Recognizing aneurysmal subarachnoid hemorrhage and understanding management

ABSTRACT:
Aneurysmal subarachnoid hemorrhage (aSAH) is a medical emergency resulting from the accumulation of blood in the subarachnoid space. The incidence of aSAH is approximately 9 per 100,000 person-years and trauma represents the most common cause of SAH followed by cerebral aneurysm rupture. A sudden and severe headache is the cardinal feature of aSAH. Investigations include non-contrast computed tomography (CT) of the head followed by a lumbar puncture in patients with a negative CT scan but a high index of suspicion. Unfortunately, recent evidence suggests that the frequency of non-traumatic SAH misdiagnosis may be between 12% to 50% in the primary care setting and data has shown that patients who are misdiagnosed are at an increased risk of complications and poor outcomes. Management is intensive and involves multiple considerations for the complications associated with aSAH. Treatment of an aneurysm rupture includes endovascular coiling or neurosurgical clipping. Despite available treatment options the case-fatality rate is approximately 50%. This review will summarize the epidemiology, diagnosis and management of aneurysmal subarachnoid hemorrhages in order to help clinicians recognize the presentation of aSAH in a primary care setting and understand its management.

INTRODUCTION
Subarachnoid hemorrhage (SAH) is a medical emergency that occurs when blood pools into the subarachnoid space often following trauma. Aneurysm ruptures constitute approximately 85% of non-traumatic SAH cases. An extremely painful and sudden headache is a cardinal but non-specific symptom in the diagnosis of aSAH. Data has shown that aSAH patients who initially present to the emergency department with an early diagnosis of aSAH have significantly lower mortality rates than those without an early diagnosis. Prior to 1985 the misdiagnosis rate of non-traumatic SAH was 64% and recent evidence suggests that misdiagnosis rate in a primary care setting is between 12% to 50%. Given the necessity for prompt management and the significant case fatality rate associated with aSAH, we present a review of the current diagnosis and management of aSAH to aid primary care physicians.

Epidemiology
The incidence of aSAH is approximately 9 – 10.5 per 100,000 person-years. Rates of aSAH increase with age and the average age at onset is between 50 to 55 years. After 55 years of age, aSAH incidence was found to be greater in women but at younger ages, incidence was higher in men. SAH originating from an aneurysmal rupture, contributes to approximately 5% of all strokes. Incidence rates of aSAH were found to be 20 per 100,000 person-years in Japan and Finland, which were higher than the general population. A higher incidence in Hispanic populations has also been noted in some areas of the US. The average case fatality rate is 51%, and one third of survivors will often require lifelong care.
RISK FACTORS AND THE ETIOLOGY OF aSAH

Risk factors associated with aSAH include hypertension, smoking, having a family history of aSAH and autosomal dominant polycystic kidney disease (ADPKD). It has been reported that first-degree relatives of patients with aSAH have a 4% prevalence of harbouring cerebral aneurysms and a 3-fold to 7-fold increased risk of having aSAH than the general population. Approximately one quarter of patients with ADPKD have been found to have aneurysms at autopsy, and approximately 2% to 8% of patients with aneurysms have ADPKD. Other factors associated with aSAH include alcohol use, cocaine use, Marfan’s syndrome, Ehlers-Danlos, pseudoaxanthoma elasticum and neurofibromatosis type I. Schievink et al reported that aSAH occurred during stressful events in 43% of patients, nonstressful events in 34%, rest or sleep in 12%, and uncertain circumstances in 11%.

Aneurysm rupture represents 80% of all non-traumatic causes of SAH. The remaining 20% are due to various other conditions, which can include but are not limited to coagulopathies, vascular malformations, use of anticoagulants, and brain neoplasms.

Classification of aSAH

The World Federation of Neurological Surgeons Scale (WFNS) was proposed in 1988 and categorized the Glasgow Coma Scale into ranges in order to grade SAH. Conflicting data exists regarding the prognostic power of the WFNS grades, however several studies have demonstrated an increase in likelihood of poor outcomes with increasing WFNS grade. Table 1 demonstrates the likelihood ratio of having a poor outcome in a series of approximately 3500 who were graded prospectively.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Glasgow Coma Scale Score</th>
<th>Clinical Appearance</th>
<th>Likelihood Ratio of poor outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>No motor deficit</td>
<td>0.36</td>
</tr>
<tr>
<td>2</td>
<td>13–14</td>
<td>No motor deficit</td>
<td>0.61</td>
</tr>
<tr>
<td>3</td>
<td>13–14</td>
<td>Motor deficit</td>
<td>1.78</td>
</tr>
<tr>
<td>4</td>
<td>7–12</td>
<td>With or without motor deficit</td>
<td>2.47</td>
</tr>
<tr>
<td>5</td>
<td>3–6</td>
<td>With or without motor deficit</td>
<td>5.22</td>
</tr>
</tbody>
</table>

