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INTRODUCTION

Twenty percent of strokes are hemorrhagic, with subarachnoid hemorrhage (SAH) and intracerebral hemorrhage, each accounting for 10 percent. Most SAHs are caused by ruptured saccular aneurysms. Other causes include trauma, arteriovenous malformations/fistulae, vasculitides, intracranial arterial dissections, amyloid angiopathy, bleeding diatheses, and illicit drug use (especially cocaine and amphetamines).

The epidemiology and risk factors of aneurysmal SAH are reviewed here. The epidemiology and management of unruptured aneurysms and the clinical features, diagnosis and treatment of aneurysmal SAH, are discussed separately. Mycotic aneurysms and nonaneurysmal subarachnoid hemorrhage are also discussed separately. (See "Unruptured intracranial aneurysms" and "Aneurysmal subarachnoid hemorrhage: Clinical manifestations and diagnosis" and "Aneurysmal subarachnoid hemorrhage: Treatment and prognosis" and "Overview of infected (mycotic) arterial aneurysm" and "Nonaneurysmal subarachnoid hemorrhage" and "Perimesencephalic nonaneurysmal subarachnoid hemorrhage".)

EPIDEMIOLOGY

In a systematic review and meta-analysis, the overall crude global incidence of aneurysmal SAH across all study periods was 7.9 per 100,000 person-years [1]. By

time trends, the SAH incidence for 2010 was 6.1 per 100,000 person-years in 2010, having declined from 1980 when the incidence was 10.2 per 100,000 person-years.

The incidence of aneurysmal SAH varies by geographic region [1]. For 2010, the incidence in North America was 6.9 per 100,000 person-years, and the rate was similar in Australia/New Zealand (7.4). A much higher rate was reported in Japan (28), while lower rates were reported in Asia excluding Japan (3.7), and in South and Central America (5.1). In a Swiss national database of patients admitted between 2009 and 2014, the incidence of SAH was 3.7 per 100,000 person-years [2].

The mean age of aneurysmal rupture is in the range of 50 to 55 years [3]. While most aneurysmal SAH occur between 40 and 60 years of age, young children and older adults can be affected [4,5]. Black Americans appear to be at higher risk than White Americans [6,7]. There is a slightly higher incidence of aneurysmal SAH in females, which may relate to hormonal status [4,8]. (See 'Estrogen deficiency' below.)

RISK FACTORS

Most SAHs are due to the rupture of intracranial aneurysms. Because of this, risk factors for aneurysm formation overlap with risk factors for SAH. Risk factors that are primarily associated with formation of intracranial aneurysms are discussed separately. (See "Unruptured intracranial aneurysms".)

Hypertension, cigarette smoking, and family history are among the most consistently observed risk factors [9,10]. Many risk factors for aneurysmal SAH are modifiable.

Cigarette smoking — Cigarette smoking appears to be the most important preventable risk factor for SAH [9,11-17]. Among various longitudinal and case control studies the reported relative risk associated with current smoking ranges from 2 to 7. Heavy smokers have a higher risk than lighter smokers, and individuals who stop smoking have a risk of SAH that decreases over time [12,16,17].

In one cohort study, the analysis suggested that smoking is a stronger risk factor for female individuals than males and that the risk factors of hypertension and smoking interact to create a joint risk that is stronger than the sum of the independent effects [18,19].

Hypertension — Hypertension is also a major risk factor for SAH [9,13-15,20,21]. In a systematic review that included 3936 patients with SAH, hypertension was significantly associated with SAH risk in both the longitudinal (relative risk 2.5, 95% CI 2.0-3.1) and case-control studies (odds ratio 2.6, 95% CI 2.0-3.1) [13].

Genetic risk — Most aneurysmal SAHs are of nongenetic origin [22]. However, a number of relatively rare inherited conditions are associated with increased risk of cerebral aneurysm and SAH. These include autosomal dominant polycystic kidney disease, glucocorticoid-remediable aldosteronism, and Ehlers-Danlos syndrome. The risk of aneurysmal SAH associated with these conditions is discussed separately. (See "Screening for intracranial aneurysm", section on 'Hereditary syndromes associated with aneurysm formation'.)

A family history of SAH also increases the risk of SAH in individuals without one of these conditions [9]. As an example, one case-control study found that patients with a family history of SAH had an odds ratio of 4.0 (95% CI 2.0-8.0) for SAH compared with controls [23]. Similarly, another study found that first-degree relatives of patients with SAH have a three- to fivefold increased risk of SAH compared with the general population [24]. Unruptured aneurysms in families with cerebral aneurysms are more likely to rupture than those that arise without a family history [25]. It may be reasonable to screen some family members for the presence of cerebral aneurysm. This issue is discussed in detail separately. (See "Screening for intracranial aneurysm", section on 'Relatives of patients with cerebral aneurysm'.)

