14 Hemorrhagic Diseases

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Abstract

The cerebrovascular event of strokes can be classified as ischemic strokes and hemorrhagic strokes. Hemorrhagic stroke occurs in approximately 10–15% of all cerebrovascular strokes. Mortality and morbidity rate is reported to be high among patients with hemorrhagic stroke.

The most typical hemorrhagic strokes are intracerebral hemorrhage, subarachnoid hemorrhage, hemorrhage due to arteriovenous malformation, and arteriovenous fistula. Computed tomography, magnetic resonance imaging, and digital subtraction angiography are used for differential diagnostic evaluations and planning of the treatment. Especially determining the cause of the stroke is essential. After a diagnosis of the hemorrhagic stroke, tailored management including medical, surgical, endovascular or radiosurgical treatment is required to prevent further neurological deteriorations.

In this chapter, epidemiology, diagnostic evaluation, management of intracerebral hemorrhage, subarachnoid hemorrhage, cerebral arteriovenous malformation, and cerebral dural arteriovenous fistula will be discussed.

14.1 Intracerebral Hemorrhage

Spontaneous intracerebral hemorrhage (ICH) accounts for 10–15% of all strokes; however, its contribution to overall stroke mortality and disability is over-proportionally high [1]. Fifty-eight percent of ICH patients die within the first year, and 2/3 of survivors remain moderately or even severely disabled [2]. Various forms of cerebral small vessel diseases underlie the majority of spontaneous ICH. Additional causes include cerebral amyloid angiopathy (CAA), vascular malformations, cerebral sinus vein thrombosis, tumors, vasculitis, and antithrombotic medication.

However, spontaneous ICH is usually caused by rupture of small perforating arteries secondary to hypertensive changes [3–5]. In developed countries, the incidence of hypertensive ICH has decreased with the improvement of blood pressure control [6]. In developing countries, the burden of ICH has not decreased [7]. The out-

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come of ICH is variable, depending on hematoma volume, location, an extension to ventricles, and other factors [8]. In this review, we will summarize the epidemiology, pathophysiology, risk factors, diagnosis, clinical manifestation, general management, prognosis, and outcomes.

14.1.1 Epidemiology

ICH accounts for approximately 8–15% in western countries [9] and 18–24% in Japan [10] and Korea [6]. The data on the frequency of hemorrhagic stroke are contained in a systematic review performed by the Global Burden of Diseases, Injuries and Risk Factors study in 2010, which included 58 studies from high-income countries and 61 studies from low-income countries; this study estimated that in 2010, a total of 5,324,997 people worldwide experienced a hemorrhagic stroke [11] The incidence of ICH is substantially variable across countries and ethnicities. Eighty percent of all ICH cases occurred in low to middle-income countries, clearly indicating that the major global burden lies in these regions. Unlike ischemic stroke, the age-specific incidence of ICH is higher in low-middle income countries than in high-income countries [11]. Another recent inpatient database study from the Netherlands based on retrospective cohort study reported that the incidence of ICH per 100,000 was 5.9 in 35–54 years, 37.2 in 55–74 years, and 176.3 in 75–94 years old in 2010 [12]. For all ages, the annual incidence rate per 100,000 persons was higher in men than in women; 5.9 vs. 5.1 in people aged 35–54 years, 37.2 vs. 26.4 in those aged 55–74 years, and 176.3 vs. 140.1 in those aged 75–94 years [13].

The rate of early fatality is high among patients who have had an ICH: The median one-month case fatality after ICH was 40.1% in a systematic review of 36 population-based studies conducted in 1983–2006 [14]. A worldwide stroke epidemiology study revealed that early stroke case fatality (21-day to 1-month) varied substantially among countries and study periods; the case fatality rate was 25–30% in high-income countries while it was 30–48% in low- to middle-income countries [15]. A decrease in the ICH fatality rate might be attributed to the improvement of critical care [16, 17].

14.1.2 Classification

Spontaneous ICH can be classified as either primary or secondary depending on the underlying cause. Primary ICH accounts for 70~80% of cases and is due to spontaneous rupture of small vessels damaged by hypertension or CAA. Primary ICH is also classified by location as lobar versus non-lobar and supratentorial versus infratentorial [18].

Lobar ICH is commonly the result of CAA. Amyloid deposition in small-sized to medium-sized cortical perforators may lead to the rupture of these vessels, resulting in asymptomatic microhemorrhages or symptomatic lobar hemorrhages [19] (Fig. 14.1a). Non-lobar ICH is most often the result of long-standing hypertension resulting in lipohyalinosis of small perforating arteries of the basal ganglia, thalamus, pons, and cerebellum, leading to deep hemorrhages, often with extension into the ventricles [17] (Fig. 14.1b–e). The most common locations of hypertensive ICH are the putamen, thalamus, subcortical white matter, pons, and cerebellum.

Secondary ICH is associated with a number of congenital and acquired conditions such as vascular malformations, tumors, coagulation disorders, use of anticoagulants and thrombolytic agents, cerebral vasculitis, drug abuse, and cerebral venous thrombosis.

14.1.3 Pathophysiology

14.1.3.1 Hypertensive Vascular Change

ICH is usually caused by ruptured vessels that are degenerated due to long-standing hypertension. Responsible arteries show prominent degeneration of the media and smooth muscles [4]. Fibrinoid necrosis of the sub-endothelium with micro-aneurysms and focal dilatations may be seen in some patients. Lipohyalinoses, promi-