Classification of cerebral aneurysms

Morphologically, cerebral aneurysms can be classified as saccular, fusiform or dissection. Saccular aneurysms, also called berry aneurysms, are rounded, single-sided outpouching attached by a neck or stem to an artery that supplies the brain. Fusiform aneurysms are formed as damage to the tunica media leads to arterial stretching and elongation, resulting in a 360° out-pouching that tapers at both ends. Dissecting aneurysms, often called pseudo-aneurysms, form as blood accumulates within a tear between the layers of the cerebral artery. Depending on the plane, either internal luminal narrowing or an external out-pouching can occur.

CLINICAL MANIFESTATIONS

Byyny et al reported that 4 out of every 27 patients in an emergency department with a severe and sudden headache were found to have aSAH on computed tomography (CT). Headaches are the cardinal feature of aSAH and 80% of patients with aSAH will eventually present with a severe and sudden headache. Some clinicians have considered the use of headaches to be overemphasized and Linn et al reported that a severe and sudden headache may be the initial symptom in only a third of patients with aSAH. Despite this, aSAH should always be included in the differential when a patient presents with a sudden, severe headache. Additional non-specific features of aSAH include nausea, vomiting, photophobia, and/or loss of consciousness. Absence of any of these clinical findings does not rule out aSAH. Headaches, nausea and vomiting can also be seen in warning leaks or sentinel hemorrhages. In 1752 patients with ruptured aneurysms from three series, 20% had a history of a sudden, severe sentinel headache before the aSAH that lead to their admission.

On admission it has been reported that two-thirds of patients with aSAH have a depressed level of consciousness, of whom half are typically in a coma. These patients may regain alertness or may
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remain in their depressed state of consciousness. Neck stiffness is also commonly seen 3-12 hours following aSAH due to the inflammatory response to blood in the subarachnoid space.3

The location of the aneurysm rupture will affect the deficits seen. Rupture of ACA aneurysms can produce transient bilateral lower extremity weakness, and a middle cerebral aneurysm rupture can lead to hemiparesis, paresthesia, hemianopia, and dysphasia. Seizures occur more commonly with aneurysms of the anterior and middle cerebral artery. Aneurysms arising at the junction of the internal carotid and posterior communicating artery can lead to third nerve palsy or unilateral retro-orbital pain. Carotid-ophthalmic artery aneurysms can produce unilateral visual field defects. Neurological deficits can also arise from mass effect due to the aneurysm’s size, vasospasm, seizures, or hematomas within the cranial space. Table 2 summarizes the possible defects following aneurysm rupture at specific locations.6,18

**Table 2: Possible defects following aneurysm rupture at a specific location**

<table>
<thead>
<tr>
<th>Location of aneurysm rupture</th>
<th>Possible deficits/complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior Cerebral Artery</td>
<td>Transient bilateral lower extremity weakness; seizures</td>
</tr>
<tr>
<td>Middle cerebral Artery</td>
<td>Hemiparesis; paresthesia; hemianopia; dysphasia; seizures</td>
</tr>
<tr>
<td>Anterior communicating artery</td>
<td>Abulia; bilateral lower extremity weakness</td>
</tr>
<tr>
<td>Posterior communicating artery</td>
<td>Third-nerve palsy</td>
</tr>
<tr>
<td>Junction of the internal carotid and posterior communicating artery</td>
<td>Third nerve palsy; unilateral retro-orbital pain</td>
</tr>
<tr>
<td>Superior cerebellar artery</td>
<td>Third nerve palsy;</td>
</tr>
<tr>
<td>Carotid-ophthalmic artery</td>
<td>Unilateral visual loss; visual field defects</td>
</tr>
<tr>
<td>Any Site</td>
<td>Coma; sixth-nerve palsy (due to increased intracranial pressure)</td>
</tr>
</tbody>
</table>

Fundoscopy is essential in patients suspected of aSAH because intraocular haemorrhages can be seen in 10% to 40% of patients with aSAH (Terson syndrome). Patients with retinal hemorrhages may report brown spots obscuring their vision. Retinal hemorrhages are due to increases in CSF pressure that causes obstruction of the central retinal vein as it traverses the optic nerve sheath.12,19

