Subarachnoid Hemorrhage: New Theories, New Treatments

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Case Presentation

A 62 year-old woman experienced a sudden onset severe headache and collapsed at work. EMS was called and, when they arrived, the patient was awake but confused. She was immediately transported to the ED.

The patient had a history of hypertension and was on HCTZ and ACE inhibitor in addition to daily aspirin. On examination, she was somnolent and had sonorous respirations at a rate of 10 per minute. Her BP was 220/110 and the heart rate was 108. Scalp and neck were not tender and there was no meningismus. The right pupil was dilated and the right eye was deviated down and out. No other cranial nerve deficits were noted and the rest of the neurologic exam was normal. Her ECG showed deeply inverted T waves throughout the precordium and in II, III, and aVF.
Key Clinical Questions

How often are patients presenting to the ED with complaint of headache found to have subarachnoid hemorrhage?

Subarachnoid hemorrhage is a relatively uncommon cause of headache. Most patients with headache who visit Emergency Departments (EDs) or physicians' offices have more benign tension-type, sinus-related or migraine headaches. Among all patients with headache who presented to EDs, retrospective studies have found that approximately 1 to 4 percent had SAH. Prospective studies found that if only patients with the "worst headache" of their lives and a normal neurologic exam were considered, 12-33% percent of such patients had SAH. This proportion increased to 25% when patients whose examinations were abnormal were included.

What is the source of bleeding in subarachnoid hemorrhage?

Of the 30,000 patients found to have nontraumatic SAH in the United States annually, roughly 80% have ruptured saccular aneurysms causing acute bleeding into the subarachnoid space primarily at the base of the brain. Among the remaining 20%, about half have nonaneurysmal peri-mesencephalic hemorrhages.

What are the complications of subarachnoid hemorrhage?

Death after subarachnoid hemorrhage stems from the effects of the initial hemorrhage, rebleeding, and vasospasm. Management of patients with recent SAH should emphasize therapies to limit the acute effects of the hemorrhage, prevent rebleeding and halt or reverse vasospasm. Early surgery to repair the aneurysm, aggressive blood and intracranial pressure control and the careful use of antifibrinolytic and antihypertensive drugs with the early use of calcium channel blocking drugs reduces short-term complications such as recurrent bleeding and vasospasm and improves outcomes.
What are the typical features of patients with SAH?

The premier symptom of subarachnoid hemorrhage is a sudden, unusually severe headache. The headache is often instantaneous or cataclysmic in onset. It can be located anywhere in the head and can be of any quality (throbbing, pressure, etc). It is often described as the “worst in my life” and has been written about as a “thunderclap” headache that is an intense, acute headache with peak intensity at its onset. Transient loss of consciousness and seizures commonly occur and frequently happen at the time of hemorrhage. Occipital or neck pain is relatively common and pain in the eye, face, or back may develop.

The signs of subarachnoid hemorrhage are often more subtle. Many alert patients present only with headache. Most patients with SAH do not have focal neurologic signs. They may have only subtle or no neurologic abnormalities and may not have meningeal signs. More common focal neurologic signs include an III nerve palsy with an internal carotid-posterior communicating artery aneurysm, hemiparesis with a middle cerebral artery aneurysm, or paraparesis/neurogenic bladder/encephalopathy with an anterior communicating artery aneurysm.

How often is subarachnoid hemorrhage misdiagnosed and by whom?

Between 20 and 50% of patients with documented subarachnoid hemorrhage report a distinct, unusually severe headache in the days or weeks before the index episode of bleeding. These headaches are considered to be limited hemorrhages or “sentinel” leaks. Overall, there is a delay in diagnosis leading to delays in treatment in approximately 25% of patients who have only a headache. Often these patients do not have neurological impairments and do not appear critically ill and these “minor” headaches are diagnosed retrospectively as warning leaks or “sentinel” hemorrhage.