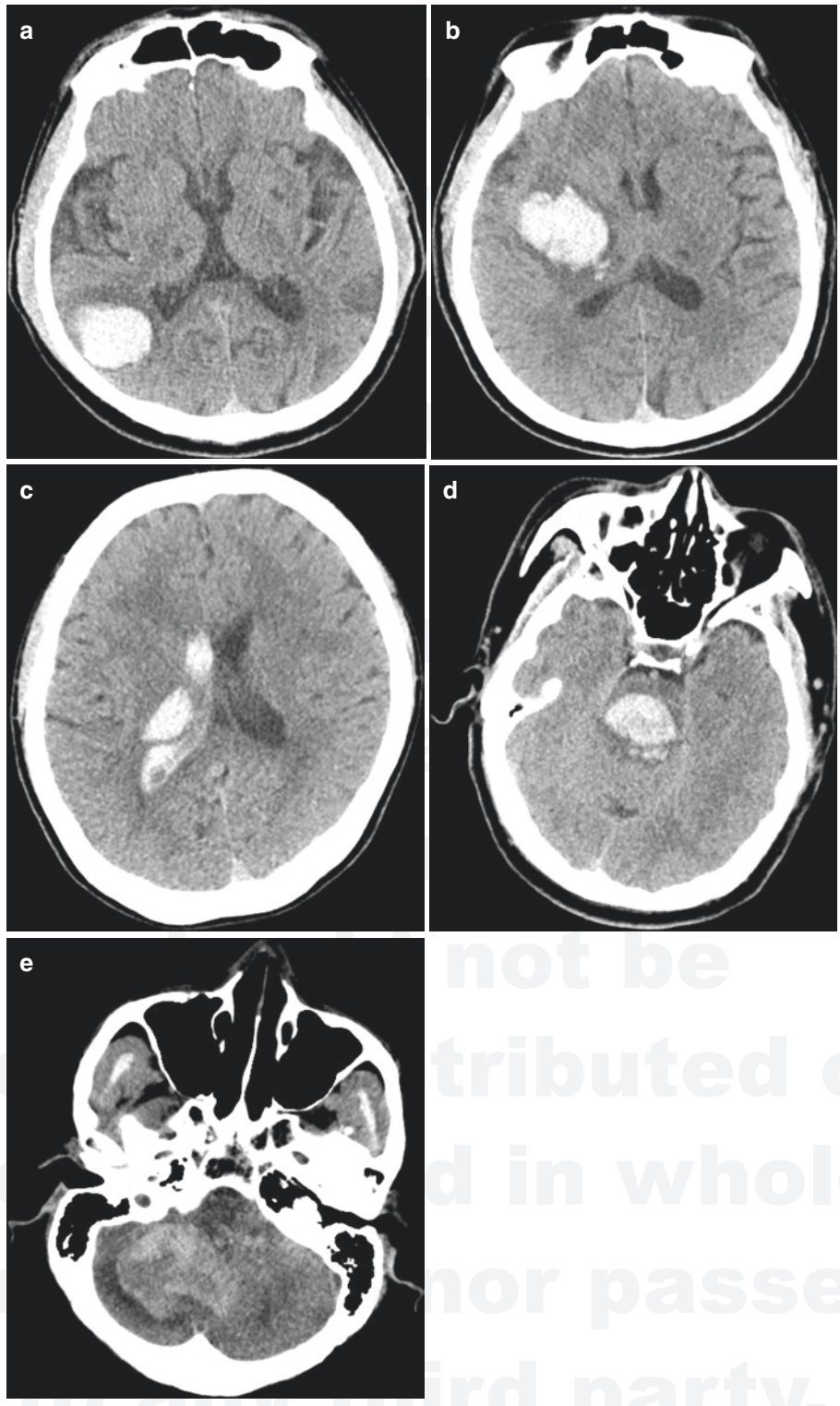


Fig. 14.1 Various types of ICH. (**a**) Lobar ICH, (**b**) ICH on basal ganglia, (**c**) Thalamic ICH with IVH, (**d**) ICH on pons, and (**e**) ICH on cerebellum

nently related to long-standing hypertension, is most often found in non-lobar ICH [16], whereas CAA is relatively more common in lobar ICH.

14.1.3.2 Cerebral Amyloid Angiopathy (CAA)

CAA is characterized by the deposition of amyloid-β peptide at capillaries, arterioles, and small- and medium-sized arteries in the cerebral cortex, leptomeninges, and cerebellum [20]. CAA in the cerebral small vessel leads to sporadic ICH in elderly people, commonly associated with variations in the gene encoding apolipoprotein E epsilon 2 and 4 in chromosome 19 [21]. Duplication of the APP locus on chromosome 21 is also found in families with familial early-onset Alzheimer disease and CAA. CAA-related ICHs occur mainly in the elderly subjects while a rare familial syndrome may manifest in relatively young patients.

14.1.4 Risk Factors

Older age, hypertension, African-American ethnicity, low LDL cholesterol, and low triglycerides increased the risk of ICH [22]. Hypertension is the most important modifiable risk factor for spontaneous ICH. Those with Stage 3 hypertension at baseline have five times the risk as those without hypertension [22]. Anticoagulation-related ICH is nowadays increasing because of the increased use of oral anticoagulation in the elderly population. Warfarin users were at a much higher risk of ICH compared with no therapy, with a marked association with an international normalized ratio >3 [23]. Antiplatelet therapy can increase the risk of ICH with a small but significant increase. Another study reported that sympathomimetic drugs and chronic kidney disease were also associated with ICH.

Cerebral microbleeds (CMBs) were more prevalent with advanced age and males and associated with hypertension, diabetes mellitus, and cigarette smoking [24]. The prevalence of CMBs is the highest in spontaneous ICH (79%), followed by atherothrombotic brain infarction (46%), and other types of infarction (39%) [25]. Among all patterns of CMB topography, the strictly lobar CMB type is the most established specific pattern for a small vessel disease that is CAA, which is commonly seen in lobar ICH in the elderly. Similar to lobar ICH, CMBs in CAA have a posterior cortical predominance and they also tend to cluster in the same lobe [26].

14.1.5 Diagnosis and Imaging

Non-contrast Computed tomography (CT) scan is highly sensitive and specific for ICH and will reveal not only the location and amount of hematoma but also intraventricular extension, mass effect, hydrocephalus and early signs of brain herniation. Magnetic resonance imaging (MRI) can be as sensitive as CT but delayed MRI is better utilized as an adjunct tool to aid in the determination of the underlying cause of the ICH (such as CAA, vascular malformations, and underlying tumor). CT angiography is very sensitive for identifying associated vascular abnormalities and contrast extravasation as "spot sign" [27]. Contrast extravasation during angiography is associated with ongoing bleeding and worsening outcome. Repeat imaging study should be considered for evaluation of any neurologic deterioration or for follow-up of any underlying lesion or vasculopathy.

14.1.6 Clinical Manifestation

ICH showed dynamic disease progress and neurologic symptoms usually aggravate over minutes or a few hours. The clinical manifestations vary by the size and location of ICH. Headache is more common in patients with large hematomas and is attributed to traction on meningeal pain fibers, increased intracranial pressure, or blood in the cerebrospinal fluid. Vomiting due to increased intracranial pressure is reported in about 50% of patients with hemispheric ICH, and more common in patients with cerebellar hemorrhages [16]. Decreased mental status indicates large ICHs that involve the brainstem reticular activat-

ing system. Seizures can be delayed but most frequently occur at the onset of ICH. About 50–70% of seizures occur within the first 24 h, and 90% occur within the first 72 h, with an overall risk of seizures of about 8% within 1 month of symptom onset [28]. The only factor independently associated with the occurrence of early and late seizures is cortical involvement of the lobar ICH. Patients with a supratentorial ICH involving the basal ganglia or thalamus have contralateral sensorimotor deficits. In patients with an infratentorial ICH, signs of brainstem dysfunction occur such as an ocular motor or other cranial nerve abnormalities, and contralateral motor deficits [4]. About 10% of patients have dementia before their first stroke, 10% develop new-onset dementia after their first-ever stroke, and more than 30% develop dementia after a recurrent stroke [29]. The most frequent underlying vasculopathies in ICH are CAA and deep perforating vasculopathy, both of which have been associated with cognitive impairment of either the vascular or Alzheimer's type.

14.1.7 Management

14.1.7.1 Emergent Management and Prevention of Hematoma Expansion

ICH is a dynamic phenomenon, and urgent therapy must be taken to fight against hematoma expansion. Indeed, over 20% of patients experience a decrease in the Glasgow Coma Scale (GCS) score between prehospital assessment and admission to hospital [30]. Securing airway, breathing, and circulation is essential to preventing secondary injury from hypoxia and hypertension. Intubation is indicated in a patient with GCS ≤8 or significant respiratory distress. And patient with intraventricular hemorrhage with hydrocephalus, mass effect, or brain herniation should be considered ventriculostomy and hyperosmolar therapy.

Approximately one-third of patients demonstrate significant hematoma expansion within the first 24 h of onset, explaining their early neurological deterioration, which further aggravates outcome. The mechanisms underlying hematoma expansion are not entirely clear, but the initial hematoma leads to twisting of the surrounding tissues which predisposes other potentially diseased microvessels to tear successively and thereby produce a "hemorrhagic avalanche" [31]. Additional therapeutically amenable forces predisposing to continued bleeding include an elevated blood pressure and a coagulopathy. Therefore, management of hypertension and correction of coagulopathy are essential to prevent hematoma expansion which would be the crucial factor for poor prognosis.