The genetic susceptibility to SAH appears to be heterogeneous; many genes on multiple chromosomes have been implicated in various families [26-37] . Some familial SAH pedigrees are most consistent with autosomal dominant inheritance, while others are more consistent with autosomal recessive or multifactorial transmission [38,39]. One study found evidence of anticipation in two successive generations of familial SAH, with affected parents significantly older than affected

children (55.2 versus 35.4 years, respectively) [40].

Familial susceptibility to SAH may be nongenetic and attributed to environmental and other shared risk factors [22].

Alcohol — Moderate to heavy alcohol consumption appears to increase the risk of SAH [13,41]. In a systematic review, excessive alcohol intake was a significant risk factor for SAH in both the longitudinal (relative risk 2.1, 95% CI 1.5-2.8) and case-control studies (odds ratio 1.5, 95% CI 1.3-1.8) [13]. This association was confirmed in a subsequent meta-analysis which also found evidence of a linear dose-response [42].

Sympathomimetic drugs — In case-control studies, phenylpropanolamine in appetite suppressants, and possibly cold remedies, appeared to be an independent risk factor for hemorrhagic stroke (including intracerebral hemorrhage and subarachnoid hemorrhage) in females [43,44]. Caffeine containing medications have also been associated with SAH [45].

Methamphetamine and cocaine abuse have also been associated with both aneurysmal and nonaneurysmal SAH [46-50]. In one study, methamphetamine use was associated with a more severe clinical presentation and worse outcome [51]. Similarly, acute cocaine use was associated with higher rates of rebleeding and in hospital mortality in one study [52]. (See "Nonaneurysmal subarachnoid hemorrhage", section on 'Other causes'.)

Estrogen deficiency — There is a female preponderance for aneurysms ranging from 54 to 61 percent [8]. Because the sex discrepancy is present in older (>50 years) but not younger individuals, hormonal influences have been suggested to play a role in the risk of SAH. In one case-control study, premenopausal females without a history of smoking or hypertension were at reduced risk of SAH compared with age-matched postmenopausal females (odds ratio 0.24) [53]. Furthermore, the use of estrogen replacement therapy was associated with a reduced risk of SAH in postmenopausal females (odds ratio 0.47). Risk reduction with the use of estrogen replacement therapy has also been seen in other observational studies [13,54,55]; however, in the Women's Health Initiative Study, which included more than 90 thousand participants, SAH risk was higher among

those who reported active use of hormone replacement therapy (relative risk 1.6) [56].

Hormonal effects may also explain the association between risk of SAH and repeated childbirth that was observed in one case-control study; each additional parity increased the risk with an odds ratio of 1.34 [57]. However, this association is not consistently observed, and physical and environmental factors during pregnancy and delivery are also likely factors [55]. Studies examining a relationship between risk of SAH and hormonal contraceptive use have had mixed results.

Antithrombotic therapy — Data are limited and conflicting as to whether anticoagulant or antiplatelet therapy increase the risk of aneurysm rupture. Most of the observational data suggest that there is a modestly increased risk of SAH with anticoagulant and antiplatelet therapy [58-60]; however, one study found that long-term aspirin use was protective (odds ratio 0.63) [59]. A systematic review of seven studies found that short-term (less than three months) use of aspirin was associated with risk of SAH, but no association was found for risk of SAH and longer durations of aspirin use [61]. Anticoagulation therapy does appear to increase the severity of a SAH. (See "Anticoagulant and antiplatelet therapy in patients with an unruptured intracranial aneurysm".)

Cholesterol status and statin therapy — The relationship between cholesterol status, statin use, and the risk of ischemic versus hemorrhagic cerebrovascular events is complex. Statin use is associated with an overall lower risk of total and ischemic cerebrovascular events, but there is some concern that low cholesterol levels and perhaps statin use may increase the risk of intracerebral hemorrhage [9]. One systematic review suggested that elevated total cholesterol levels elevate the risk for SAH in males (relative risk 1.33) [62]. (See "Overview of secondary prevention of ischemic stroke".)

One case control study found that current statin use was not significantly associated with a lower SAH risk; however, recent statin drug withdrawal increased the risk of SAH [63]. However, the effect of statin withdrawal was highest in patients who had also stopped taking antihypertensive drugs.

PATHOGENESIS

A rupture of a saccular aneurysm is the cause of most aneurysmal SAH. Saccular aneurysms are acquired rather than congenital lesions; the pathogenesis of their formation is discussed separately. (See "Unruptured intracranial aneurysms", section on 'Aneurysm formation'.)