Patients later found to have SAH are often diagnosed as having other causes of headache such as migraine or tension headaches, viral illness (especially meningitis), drug or alcohol intoxication, or hypertensive encephalopathy
What is the prognosis of a patient with a “warning” headache and unrecognized SAH?

Misdiagnosed “warning” headaches are generally followed by major aneurysmal SAH in approximately 50% of patients.

What are the ECG changes found with intracranial events and why do they occur?

Electrocardiographic alterations in the course of subarachnoid hemorrhage have long been recognized and in most patients during the acute stage of SAH. The most frequent abnormalities involve the ST segment and very negative or positive deep T waves, lengthening of the QT interval, and U waves are often seen. In most cases, these abnormalities are clinically inconsequential and are attributed to neurally mediated electrophysiologic effects and have been correlated with the severity of the neurologic injury.

In some cases, there is evidence of structural cardiac damage. Plasma levels of creatine kinase myocardial isoenzyme (CK-MB) are mildly elevated in 20% to 50% of patients. A characteristic form of myocardial pathology, contraction band necrosis, is commonly found at autopsy and has been produced in experimental SAH models. More recently, echocardiography studies have demonstrated reversible abnormalities of left ventricular contraction and, in severely affected patients, reductions in cardiac output after SAH. And, important in the acute setting, are the findings that symmetrical T wave inversion and severe QTc segment prolongation can identify patients at risk for myocardial dysfunction. These findings suggest that abnormal early ECG findings or elevations of CK-MB should be pursued with echocardiography. Echocardiography can identify those patients with wall motion abnormalities. These structural cardiac abnormalities can lead to reductions in cardiac output resulting in lowered blood pressure and cerebral perfusion. Reductions in cerebral blood flow, intracerebral volume and perfusion can increase the risk of vasospasm and cerebral ischemia. These patients are more likely to benefit from anti-ischemic medications. The potential impact of neurogenic cardiac injury on left ventricular performance after SAH may have important implications because some 30% of patients develop delayed cerebral ischemia related to vasospasm. Vasospasm is generally associated with a loss of autoregulation. Cerebral blood flow in ischemic area can vary passively with changes in blood pressure and cardiac output. Hypovolemia can, then, cause of
symptomatic vasospasm, echocardiography can identify those patients likely to benefit from blood pressure and cardiac output augmentation.

**How valuable is a negative CT scan in SAH?**

Computed tomography is the single most important diagnostic test in the evaluation of a patient with suspected SAH. Its yield on the day of the ictus approaches 95 to 98%. However, the value of CT depends on the quality of the study, the timing of the study, the severity of the hemorrhage, and on the skill level of the reader. It is recommended that very thin cuts (3 mm in thickness) be done through the base of the brain because thicker cuts are likely to miss small collections of blood. The plane of scanning should be parallel to the hard palate. Also, because the visualization of blood on CT is a function of the hemoglobin concentration, the subarachnoid blood of anemic patients may appear isodense rather than white.

The sensitivity of CT decreases over time from the onset of symptoms. The process of clearing the blood and clot lysis begins early after hemorrhage making the detection of small amounts of blood more difficult over a short period of time. Even using modern CT scanners, the sensitivity of CT to detect SAH decreases from as high as 98% to 100% when studies were done within the first 12 hours after the onset of symptoms to 93% when done between 12 and 24 hours after the start of symptoms.

The sensitivity of any diagnostic test that requires interpretation depends on the skill level of the reader. CT scans are typically read by emergency physicians, neurologists and general radiologists or neuro-radiologists depending on when the study is done and whether a consulting physician is available. The skill levels between these physicians vary greatly. The impetus is on the primary or emergency physician to understand the limitations of diagnostic tests, particularly those that require interpretation.

The sensitivity of CT to detect blood is also correlated with the amount of blood present. Therefore, patients with smaller bleeds who often present with subtler signs are more likely to have normal CT scans than those with diminished mental status. Patients with small hemorrhage, who are the most likely to receive an incorrect clinical diagnosis, are also more likely to have negative results on CT.
How does CT Angiography impact on the diagnosis and treatment of patients with SAH?