14.1.7.2 Management of Hypertension

Initial post-ICH blood pressure (BP) is often much higher than the last premorbid level (mean increase of 40.7 mm Hg). And not only recent premorbid BP increase but also poststroke factors may contribute to elevated BP in acute ICH. Elevated admission BP was significantly associated with increased odds of death or disability [32]. Lowering arterial blood pressure in acute ICH has been studied in several trials. The INTERACT-2 trial comparing early lowering of SBP to <140 mm Hg with <180 mm Hg showed no increase in adverse events in the aggressive treatment group [33]. There was no significant difference in death or severe disability at 90 days. Ordinal analysis of modified Rankin scores indicated improved functional outcomes with intensive lowering of BP [33]. Based on the INTERACT-2 trial, the current AHA/ASA guideline states that early aggressive BP lowering to 140 mmHg or lower is safe and can be effective to improve functional outcomes [34].

In the multicenter Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) II trial used intravenous nicardipine, ICH patients with a GCS of 5 or more were randomized within a 4.5 h time window to an intensive systolic BP target of 110–139 mmHg or a standard target of 140–179 mmHg [35]. The primary outcome was death or disability (modified Rankin Scale 4~6) at 3 months after randomization. There was no significant difference in the primary end points of death or disability (38.7% in intensive lowering

group vs 37.7% in the standard treatment group) and the rate of hematoma expansion [35]. However, the study showed a higher incidence of adverse renal events (9.0% vs 4.0%, $p = 0.002$) in the intensive treatment than the standard treatment group [35]. The mean minimum SBPs of the two groups during the first 2 h were 128.9 ± 16 and 141.1 ± 14.8 mm Hg, respectively; thus, it is likely that the neutral results of the trial were a result of the already good BP management in the group receiving standard treatment. Of note, the much lower minimum SBPs in the intensive treatment group in the ATACH II trial might explain the higher incidence of renal adverse events. In addition, efforts should be taken to ensure stability and consistency in BP lowering, not only in the first 24 h but also in the several days following ICH.

A wide range of agents is available for BP control, though a lack of comparative effectiveness studies means that there is no one ideal recommended drug in the context of acute ICH. Current guidelines cite labetalol and nicardipine as agents to consider as first-line treatment, given their short half-life and ease of titration [36]. Labetalol, a combined selective alpha 1 adrenergic and nonselective beta-adrenergic receptor blocker, has a rapid onset (2–5 min) after intravenous administration and can be given as a bolus without invasive BP monitoring. It is not dependent on renal or hepatic function and therefore may be used in those with renal or hepatic impairment. The second-generation calcium channel blocker nicardipine has an onset of action of 5–10 min and has cerebral and vasodilatory properties that may improve cerebral perfusion. The new third-generation calcium channel blocker clevidipine has a rapid onset (<1 min) and is easily titratable; therefore, several studies have confirmed its efficacy and safety in BP reduction in hypertensive crises in cardiac surgery or emergency department settings [37]. Thiazide should be used with caution because it may cause hyponatremia and worsen cerebral edema in patients with large hemorrhage. In a recent randomized trial, spironolactone was shown to be very effective for patients with resistant HTN [38].

14.1.7.3 Reversal Strategies for Vitamin K Antagonists

Anticoagulant agents are frequently used for the prevention and treatment of a wide range of cardiovascular diseases. Indeed, approximately 12–20% of patients presenting with ICH are taking oral anticoagulants [39]. The most often used anticoagulants are heparin and its derivatives; vitamin K antagonists (VKA) and antiplatelet agents, including aspirin and thienopyridine derivatives such as clopidogrel. The most important complication of treatment with anticoagulants is hemorrhage and each of specific clinical situations requires a careful and balanced assessment of the benefits and risks of reversing anticoagulants. In well-controlled patients in clinical trials, treatment with VKA increased the risk of major bleeding by 0.5%/year and the risk of intracranial hemorrhage by about 0.2%/year [40].

The most straightforward method to counteract the effect of VKA is the administration of vitamin K. However, VKA anticoagulants via inhibiting the synthesis of vitamin K dependent coagulation factors in the liver. Rapid replacement of deficient coagulation factors is preferred for reversal of anticoagulation in cases of clinically significant bleeding. Substitution of vitamin K is crucial but, not enough for an immediate reversal of VKA, as measurable effects take hours to days especially oral administration. Prothrombin complex concentrates (PCC), containing all vitamin K-dependent coagulation factors, are more useful. In a prospective study, in patients using VKAs and presenting with bleeding, the administration of PCC resulted in at least satisfactory and sustained hemostasis in 98% of patients [41]. Moreover, in contrast to fresh frozen plasma (FFP) which are stored in blood banks, PCC are readily available, do not need compatibility testing before transfusion, and can be infused over a few minutes without volume overloading. For all patients taking vitamin K antagonists, vitamin K 10 mg and 3-factor or 4-factor PCC should be administered intravenously for patients with the international normalized ratio (INR) ≥1.4. If repeat INR 15–60 min after PCCs administration shows continued INR elevation above 1.4, consider further correction

with 2–4 units FFP. Reversal of unfractionated heparin is recommended for patients who develop ICH with prolonged activated partial thromboplastin time (aPTT) while on heparin infusion. Intravenous protamine sulfate is the antidote of choice and each milligram of protamine will neutralize approximately every 100 units of heparin given in past 2–3 h. If repeat aPTT remains elevated, repeated at half of the initial dose should be administrated, maximum 50 mg dose.

14.1.7.4 Reversal of Non-vitamin K Antagonist Oral Anticoagulants (NOACs)

NOACs comprise the factor Xa inhibitors apixaban, edoxaban, and rivaroxaban and the direct thrombin inhibitor dabigatran. NOACs are safer than VKA in terms of major bleeding for stroke prevention and they carry about a 50% lower risk of ICH compared to VKA. These agents have relatively stable pharmacokinetic and pharmacodynamic properties; therefore, do not need for repeated dose adjustments.

For patients taking factor Xa inhibitors, activated charcoal can be administrated to prevent drug absorption (within 2 h of drug exposure). Depending on the severity of the clinical situation and in view of the half-lives of the direct Xa inhibitors, the cessation of medication may be sufficient to reverse the anticoagulant effect; however, PCC (50 units/kg) is recommended if the hemorrhage occurred within 3–5 half-lives of drug exposure. In the ANNEXA-4 trial, an infusion of andexanet alfa, a recombinant, genetically modified factor Xa can reverse rapidly by a partial rebound of the oral and parenteral anticoagulant effect including rivaroxaban, apixaban, and edoxaban [42]. It has not been approved by the FDA for clinical use.

Direct thrombin inhibitors (DTIs; e.g., dabigatran, argatroban, and bivalirudin) have good and relatively stable bioavailability after oral ingestion and have the significantly less adverse effect of causing bleeding than VKA. Dabigatran was shown to be effective in the prevention and treatment of both venous and arterial thromboembolism. Furthermore, the half-lives of most of the agents are relatively short; hence, in the case of less serious bleeding, interruption of the treatment will be sufficient to reverse the anticoagulant effect. However, reversal of coagulopathy is indicated if the patient presents within 3–5 half-lives of drug exposure. Idarucizumab (5 g intravenous divided into two doses) is a fragment of an antibody that is an only currently licensed specific antidote for the oral direct thrombin inhibitor dabigatran [43]. Monitoring of the anticoagulant effect of thrombin inhibitors is difficult and the ecarin clotting time may be accurate than aPTT but is not readily available in most routine clinical settings. Practically applicable measure for monitoring the anticoagulant effect may be the diluted thrombin time, which needs to be standardized for the specific agent that was used [44].