**DIAGNOSIS**

The frequency of aSAH misdiagnosis may be up to 50 percent in patients presenting to a physician in a primary care setting. The common incorrect diagnoses are migraine and tension-type headaches. Obtaining inappropriate imaging study accounts for 73% of misdiagnoses, and failure to perform or correctly interpret the results of a lumbar puncture accounts for 23%.3 Additionally, patients who are misdiagnosed typically have a normal neurological examination and may only present with a headache. No reliable clinical features distinguish a sentinel headache from a benign headache, but any patient experiencing the most painful headache of their life over an acute time period may suggest aSAH and deserves consideration of a CT scan of the head.3,6

The Ottawa SAH Rule was developed in 2013 to help reduce misdiagnosis. It is a clinical decision making tool to help primary care providers rule out SAH and understand when further investigations are required for patients presenting to the emergency department with an acute non-traumatic headache that reached maximal intensity within 1 hour and who had normal neurologic examination findings. The rule states that CT imaging of the head is warranted if the patient presents with one or more of the following risk factors: i) age ≥40 y; ii) neck pain or stiffness; iii) witnessed loss of consciousness; iv) onset during exertion; v) thunderclap headache (instantly peaking pain); vi) limited neck flexion on examination. When the rule was tested in 2131 patients, it was found to have 100% (95% CI, 97.2%-100.0%) sensitivity and 15.3% (95% CI, 13.8%-16.9%) specificity. The Ottawa SAH Rule is summarized in box 1.50

**Box 1. Ottawa SAH Rule**

Use for patients who are: alert; greater than 15 years old; new severe nontraumatic headache reaching maximum intensity within 1 h

Do not use for patients with: new neurologic deficits; previous aneurysms, SAH, brain tumors; or history of recurrent headaches (>3 episodes over the course of >6 mo)

Investigate for SAH if ≥1 high-risk variables present:

1. Age ≥40 y
2. Neck pain or stiffness
3. Witnessed loss of consciousness
4. Onset during exertion
5. Thunderclap headache (instantly peaking pain)
6. Limited neck flexion on examination

Non–contrast-enhanced cranial CT is the first choice of investigation in patients with suspected aSAH. The probability of detecting the hemorrhage is proportional to the volume of blood in the subarachnoidal space, the time after hemorrhage, and the quality of the scan.18 Acutely, aSAH will present as hyperdense areas in the basal cisterns, major fissures, and sulci. Since small amounts of blood can be missed, all scans should be performed with thin slices throughout the base of the brain. CT scans may also reveal subdural or parenchymal haemorrhage in 100% of cases within 12 hours.4 The sensitivity of CT imaging declines as time progresses and the sensitivity of detecting aSAH is 93% within 24 hours, 68% on day 3, 58% on day 5 and 50% on day 7.8,9,32 The declining sensitivity with time highlights the need for additional studies.
Lumbar puncture should be performed in any patient with suspected subarachnoid hemorrhage and negative or equivocal results on head CT scanning. CSF should be collected in four consecutive tubes, with the red-cell count determined in each of them. It is important to distinguish between a traumatic tap and aSAH. Generally, an LP in a patient who had aSAH may reveal an elevated opening pressure, persistently bloody tubes, and xanthochromia. In comparison a traumatic tap typically will present with a normal opening pressure, tubes that are initially bloody but start to clear, and no xanthochromia. Table 3 summarizes some key differences between a traumatic tap and aSAH CSF. In patients with aSAH presenting within the first 12 h, typically all CSF samples will be bloody and approximately half will already have visually apparent xanthochromia. In patients presenting more than 12 h but within 2 weeks, most but not all CSF samples will have blood but almost invariably they will have xanthochromia (by visual or spectrophotometry). In patients presenting later than 2 weeks, there will likely not be any blood or xanthochromia present. Assessing for xanthochromia is one of the best tools to distinguish traumatic lumbar puncture from aSAH. Visually assessing for xanthochromia is subjective and discoloration due to oxyhemoglobin or other substances can be mistaken for bilirubin. Spectrophotometry may be more accurate but may not be available in certain hospitals. If the LP is not consistent with aSAH and the clinician’s index of suspicion is still high, an imaging study, such as CT angiography (CTA) of the head or cerebral angiography, should be the next steps to detect the presence of an aneurysm.6