Epidemiologic studies suggest that most aneurysms do not rupture. The prevalence of intracranial saccular aneurysms by radiographic and autopsy series is 5 percent, or 10 to 15 million people in the United States [64], while aneurysmal SAH occurs at an estimated rate of 3 to 25 per 100,000 population, or, in North America, approximately 30,000 affected persons per year [65-67].

Both aneurysm size and location influence its risk of rupture. This is discussed in detail separately. (See "Unruptured intracranial aneurysms", section on 'Risk factors for aneurysm rupture'.)

An acute trigger event preceding SAH occurs in some cases but is not invariable; some aneurysmal ruptures occur during sleep [48,68]. One trigger is physical exertion. A case-crossover study in 338 patients with SAH found that patients were more likely to have engaged in moderate or greater exertion in the two hours prior to SAH than in the same two-hour period on the previous day (odds ratio 2.7, 95% CI 1.6-4.6) [69]. Acute elevation in blood pressure is believed to be the mechanism by which physical exertion acts as a trigger for SAH and may also play a role in the observed associations between caffeine consumption, acute anger or startling, and sexual exertion as triggers for SAH [70]. Emotionally stressful life events have not been convincingly shown to be a trigger for SAH [71,72].

Rupture of an aneurysm releases blood directly into the cerebrospinal fluid (CSF) under arterial pressure. The blood spreads quickly within the CSF, rapidly increasing intracranial pressure. The blood often spreads into the intraventricular space, but can also spread into the brain parenchyma or rarely, the subdural space, depending on the location of the aneurysm [73,74]. The bleeding usually lasts only a few seconds, but rebleeding is common and occurs most often within the first day.

In addition to rebleeding, secondary events after aneurysmal rupture contribute to brain injury and outcome:

- Hydrocephalus after SAH is thought to be caused by obstruction of CSF flow by blood products or adhesions, or by a reduction of CSF absorption at the arachnoid granulations [75]. The former occurs as an acute complication; the latter tends to occur two weeks or later, and is more likely to be associated with shunt dependence. (See "Aneurysmal subarachnoid hemorrhage: Clinical manifestations and diagnosis".)

- Vasospasm is believed to be produced by spasmogenic substances generated during the lysis of subarachnoid blood clots which cause endothelial damage and smooth muscle contraction [76]. The vascular endothelium produces nitric oxide, which tonically dilates the cerebral vasculature; endothelial damage may interfere with nitric oxide production, leading to vasoconstriction and an impaired response to vasodilators [77]. In addition, increased release of the potent vasoconstrictor endothelin may play a major role in the induction of cerebral vasospasm after SAH [76]. Vasospasm, in turn, can cause regional cerebral hypoperfusion and delayed cerebral ischemia and infarction [78]. (See "Aneurysmal subarachnoid hemorrhage: Treatment and prognosis", section on 'Vasospasm and delayed cerebral ischemia'.)

- Increased intracranial pressure results from a number of factors, including hemorrhage volume, acute hydrocephalus, reactive hyperemia after hemorrhage and or ischemia, and distal cerebral arteriolar vasodilation [79-82]. (See "Aneurysmal subarachnoid hemorrhage: Treatment and prognosis", section on 'Elevated intracranial pressure'.)

Spreading depolarization has also been hypothesized to mediate brain injury after SAH [83].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Stroke in adults".)

SUMMARY

- Most subarachnoid hemorrhages (SAH) are caused by ruptured saccular aneurysms. The causes of nonaneurysmal SAH are diverse. (See "Nonaneurysmal subarachnoid hemorrhage".)
- Aneurysmal SAH occurs at an estimated rate of 3 to 25 per 100,000 population; the incidence appears to vary geographically. Most aneurysmal SAH occur in individuals between 40 and 60 years of age; however young children and older adults can be affected. There is a slight preponderance of aneurysmal SAH in female individuals. (See 'Epidemiology' above.)
- Cigarette smoking appears to be the most important preventable risk factor for SAH. Family history, hypertension, moderate to heavy alcohol consumption, and sympathomimetic drug use are other risk factors. (See 'Risk factors' above.)
- Most aneurysms do not rupture. Aneurysm size and location influence the risk of aneurysmal SAH. (See "Unruptured intracranial aneurysms", section on 'Risk factors for aneurysm rupture'.)
- Physical exertion may trigger some aneurysmal ruptures, perhaps by precipitating an acute rise in blood pressure. Most aneurysmal SAH occur without an identifiable trigger. (See 'Pathogenesis' above.)
- Rupture of an aneurysm releases blood directly into the cerebrospinal fluid (CSF) under arterial pressure. Rebleeding is common, especially within the first 24 hours. Blood spreads throughout the CSF space and leads to secondary complications of increased intracranial pressure, vasospasm, and hydrocephalus. (See 'Pathogenesis' above.)

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