14.1.7.5 Reversal of Antiplatelets

Cyclooxygenase inhibitors such as aspirin and the P2Y2G inhibitors clopidogrel, prasugrel, and ticagrelor irreversibly block their targets in platelets and thereby attenuate platelet aggregation. In current clinical practice, bleeding can almost always be managed with local hemostatic procedures or conservative strategies without interrupting aspirin use. Rather, interruption of aspirin has been associated with an increased risk of thromboembolic complications. In a multicenter, randomized open-label trial, platelet transfusion seems inferior to standard care for patients taking antiplatelet therapy before ICH with increased mortality or dependence at 3 months (OR 2.1, $p = 0.0114$) [45]. Platelet transfusion is not recommended for nonsteroidal anti-inflammatory drugs (NSAIDs) or glycoprotein (GP) IIb/IIA inhibitor-related ICH. Nevertheless, under special clinical circumstances, such as ICH need to undergo a neurosurgical procedure, the anti-hemostatic effect of aspirin needs to be reversed immediately. The most rigorous measure to achieve that is the administration of platelet concentrate after the cessation of aspirin. Another approach is the administration of de-amino d-arginine vasopressin (desmopressin) which can be considered in ICH associated with cyclooxygenase inhibitors or ADP receptor inhibitors.

14.1.7.6 Management of IVH

Intraventricular hemorrhage (IVH) can occur in isolation or more frequently as part of parenchymal ICH in up to 45% of patients with ICH. Because it is associated with poor outcome, external ventricular drain (EVD) placement should be considered in patients with GCS ≤8, significant IVH with hydrocephalus due to obstruction of cerebrospinal fluid circulation or evidence of transtentorial herniation [46]. Moreover, intraventricular clots cause inflammation of the ependymal layer and fibrosis of the arachnoid granulations, leading to delayed communicating hydrocephalus. In the recent multicenter, randomized placebo-controlled CLEAR-III trial, a dose-dependently better result of the intraventricular clot lysis was observed in intraventricular t-PA administrated patients, but this showed no benefit of the overall outcome [47]. Subgroup analysis showed reduced mortality in patients with large IVH.

14.1.7.7 Surgical Intervention

The randomized, controlled STICH trial and the subsequent STICH-II demonstrated no benefit for early surgery with hematoma evacuation in patients with supratentorial ICH [48, 49]. Subgroup analysis shows a small survival benefit in patients with lobar hematoma location without significant improvement in functional outcomes. STICH II revealed a trend toward improved outcomes, particularly in those patients whose GCS was between 9 and 12 initially. However, in cases of cerebellar ICH, emergency craniotomy for hematoma evacuation is generally recommended given the high morbidity from the rapid development of brainstem compression (Fig. 14.2). Surgical indications include >3 cm sized hematoma, upward herniation, brainstem compression or hydrocephalus which is not sufficient with EVD alone and further neurological deterioration [50]. With respect to the benefit observed in patients with malignant middle cerebral artery infarction, hemicraniectomy should be considered when targets the space-occupying effect of the massive hematoma.

Recent, less invasive techniques for hematoma evacuation may be promising. The Minimally Invasive Surgery plus tPA for Intracerebral Hemorrhage Evacuation (MISTIE) phase II trial evaluated the stereotactic guided clot catheterization and intermittent dosing of intraventricular tPA to facilitate clot liquefaction and aspiration [51]. It suggested that the procedure is safe and showed a trend toward improved outcomes in the surgical patients compared with the medically treated patients. And MISTIE II study also revealed the association of hematoma evacuation and reduction of brain edema in the surgically treated group. The ongoing MISTIE III trial has added a stereotactic CT-guided Endoscopic Surgery arm and the results are expected soon. Preliminary data showed that the newer trans-Sylvian, trans-insular minimal invasive approaches may yield better results due to relative sparing of cortical function [39]. Evidence from clinical trials suggests that craniotomy is indicated for lobar ICH because the clot reaches the surface of the brain and because access is easy and safe. Meanwhile, EVD catheters may be better for patients with deep ICH. These principles do not apply to aneurysmal or cerebellar ICH [52].

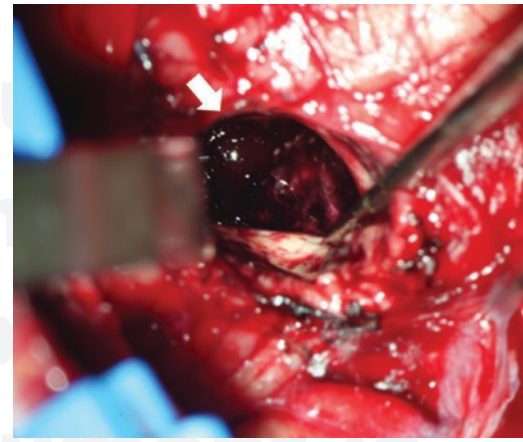


Fig. 14.2 Surgical view of craniotomy and hematoma evacuation for intracerebellar hematoma. After suboccipital craniotomy and minimal corticectomy, thick hematoma was observed in the cerebellar hemisphere

14.1.7.8 Critical Care of Intracerebral Hemorrhage

Patient with ICH has up to 16% risk of clinical seizures within 1 week which are defined as early

seizure [53]. Among them, 50–70% of seizures occur within the first 24 h, and 90% occur within the first 72 h, with an overall risk of seizures of about 8% within 1 month of symptom onset [54]. The incidence of late seizures is around 4 new cases/100 person-years, with a median delay between ICH and seizures of 9 months [55]. The lobar ICH with cortical involvement is an independent predictor of both types of seizures [54]. In contrast with early seizures, the occurrence of late seizures has been associated with worse functional outcome. In addition, the incidence of subclinical seizures which can be detected through the continuous electroencephalography after ICH is 29–31%. Clinical seizures should be treated with antiepileptic medications, as should electrographic seizures accompanied by mental change.

Fever (>37.5 °C) is very common (about 40%) in patients with ICH, particularly in cases of intraventricular extension due to damage to any structures of the central temperature homeostasis pathways [56]. Sustained fever after ICH is an independent risk factor associated with poor outcome and death [57]. However, insufficient data is available to establish whether treatment of fever leads to an improved functional outcome. We consider therapeutic normothermia as a basic principle of neuroprotection and recommend early treatment of elevated body temperature associated with increased duration of sedation or mechanical ventilation.

It has also been shown in many small trials that hyperglycemia (blood glucose levels >140–200 mg/dl) on admission is associated with hematoma expansion as well as higher morbidity and mortality rates in patients with ICH [58]. There are no specific recommendations for lowering the blood glucose levels to a certain level in acute ICH. Also, hypoglycemia (<40–50 mg/dL) may lead to neurological deterioration in ICH patients; therefore, it is reasonable to target glucose level at 100–150 mg/dL for patients with ICH.