**Table 3: Lumbar puncture results in a traumatic tap vs aSAH**

<table>
<thead>
<tr>
<th></th>
<th>Traumatic Tap</th>
<th>aSAH (within 12 hours)</th>
<th>aSAH (between 12 hours to 2 weeks)</th>
<th>aSAH (greater than 2 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opening Pressure</td>
<td>Normal</td>
<td>Typically elevated</td>
<td>Normal to elevated</td>
<td>Normal to elevated</td>
</tr>
<tr>
<td>Appearance</td>
<td>Initially bloody but will start to clear</td>
<td>Persistently bloody</td>
<td>Mostly bloody</td>
<td>Clear</td>
</tr>
<tr>
<td>Xanthochromia</td>
<td>Absent</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
</tr>
</tbody>
</table>

Other tests may include a CBC which is non-specific but may demonstrate leukocytosis. Clotting profile may reveal an elevated INR or prolonged PTT. Electrolyte abnormalities may include hyponatremia due to cerebral salt wasting. It has also been reported that 50% of patients with aSAH have abnormal ECG findings including arrhythmias, prolonged QT, ST segment, or T wave abnormalities. It should be noted that although these tools are available, a CT head should still be the primary tool in the diagnosis of aSAH. Figure 1 summarizes the diagnostic approach for an aneurysmal SAH

**COMPLICATIONS OF aSAH**

Non-neurological complications of aSAH include fever, anaemia, hypertension and hypotension, hyperglycaemia, hypernatraemia and hyponatraemia, hypomagnesaemia, cardiac failure and arrhythmias, and pulmonary oedema and pneumonia. Aneurysm rebleeding is an important complication that is a significant cause of mortality after aSAH. The International Cooperative Study on the Timing of Aneurysm Surgery demonstrated that for untreated aSAH, 4% of patients rebled within 24 hours of aSAH and 19% rebled within the first 2 weeks of aSAH. In comparison, rebleeding following endovascular coiling has been estimated to occur at approximately 0.3%/year and rebleeding following surgical clipping has been reported to occur at approximately 0.14% after 8 years. Epilepsy has been reported to develop in one of every 14–20 patients following discharge from the hospital. Cerebral vasospasm has been noted to occur in approximately 46% of patients following aSAH typically within 4 to 14 days following aSAH. Approximately 20% of patients will develop hydrocephalus following aSAH. Cognitive deficits and psychosocial dysfunction in the first year after subarachnoid haemorrhage are common.1

**APPROACH TO MANAGEMENT**

**General therapy and stabilisation**

Aneurysmal SAH is a medical emergency and requires an early referral to a centre with neurovascular expertise and preferably with a dedicated neurologic critical care unit to optimize care. Stabilisation of patients is necessary in order to prevent early complications. Consciousness levels should be assessed using the Glasgow Coma Scale (GCS). Airway adequacy and cardiovascular function should also be assessed early. A poor level of awareness and seizures on presentation are risk factors for aspiration and an endotracheal intubation or mechanical ventilation may be necessary.7 A full neurological examination should be performed. Unilateral dilation of one pupil and loss of the pupillary light response may indicate brain herniation due to increased ICP. A poor neurological exam may predict cardiac abnormalities due to enhanced sympathetic activation (Takotsubo cardiomyopathy). Vitals should be closely monitored and blood pressure should be maintained within normal limits of 90 – 140 mm Hg. If necessary, intravenous antihypertensive agents such as labetalol and nicardipine can be used to maintain a normal blood pressure. It is important to balance the risk of stroke, hypertension-related rebleeding and CPP when assessing blood pressure. Once the aneurysm is secured, hypertension is tolerated but there is debate in regards to what blood pressure range is acceptable. Hyperglycaemia and hyperthermia are two important factors that should be assessed and are associated with poor outcomes. The core body temperature should be kept at or below 37.2 degrees Celsius and acetaminophen may be necessary or cooling devices may be indicated. Glucose levels should be maintained at levels between 4.4 – 6.7 mmol/L and a sliding scale or continuous infusion of insulin may be necessary.
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Figure 1: Diagnostic Algorithm for Patients with suspicion of aneurysmal SAH

CTA = computed tomography angiography; LP = lumbar puncture
Analgesia

Analgesia is often necessary for headaches, and narcotics can be used. That being the case, mental status needs to be closely monitored in the event of reperutation of the aneurysm, acute hydrocephalus, or vasospasm. As a result, judicious use of analgesia is recommended.6

Anticonvulsants

The use of prophylactic anticonvulsants is controversial, however it is associated with increased in-hospital complications and worse outcome. Antiepileptic medications are sometimes administered following aSAH to patients with a history of seizures.44,45

