She has been on nimodipine 60 mg every 4 hours since admission. On the following day, routine morning laboratory analysis reveals a serum sodium of 132 mmol/L. She appears more confused.

What is the possible etiology of her hyponatremia and how should this be managed?

Hyponatremia
In SAH, excess secretion of ADH and various natriuretic factors can lead to abnormalities in fluid and sodium regulation [94]. Hyponatremia is seen in 30% of patients and can increase cerebral edema, ICP, and worsen the neurologic examination (particularly mental status) [95]. Fall in serum sodium may relate to increased water resorption in the kidneys (related to excess antidiuretic hormone, ie, syndrome of inappropriate antidiuretic hormone [SIADH]) or excess sodium excretion (ie, cerebral salt wasting). These 2 syndromes may be difficult to distinguish clinically or even with urine studies. The only reliable differentiating factor is the patient’s volume status. Natriuresis will result in water loss, so patients with cerebral salt wasting will be hypovolemic. This may be evidenced by a drop in body weight over time, rising blood urea nitrogen (BUN) levels or uric acid, and other indicators of impaired perfusion. In SIADH, patients are euvoicmic but have excess free water. Both hypovolemia secondary to cerebral salt wasting and fluid restriction to treat water excess in SIADH have been shown to be harmful in patients with SAH. In a study from 1985, cerebral infarction occurred in 61% of patients with hyponatremia compared with 21% of patients without hyponatremia [96]. This seemed to be secondary to the practice of fluid restriction utilized in the hyponatremic patients rather than hyponatremia per se. In this study, 81% of patients with hyponatremia that were fluid restricted developed infarction compared with only 33% of those with hyponatremia who were not fluid restricted. Therefore, regardless of serum sodium or the suspected underlying etiology (even if SIADH), fluid restriction and hypovolemia must be avoided in SAH. The patient’s volume status should be closely monitored to maintain euvoicmic while salt is administered to raise serum sodium. This is most commonly in the form of hypertonic saline solutions in concentrations usually ranging from 1.5% to 3%, although sodium chloride tablets have been used. Some patients require many liters per day of hypertonic solutions to maintain euvoicmic and normal serum sodium in the face of salt wasting. Oral fluids may be restricted to limit free water intake, but intravenous fluids should always be continued. Vasopressin-receptor antagonists (ie, “vaptans”), which raise serum sodium by inducing renal loss of free water and are theoretically ideal for SIADH, should be utilized with caution in patients after SAH as they may induce hypovolemia [97].

Further Assessment
Further assessment shows a normal volume status. Central venous pressure is 6 mm Hg. BUN is 14 mg/dL and creatinine is 0.8 mg/dL. Her intravenous fluids are changed from normal saline to 1.5% saline at 125 mL/hr (1.5 mL/kg). She is placed on an oral fluid restriction of 1 L.

What other serious systemic complications can occur in patients with SAH?

Cardiopulmonary Dysfunction
The intense sympathetic activation that occurs following aneurysmal rupture may lead to a spectrum of cardiac abnormalities following SAH. These range from ECG abnormalities to cardiac enzyme release, arrhythmias and a catecholamine-induced transient cardiomyopathy. ECG abnormalities occur in the majority of patients and include T-wave inversions, ST changes, QTc prolongation, and both supraventricular and ventricular cardiac arrhythmias [98]. Troponin elevation may be seen in up to 30% of patients [99]. Ten percent of patients, especially those with severe SAH, develop a significant but usually reversible cardiomyopathy associated with depressed systolic function [100]. This has been termed “neurogenic stunned myocardium” (NSM) and is similar to stress-induced cardiomyopathy. The echocardiographic pattern has been termed Takotsubo (Japanese for octopus pot) cardiomyopathy as the apical-sparing pattern commonly seen resembles a traditional Japanese octopus pot with wide base and narrow mouth. Patients with NSM may develop congestive heart failure or cardiogenic shock and may require inotropic support. Hypoxemia, either as a result of cardiac failure or due to direct pulmonary endothelial injury (ie, “neurogenic pulmonary edema”), may require supplemental oxygen, mechanical ventilation, and high levels of positive end-expiratory pressure. With supportive care, these abnormalities tend to resolve over the course of a few days. No specific interventions have been shown to hasten recovery, but adrenergic blockers appear promising to mitigate the cardiac injury [101]. While it is unclear whether cardiac injury increases the risk of cerebral ischemia, the concomitant presence of cardiac impairment may complicate the hemodynamic management of vasospasm.
Prognosis

Survival and recovery after SAH is most strongly related to the clinical condition at presentation. Those with reduced level of consciousness have a worse prognosis, with a majority of those in coma not surviving or regaining meaningful functional status. Admission neurologic status can be graded using 2 common scales, the Hunt and Hess scale [102] (Table 4) and the World Federation of Neurosurgical Societies (WFNS) scale [103] (Table 5). The Hunt and Hess scale was introduced in 1968 and is the most widely recognized scale, but is limited by vague terms (eg, “drowsy”) and arbitrary classification. The WFNS is based on the Glasgow Coma Scale and is more reproducible. Higher grades are associated with worse outcome and patients with such severe clinical presentations were traditionally thought to be hopeless. However, aggressive ICU management including CSF drainage for acute hydrocephalus may allow meaningful recovery in a not insignificant subset who are not initially devastated and show improvement within a few days [104]. The other major predictors of poor outcome after SAH include older age, greater amount of blood (subarachnoid and intraventricular), and development of cerebral infarction [105].

Case Conclusion

On day 7, the patient’s sodium is 138 mmol/L and remains stable for the remainder of the admission. Hypertonic saline is eventually discontinued without further hyponatremia. Phenytoin is gradually weaned as her MAP goals are slowly decreased without recurrence of cerebral ischemia. EVD is clamped without recurrence of hydrocephalus and is then removed. On day 14 of her admission, she is transferred to the floor where she continues physical therapy and plans are made for transfer to an acute rehabilitation facility. Follow-up head CT shows no infarcts.

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