Because of their immobility and paresis, patients with ICH are at high risk for deep venous thrombosis (DVT), with the rate of symptomatic DVT at 1–5%. And consecutively, the incidence of symptomatic pulmonary embolism (PE) is ~0.5–2% [59]. and about half of the PE are fatal. Thigh-length graduated compression stockings did not prevent DVT based on the Clots in Legs Or sTockings after Stroke-1 (CLOTS-1) trial [60]. In contrast, the use of elastic stockings combined with intermittent pneumatic compression devices decrease the rate of DVT in patients both hemorrhagic and ischemic stroke and may lead to a better outcome [61]. Other recent guidelines recommend the initiation of mechanical VTE prophylaxis, preferably with intermittent pneumatic compression devices at the time of admission [62]. Prophylactic doses of subcutaneous unfractionated heparin might be started in patients with stable hematomas within 48 h of admission [39].

14.1.7.9 Prognosis and Outcomes

ICH is the most debilitating type of stroke. Known poor prognostic factors of ICH include large hematoma volume, hematoma expansion, GCS score on admission, an intraventricular extension of hemorrhage, hemorrhage location, old age, contrast extravasation on CT scan (spot sign) and anticoagulant use [16] (Table 14.1). The most widely used simple clinical grading scale for evaluating 1-month prognosis is the ICH score, which includes age, GCS score at admission, ICH volume,

Table 14.1 Poor prognostic factors of intracerebral hemorrhage

Intracerebral hematoma volume (≥30 ml)
Expansion of intracerebral hemorrhage
Low Glasgow Coma Scale (GCS) at initial presentation
Intraventricular extension of hemorrhage on initial computed tomography
Infratentorial origin of intracerebral hemorrhage
Old age (≥80 years old)
Contrast extravasation on computed tomography (“spot sign”)
Anticoagulant use
Hyperglycemia at admission
Chronic kidney disease (estimated glomerular filtration rate < 60 mL/min/m^2)

Table is from An SJ, Kim TJ, Yoon BW. Epidemiology, Risk Factors, and Clinical Features of Intracerebral Hemorrhage: An Update. Journal of stroke. 2017;19(1):3–10 [16]

ICH location, and intraventricular extension [8]. These prognostic factors may help to stratify the 30-day mortality risk and functional outcomes at 1 year. Hyperglycemia at admission was also associated with an increased risk of 30-day mortality and, chronic kidney disease was also reported to be associated with poor outcome [16]. Most patients die from ICH due to presumed poor outcome leading to the early withdrawal of care such as do-not-resuscitate (DNR) decisions within the initial hospitalization in the United States [63]. The current AHA/ASA guidelines recommend early and aggressive care after ICH and postponement of any new DNR orders until at least the second full day of hospitalization [34].

14.2 Subarachnoid Hemorrhage

Subarachnoid hemorrhage (SAH) is defined as the extravasation of blood into the subarachnoid space which is the area between the arachnoid membrane and the pia mater surrounding the brain. Trauma to the brain is the most common cause of SAH. Besides trauma, spontaneous SAH can be classified into aneurysmal, nonaneurysmal, and perimesencephalic causes. Around 80–85% of the SAH are caused by rupture of an intracranial aneurysm, and rest of SAH are caused by vascular malformations, vasculitis, etc. [64] As traumatic SAH is beyond the scope of this chapter, and the preponderance of morbidity and mortality of SAH is related to aneurysmal SAH, the chapter focuses on this entity.

14.2.1 Epidemiology

Intracranial aneurysms usually arise from the branching points of arteries which are assumed to have hemodynamic stress on the wall, and it occurs in 1–2% of the population [65]. Annual rupture rate of an intracranial aneurysm is 0.95% from UCAS study [66]. The reported Age-adjusted average annual aneurysmal SAH incidence varies from 2.0 to 22.5 cases per 100,000 persons widely across the world, and it is known to participate in 5–10% of all strokes in the United States [67, 68].

Comparing to other subtypes of stroke, aneurysmal SAH tends to present at younger age. Therefore, loss of productive life is relatively greater than that of other subtypes of stroke [69]. Mortality of aneurysmal SAH within 30 days is approximately 45%, and 30% of the survivors suffer neuropsychological effects and decreased quality of life [70].

The pathophysiology of the intracranial aneurysm is not well defined. However, family history, a genetic disorder related to the connective-tissue disorder and polycystic kidney disease is a commonly reported risk factor [71, 72]. Risk factors associated with SAH can be categorized to modifiable and nonmodifiable risk factors. Modifiable risk factors include hypertension, current smoking, alcohol abuse, use of sympathomimetic drugs, whereas, nonmodifiable risk factors include female gender, black race, Hispanic ethnic group, genetic disorders and an aneurysm larger than 7 mm [71, 73, 74].

14.2.2 Clinical Manifestations

The hallmark presenting symptom of aneurysmal SAH is an abrupt onset of a severe headache which can be observed up to 97% [75, 76]. The patients usually describe their headaches as the worst headache of their life. And in 10–40% of patients, headaches due to a warning leak or "sentinel" a headache can occur 5–20 days before the full presentation of the SAH [77]. Although a severe headache is one of the most important symptoms of aneurysmal SAH, it can commonly occur during physical or psychological stress during daily activities. The previous study reports that a headache due to aneurysmal SAH is only 1% of all headaches evaluated in the emergency department [78]. Furthermore, a sentinel headache can be easily regarded as a migraine headache or other headaches which can lead to four times more morbidity and mortality comparing to properly diagnosed sentinel headache [79]. Therefore, careful documentation of the onset, character, severity, and associated symptoms or

findings that accompany a headache should be taken from the patient's history to avoid misdiagnosis and potential lifesaving [74, 80].

Seizure is another important symptom that present up to 26% of patients with aneurysmal SAH [81–84]. It can be the cause of aneurysmal rebleeding which can lead to intracranial hypertension and herniation. The poor grade in Hunt and Hess scale and Fisher scale is well-known risk factor post aneurysmal SAH seizures [85]. And early seizures at the onset of aneurysmal SAH symptoms are often a sign of rebleeding and a predictor of poor clinical outcomes [81, 85].

With more severely affected aneurysmal SAH cases, patients present with altered mental status. The range of altered mental status can vary from mild lethargy to deep coma. The initial mental status at arrival to the hospital is regarded as the degree of encephalopathy, and it is the major determinant of the prognosis [80]. These patients had a 2.8-fold increase in death or severe disability based on the modified Rankin Scale at 1 year, even when controlling for age, severity at presentation, and aneurysm size [86].

Other symptoms or signs associated with aneurysmal SAH include nausea, vomiting, photophobia, neck stiffness, focal neurologic deficits, and sudden death [87]. As these symptoms or signs are not specific with aneurysmal SAH, as a result, they can easily lead to misdiagnosis.

14.2.3 Grading Scales Used with Aneurysmal SAH

A variety of grading scales were introduced which correlates with prognosis, vasospasm, and aneurysm rupture rate. Although some of the factors overlap with each other, each grading scales represents the nature of aneurysmal SAH.

The Hunt–Hess classification and the World Federation of Neurosurgical Societies classification are the most commonly used grading systems correlated with long-term prognosis [88, 89]. These two grading systems are based on the severity of encephalopathy which is the most important factor in the outcome of patients with aneurysmal SAH. Aneurysm rupture causes immediate brain dysfunction and late events such as vasospasm and delayed cerebral ischemia (DCI) which is potentially related to poor outcome; however, its mechanism is poorly understood [90, 91].