Electrolytes

Electrolyte imbalances (e.g., hyponatraemia) are common and should be corrected. If SIADH is present, restrict fluid intake. In instances of cerebral salt-wasting syndrome, aggressively replacing fluids with 0.9% saline or hypertonic saline solution may be required.6 The effects of other electrolytes on aSAH outcomes have also been studied. The Magnesium for aneurysmal subarachnoid haemorrhage (MASH-2) trial demonstrated that intravenous magnesium sulphate did not improve clinical outcome after Aneurysmal Subarachnoid Haemorrhage.46

Coagulation

If present, coagulopathy should be treated aggressively using fresh frozen plasma and anticoagulant K. Prophylaxis of deep venous thrombosis started early with sequential compressive devices, and subcutaneous heparin should be used following treatment of the aneurysm. Extended use of antifibrinolytic agents reduces rebleeding but is associated with an increased risk of cerebral ischemia and systemic thrombotic events. Early treatment of aneurysms has become the mainstay of rebleeding prevention, but antifibrinolytic therapy may be used in the short term before aneurysm treatment.6

Calcium-channel blockers

Calcium-channel blockers should be started on admission for vasospasm prophylaxis. Calcium antagonists reduce the risk of poor outcome from ischemic complications, and oral nimodipine is currently the medication of choice. Nimodipine is often started within 96 hours of aSAH at a dose of 60mg orally every 4 hours for 21 days.6

Additional Management

Coughing can be suppressed with antitussives to prevent potential rebleeding before definitive treatment of the aneurysm. Stool softeners are often used to prevent straining that may lead to rebleeding. Typical aSAH precautions may also involve a Foley catheter and keeping patients in a dark room with a low stimulation environment.6,47

TREATMENT OPTIONS FOR ANEURYSMS

The two main options for securing a ruptured aneurysm are microvascular microsurgical clipping or endovascular coiling. In endovascular coiling, platinum coils are attached to a delivery wire and advanced into the aneurysm lumen using a catheter. By packing multiple coils, the aneurysm is separated from the cerebral circulation, reducing the risk of rebleeding. Surgical clipping involves a craniotomy, followed by placing a clip over the neck of the aneurysm to exclude it from the blood flow.

Historically, microsurgical clipping has been the preferred method of treatment. Currently there is debate between surgical clipping and endovascular coil embolization.48,50 The International Subarachnoid Aneurysm Trial (ISAT) included 1070 patients who underwent surgical clipping and 1073 patients who underwent endovascular coiling. One year postoperatively, 23.5% of patients who underwent endovascular coiling were dead or dependent at 1 year, compared with 30.9% patients in the surgical clipping group. The study reported an absolute risk reduction of a poor outcome of 7.4% for endovascular coiling as compared to the clipping procedure.90 Criticisms of the study included uneven distribution of enrolled patients, participants were almost entirely from Europe, varying levels of expertise among the health care providers, and enrolment criteria that aneurysms had to be considered suitable for either surgical or endovascular repair.90 Long-term follow-up of patients enrolled in ISAT has revealed an increased risk of recurrent bleeding in the coiling group, but a significant 5-year death risk for patients within the clipping group.51 Another study followed the UK cohort of ISAT patients for up to 18 years, and revealed that patients who underwent coiling were more likely to be alive and independent 10 years postoperatively than patients in the clipping group.52

Factors including the patient’s age, comorbidities, medical condition, aneurysm’s location, morphology, and relationship to adjacent vessels affect the treatment approach. Generally, aneurysms with a favourable dome to neck ratio (greater than 2), or posterior circulation aneurysms are more suitable for endovascular coiling. On the other hand, wide-neck aneurysms, aneurysms associated with large hematomas and middle cerebral artery aneurysms are more suited for surgical clipping. Regardless, clinical trials have demonstrated that patients undergoing early treatment have lower rates of rebleeding and tend to fare better than those treated later. Securing the aneurysm also facilitates the treatment of complications such as cerebral vasospasm, which may require vasopressor medications to induce hypertension.

CONCLUSION

Despite advancing technology and treatments, aSAH continues to have a high case-fatality rate and is frequently misdiagnosed in patients who present with a normal neurological examination. It is important for health care providers to identify non-traumatic SAH since early treatment results in better outcomes for patients. The cardinal feature of aSAH is a sudden and severe headache, and additional features may include nausea, vomiting, photophobia, and meningismus. The first choice of investigation should include a non-contrast CT of the head, followed by a lumbar puncture in patients with a negative CT but a high probability of aSAH based on history. The aSAH patient is best managed in a hospital with a neurological critical care unit and access to neurovascular surgeons or neurointerventionalists. Treatment options for aneurysms include endovascular coiling or neurosurgical clipping, with more recent studies favouring endovascular coiling if the anatomy of the aneurysm is appropriate.