Spiral CTA is a highly accurate and non-invasive imaging method in diagnosis of intracranial aneurysms in cases with SAH. CTA has been shown to be equivalent to digital subtraction angiography (DSA) to detect both ruptured and unruptured cerebral aneurysms in the anterior in middle cerebral circulation. While detection of small lesions and aneurysms of the posterior communicating artery is somewhat problematic, CTA is considered to be technically comparable to DSA. Eventually, CTA is likely to replace DSA as the only diagnostic and pretreatment planning study for patients requiring early intervention (surgery or endovascular coiling) for ruptured cerebral aneurysm.

Is a lumbar puncture still indicated with the new ‘high-resolution’ CT scanners?

Lumbar puncture to obtain CSF for examination remains an important diagnostic tool when the clinical presentation suggests SAH and a CT scan is equivocal, or technically inadequate. The cerebrospinal fluid (CSF) is tested for the presence of persistent blood and/or xanthochromia. CSF obtained from patients with SAH having symptoms of less than about 12 hours duration will be persistently bloody. In order to help differentiate a “traumatic” lumbar puncture from truly bloody CSF, the CSF should be centrifuged and examined as quickly as possible looking for xanthochromia. Also, the blood in the CSF of patients with SAH will not ‘clear’ or decrease precipitously.

When the lumbar puncture is delayed several days following the subarachnoid hemorrhage, CSF findings will be only xanthochromia or perhaps an inflammatory reaction similar to aseptic meningitis. Xanthochromia is the discoloration caused by the presence of pigmented oxyhemoglobin (reddish pink) and bilirubin (yellow) that result as hemoglobin, released from lysed erythrocytes, is metabolized. Oxyhemoglobin can be detected within hours but bilirubin generally takes up to 12 hours or so to manifest. This makes the timing important when interpreting the results of a lumbar puncture.
What is the role of MRI/MRA in SAH?

Standard MRI is considered inferior to CT for the detection of acute subarachnoid hemorrhage. However, as MR imaging is becoming more available and MR angiography is becoming an attractive alternative to angiography, more and more clinicians encourage the use of MRI/MRA in SAH. MRI does not rely on ionizing radiation and MRI can delineate infarction, often better and earlier than CT. Also, without the limitations caused by transverse artifact from bone on CT, lesions in the posterior fossa are better visualized with MRI.

The sensitivity of MRI alone has been found to be quite high in the diagnosis of subarachnoid hemorrhage. However, images can be obscured by flow artifact. Nonetheless, there is a general sense that as the modality is perfected, it will provide information not only about the anatomy but also about the dynamic status of the brain and go beyond the capability of CT.

Koegh and Vhora found that MR imaging and angiography could adequately identify and characterize lesions so as to enable early surgery on ruptured intracranial aneurysms without resorting to intra-arterial digital subtraction in the acute phase of the illness. Over a 25-month period, sixty-three aneurysms in 122 patients were demonstrated and 55 of these were surgically corrected. The authors concluded that, in view of the multiple images obtained from MRI/MRA, it may often be superior to conventional digital subtraction angiography. The fact that it avoids radiation, is non-invasive, and is relatively easily obtained makes this modality very attractive in the acute phase of care to help plan early aneurysm clipping after SAH.

Using a combination of diffusion-weighted (DW) and hemodynamically weighted (HW) MRI can identify tissue ischemia and early ischemic injury in patients with vasospasm after SAH. By analyzing the passage of an intravenous contrast bolus through the brain a multi-slice map of relative cerebral blood volume (rCBV), relative cerebral blood flow (rCBF), and tissue mean transit time (tMTT) can be constructed. Ischemic lesions on DW images were seen encircled by a large area of decreased rCBF and increased tMTT in all patients with symptomatic vasospasm. Importantly, MRI images were normal in the asymptomatic patient with angiographic vasospasm and the patient with normal angiogram and no clinical signs of vasospasm. If DW/HW MRI can detect early changes in tissue hemodynamics associated with ischemic injury and can identify those patients with vasospasm at risk for ischemia, the technique could become a useful tool in the clinical management of patients with SAH.
What is the role of an antifibrinolytic agent to avoid rebleeding after SAH?