The Fisher scale and modified Fisher scale is the grading system which correlates with the risk of vasospasm [92, 93]. These scales are based on the amount of SAH and intraventricular hemorrhage presented on CT images. Currently, the mechanism of vasospasm is unclear, but it is believed that by-products from hematoma degradation have an important role in arise of vasospasm.

PHASES score is one of the grading systems which prediction of risk of rupture of an intracranial aneurysm [94]. This grading system is a result of systemic analysis of prospective cohort studies. Although it is not a systemic for the prognosis of aneurysmal SAH, it gives an idea of factors that cause the rupture of an aneurysm. According to PHASES score Population (race), Hypertension, Age, Size of the aneurysm, Earlier SAH from another aneurysm, and Site of an aneurysm are the risk factors of an aneurysm.

14.2.4 Diagnostic Evaluation

In patients with suggestive history and physical examination of aneurysmal SAH, brain CT without contrast enhancement is the first step to confirm the presence of bleeding in subarachnoid space which presents typical star shape hemorrhage localized to the basal cistern (Fig. 14.3) [87, 95]. The sensitivity of the CT scan is close to 100% in the first 3 days after the onset of symptoms, and declines to 50% by 5–7 days after the onset of symptoms [96, 97]. Besides time from rupture of the aneurysm, various factors can influence the sensitivity and specificity of non-contrast head CT, which includes the scanner, the radiologist, the amount of the hemorrhage, the patient's hematocrit level (<30%), and the presence of motion or bone artifact [64, 98–100].

If the CT shows negative results, MRI can be an alternative method to diagnose aneurysmal SAH. Although MRI takes more time to scan the

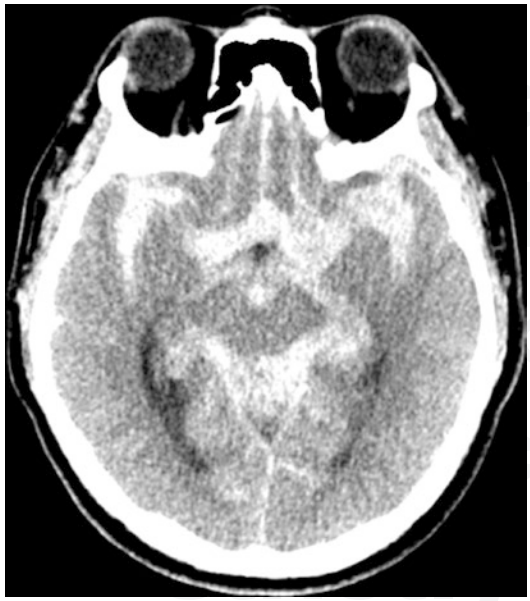


Fig. 14.3 Typical diagnostic image of SAH on CT is a hyperattenuating material seen filling the subarachnoid space, most commonly apparent around the circle of Willis and extending to sulci, fissures, and ventricles

brain image, it has the additional advantage of better sensitivity for detecting chronic bleeding than that of CT. MRI with fluid-attenuated inversion recovery, proton density, and gradient-echo sequences are reported to have high sensitivity to heme in the cerebrospinal fluid [101]. Due to longer study time is required than CT, usually MRI is not the first choice for aneurysmal SAH unless the patient is stable; however, there are physicians who prefer MRI as the first diagnostic choice.

If there CT or MRI is negative from patients with suspicious aneurysmal SAH, detecting blood or xanthochromia in cerebrospinal fluid by lumbar puncture (LP) can be another option [102]. LP has several drawbacks which are an invasive and time-consuming procedure with difficulty in distinguishing between subarachnoid hemorrhage and trauma during the procedure [97]. Furthermore, the sensitivity and specificity of CT and MRI are very high, the value of LP after negative CT or MRI is decreasing. As a result, LP as a diagnostic tool for aneurysmal SAH is in the debate. However, from a recent meta-analysis, there is still a chance of missing aneurysmal SAH by approximately 1% [103]. The value of LP as a diagnosis tool for aneurysmal SAH is diminishing due to low diagnostic yield and high sensitivity and specificity of CT and MRI, it still takes place in American Heart Association and American Stroke Association (ASA) guidelines published in 2012, which recommend to use after negative CT to adequately rule out SAH [95]. LP has an additional value that it can diagnose other cause of headaches, including idiopathic intracranial hypertension (pseudotumor cerebri), spontaneous intracranial hypotension, encephalitis, or meningitis and measure intracerebral pressure during the procedure [104]. Therefore, although LP can be an unnecessary procedure in the near future in diagnosing aneurysmal SAH, it should be kept in mind in the worst scenarios.

Once aneurysmal SAH is diagnosed, the next step is determining the specific location of the aneurysm which is ruptured. CT angiography can be performed immediately after the initial CT, and it can provide the essential information which is required for the surgical treatment [105]. MR angiography can be used as an alternative method also can be used for detecting an aneurysm. CT angiography and MR angiography can detect aneurysms as small as 2–3 mm, but tiny blister aneurysms or aneurysms filled with thrombi may be missed [106]. Although CT angiography and MR angiography provide reliable sensitivity, still they do not give information whether it is ruptured or not.

Digital subtraction angiography (DSA) remains the gold standard for diagnosing an aneurysm and for defining relevant anatomy for treatment [105]. Two-dimensional angiography in DSA provides information on vascular burden and dynamics of the blood flow. In some cases, it can also detect extravasation of blood from the aneurysmal dome which needs urgent treatment. With a combination of three-dimensional angiography reconstructions provides more sensitivity and more accurate anatomical data of the aneurysm and surrounding vessels which can be helpful in planning treatment [80].

14.2.5 Management

The goal of management of aneurysmal SAH is to prevent further neurological deterioration by rebleeding, brain edema, vasospasm, and hydrocephalus. Especially, the path to securing the ruptured aneurysm from rebleeding is the most important goal. Therefore, the management of aneurysmal SAH can be determined into three phases: management prior to secure of the ruptured aneurysm, securing the ruptured aneurysm, and management after securing the ruptured aneurysm. Before securing the aneurysm, the management of aneurysmal SAH management is basically focused to prevent rebleeding and minimize the encephalopathy which can result in high mortality and morbidity. Then surgical of endovascular treatment is performed to secure the ruptured aneurysm. Finally, management to prevent further neurological deterioration by delayed complications such as vasospasm, and hydrocephalus follows.

14.2.5.1 Management Prior to Secure of the Ruptured Aneurysm

Rebleeding is most common within the first 24 h, some studies report that the risk of rebleeding is highest within 2 h [107, 108]. Longer time to aneurysm treatment, worse neurologic status on presentation, initial loss of consciousness, previous sentinel headaches, larger aneurysm size, and hypertension are risk factors of rebleeding [109, 110]. Although early definitive treatment of ruptured aneurysms can reduce the risk of rebleeding, over 12% of patients decease during transportation to the hospital [109, 111].

Seizure; Antiepileptic Drugs

Seizure can be both cause and result of rebleeding and it is also a predictor of bad prognosis [81, 85]. Seizure-like episodes have been reported in up to 26% of patients with aneurysmal SAH, most occurring before arriving at the hospital [81–84]. The risk of seizures increases with poor Hunt and Hess grade and Fisher grade [85]. And delayed seizures occurred in 3–7% of patients [84, 85]. Routine prophylactic antiepileptic drug use in patients with aneurysmal SAH is commonly used by physicians; however, still, there are no randomized controlled trials for the safety and effectiveness of antiepileptic drugs in aneurysmal SAH [112]. Guideline from ASA suggests that short-term prophylactic antiepileptic drug can be used in the immediate posthemorrhage period, meanwhile, the routine long-term use of anticonvulsants is not recommended [95].

Hypertension

High blood pressure is regarded as a risk factor of rebleeding in aneurysmal SAH; therefore, there is the general consensus of strict control of hypertension unless the aneurysm is treated. However, the specific parameters for blood pressure have not been defined. According to ASA guideline maintaining systolic blood pressure less than 160 mmHg and mean arterial pressure less than 110 mmHg is recommended with Class I; Level of Evidence B [95]. In our institute, target blood pressure in aneurysmal SAH is under 140 mmHg which is widely used by many practicing neurosurgeons and endovascular specialists [74]. Blood pressure must be carefully controlled not to effect on lowering cerebral blood flow and an increase of intracranial pressure. Therefore, labetalol, nicardipine, and clevidipine are agents recommended for controlling hypertension [95].

Antifibrinolytic Therapy

Antifibrinolytic therapies such as aminoepsilon caproic acid or tranexamic acid can be considered to reduce the risk of aneurysmal rebleeding in case of an impossible situation of early secure of the aneurysm. Studies on the early and short-term use of antifibrinolytics showed benefits on prevention of rebleeding, but there were no significant benefits on long-term outcomes [113, 114]. ASA guideline suggests short-term (<72 h) therapy with antifibrinolytics is reasonable (Class IIa; Level of Evidence B), but it should be carefully used on a case-by-case basis [74, 95].

Other Medical Management

Various medical problems occur in patients with aneurysmal SAH, includes fever, electrolyte imbalance, cardiac decompensation, and deep vein thrombosis. Fever is one of the most com-

mon medical complications of aneurysmal SAH. Presence of fever in patients with aneurysmal SAH is associated with worse outcomes [115, 116]. As fever induces cerebral metabolism which leads to the production of metabolic by-products such as various cytokines and free radicals, it can accelerate the encephalopathy procedure. Therefore, induced normothermia reduces episodes of cerebral metabolic crises [117]. Evidence of encephalopathy which can be measured with poor Hunt and Hess grade and presence of intraventricular hemorrhage are strong predictors of fever [118].

14.2.5.2 Securing the Ruptured Aneurysm

Once the aneurysm is ruptured, securing the ruptured point to prevent rebleeding is the most important goal of the management of aneurysmal SAH (Fig. 14.4a). There are two major treatments, which is an option in securing the ruptured aneurysm. One is surgical clipping and the other is endovascular treatment. Recently, flow diversion device such as pipeline device emerged as a new treatment method for the treatment of aneurysmal SAH in the endovascular division [119, 120]. Each treatment method will be described in this section.

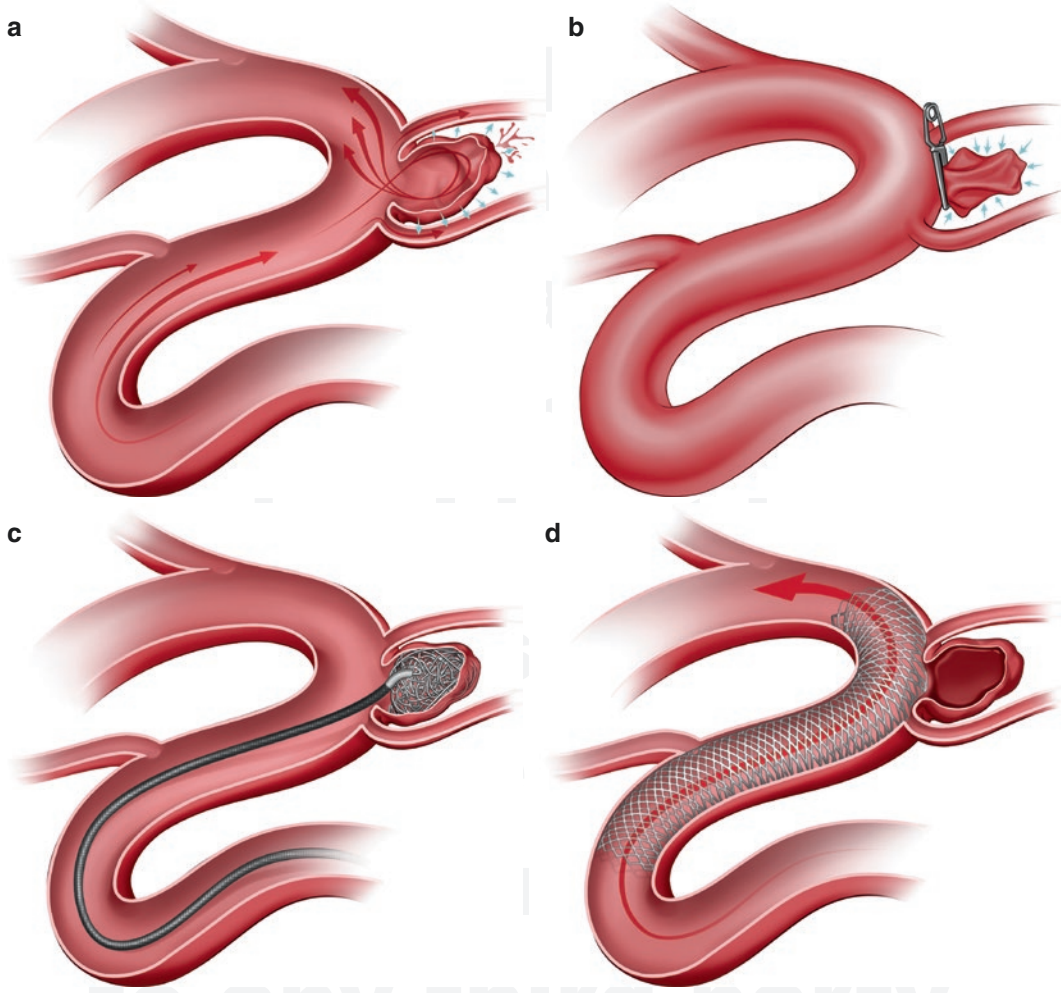


Fig. 14.4 Nontraumatic subarachnoid hemorrhages are usually caused by rupture of the aneurysm. (**a**) a ruptured aneurysm from origin of posterior cerebral aneurysm. Various treatment can be considered, including aneurysmal neck clipping (**b**), endovascular coiling (**c**), and flow diverting devices (**d**)

External Ventricular Drainage

Acute hydrocephalus is common in aneurysmal SAH with intraventricular hemorrhage which causes early neurologic decline. External ventricular drainage can be the treatment option for symptomatic hydrocephalus which can provide ICP monitoring as well as CSF drainage. Acute hydrocephalus can end up with intracranial hypertension and cerebral ischemia eventually cerebral herniation unless it is treated properly. Therefore, identification of the presence of the hydrocephalus on CT is essential to step on the management of aneurysmal SAH.