Rebleeding following aneurysmal subarachnoid hemorrhage is a major factor contributing to unfavorable outcome. Antifibrinolytic agents can reduce the rate of rebleeding. However, there is concern that they can potentially increase the risk of cerebral ischemia and infarction and hence provide no overall benefit. Recent studies have revealed no evidence of cerebral ischemia in the first patients treated with recombinant Factor VII.

What is the role of thrombolytic therapy in the management of patients with subarachnoid hemorrhage?

Instillation of small doses (1 to 10 mg) of plasminogen activator into the basal cistern just after aneurysm clipping of patients with large SAH has been shown to facilitate earlier ‘clearing’ of blood clots and ventricular drainage. Also, thrombolysis has been shown to avert cerebral ischemia inevitable in patients with large SAH. Just after the patient is beyond the complications that surround the initial hemorrhage and beyond the risk of early rebleeding, the risk of arterial vasospasm and ischemic injury becomes most important. Vasospasm occurs in upwards of 70% of persons with ruptured aneurysms and produces symptoms in 20-30%. Vasospasm usually manifests in the first 3 to 4 days after the hemorrhage, peaks at one week, and generally resolves over the next 2 to 3 weeks.

How is vasospasm detected after SAH?

Vasospasm can be localized or involve several intracranial arteries. Factors released at the time of the bleeding induce vasoconstriction that decreases cerebral blood flow. The reduction in blood flow leads to brain ischemia and stroke. Transcranial Doppler ultrasonography is an effective screening tool for detection of vasospasm. Doppler can noninvasively measure cerebral flow velocities that have been correlated with the severity of arterial narrowing. It can detect changes in flow velocities that precede the appearance of neurological signs by 24-48 hours, and therapies to prevent ischemia can be started before ischemia begins.
Can early intervention (in the ED) impact on the incidence of vasospasm?

Several measures can help prevent ischemia and the complications of vasospasm after SAH. Treating hypovolemia, generally by avoiding dehydration, will improve circulation. Lowering increased intracranial pressure will also improve cerebral perfusion pressure. As above, careful administration of antifibrinolytic and antihypertensive medications and, in particular, calcium channel blocking drugs, will also lessen the likelihood of ischemic injury.

High levels of intracellular calcium also contribute to cell ischemia. Drugs that block calcium channels limit transmembrane fluxes, which may be effective in the prevention of ischemic stroke following subarachnoid hemorrhage. The ideal calcium channel blocking agent is one that has selective cerebrovascular effects, crosses the blood-brain barrier, and has limited cardiovascular effects. Early administration of a specific 'cerebral' calcium antagonist like nimodipine after SAH protects neural cells and prevents Ca2+-induced smooth-muscle contraction of cerebral vessels by preventing intracellular calcium overloading which encourages ischemic deficits after SAH. Clinical studies of nimodipine, a cerebrovascular-specific calcium channel blocker, have shown an improvement in outcome after SAH with a decrease in the number of deaths due to delayed ischemic deterioration. Oral nimodipine reduces the incidence of cerebral infarction and improves outcome when administered within four hours of SAH.
Outcome of Case

The patient was placed on a monitor and found to have a variety of unsustained atrial arrhythmias. CT scan showed subarachnoid hemorrhage. Neurosurgical consultation was obtained and oral Nimodipine administration was suggested. During the hospital course, she underwent angiography that revealed a ruptured right posterior communicating artery aneurysm. She underwent endovascular coiling on the second hospital day. She developed symptomatic vasospasm 4 days and, after rehab, was left with only a mild right hemiparesis.
References