Microsurgical Clipping

Surgical clipping of a ruptured aneurysm is performed under craniotomy. Usually, subarachnoid hemorrhage spread throughout subarachnoid spaces and adhere to arachnoid and surrounding vessels. Careful dissection is performed around the cerebral arteries under the surgical microscope, to minimize the brain tissue injury. Once the aneurysm is exposed, titanium clip(s) is applied to the aneurysmal neck for mechanical closure of the aneurysm sac (Fig. 14.4b). This procedure preserves blood flow to the normal arteries and prevents rebleeding of the ruptured aneurysm. The majority in the surgical strategy of aneurysmal SAH is similar to that of the unruptured aneurysm. But it has various factors that can alter the surgical difficulties, and it has a larger chance of intraoperative rupture of the aneurysm. In case of presence of cerebral edema, drainage of cerebrospinal fluid via ventriculostomy from Paine's point or fenestration of lamina terminalis could be necessary and additional craniectomy with/without temporalis muscle resection could also be required. And in case of large amount hematoma in cisternal space or intraparenchymal hematoma could alter the anatomic relation in the surgical field. To deal with intraoperative rupture of the aneurysm, proximal control of the parent artery is essential. In the case with difficulty in exposing the proximal parent artery for temporary clipping, the physicians must not hesitate to expose the cervical internal cerebral artery.

Endovascular Treatment

Endovascular treatment of a ruptured aneurysm is performed under fluoroscopic guidance usually via the femoral artery or radial artery. Microcatheter is carefully navigated up to the parent artery of the aneurysm and the tip of the microcatheter is advanced into the aneurysm sac. Metal coil is carefully deployed inside the aneurysm sac, forming a framework like a bird cage (Fig. 14.4c). Once the framework is done, additional coils are introduced to fill the aneurysm sac. This process arrests intraaneurysmal blood flow and proceeds induced thrombus formation which leads to preventing rebleeding of the ruptured aneurysm.

Recent reports present successful results in the treatment of large proximal internal cerebral artery aneurysms with flow diversion devices [121]. Various devices have been introduced to the market, such as Pipeline, Surpass, SILK, FRED, and p64. High metal coverage of flow diversion device forms static intraaneurysmal blood flow which leads to intraluminal thrombus formation (Fig. 14.4d). There are studies that show that flow diversion devices can be used in a selective case in aneurysmal SAH, such as small or blister aneurysm [119, 120].

14.2.5.3 Management After Securing the Ruptured Aneurysm

Cerebral Edema

Global cerebral edema is reported in up to 20% of patients with aneurysmal SAH which is the cause of increased intracranial pressure [122]. Early global cerebral edema is caused by the ictal intracranial circulatory arrest at the time of aneurysm rupture. Various factors can lead to delayed cerebral edema which are cytotoxic effects of blood products, microvascular ischemia, and autoregulation dysfunction [123]. Both early and delayed global cerebral edema can present loss of consciousness. This is an independent predictor of mortality and poor outcomes.

Vasospasm and Delayed Cerebral Ischemia

Vasospasm and DCI is one of the most serious complications associated with aneurysmal

SAH. One-third of patients suffer from SCI who survive the aneurysmal SAH and results in poor outcome in half of the patients with this complication [124]. Approximately 70% of aneurysmal SAH patients present narrowing of cerebral arteries angiographically which is also known as vasospasm. Vasospasm generally starts 3–4 days after aneurysm rupture, peaks at 7–10 days, and resolves by 14–21 days [125] (Fig. 14.5a, b). DCI is a clinical syndrome of focal neurologic deficits that develop in 30% of aneurysmal SAH patients. Delayed cerebral ischemia generally occurs 4–14 days after aneurysm rupture [91]. Delayed cerebral ischemia is one of the major causes of morbidity and mortality after aneurysmal SAH [64]. There is a common belief among physicians that vasospasm is the cause of cerebral ischemia, but each may occur independently of the other. In addition, a recent study suggests that various factors contribute to DCI [126]. Amount of hemorrhage and presence of intraventricular hemorrhage are the most widely known factors of vasospasm and this is also represented on Fisher grade and modified Fisher grade [92, 93].

Classically, induced hypertension, hemodilution, and hypervolemia, the so-called triple-H therapy has been used for the management of hypoperfusion after aneurysmal SAH [127]. However, triple-H therapy was not supported by any controlled studies and adverse effect followed by serious complications arises. Recent systemic review study reports that only induced hypertension seemed beneficial in increasing cerebral blood flow [128], but the single-blind randomized clinical trial of induced hypertension in DCI showed no significant benefit in patients' outcome [129]. However, ASA guideline suggests that induced hypertension is recommended for patients with DCI unless the patient has initial hypertension or cardiac problem and maintenance of euvolemia and normal circulating blood volume is recommended whereas prophylactic hypervolemia is not recommended [95]. Therefore, in current status, maintaining normotension or induced hypertension with euvolemia in aneurysmal SAH must carefully apply to the aneurysmal SAH patients on a case-by-case basis.

Nimodipine is a calcium antagonist that is thought to reduce the rate of cerebral vasospasm

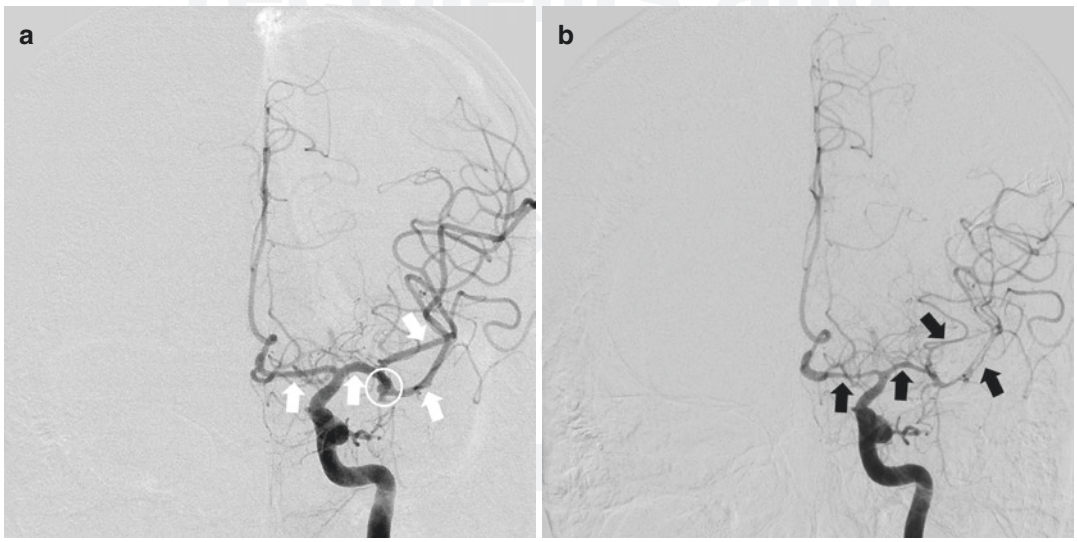


Fig. 14.5 A 57-year-old female administrated due to ruptured aneurysm on left MCA bifurcation. Severe headache with mild fever occurred 10 days after the aneurysmal neck clipping and DSA revealed broad vasospasm at ACA and MCA. (**a**) White circle, MCA aneurysm; White arrow, normal ACA and MCA; (**b**) Black arrow, ACA, MCA with vasospasm

by reducing the influx of calcium into the vascular smooth muscle cells. A Cochrane Review that includes a large randomized controlled trial shows a reduced risk of poor outcome [130]. The administration of nimodipine to reduce the risk of poor outcome and DCI is the only level IA evidence recommended by the ASA [95]. Use of nimodipine showed significant reduction of the risk of angiographic vasospasm; however, no measurable effect was observed on the development of DCI or on clinical outcomes [90, 91]. A Cochrane review of randomized trials indicated that nimodipine reduced the risk of poor outcomes in one-third of patients with aneurysmal SAH [130]. Oral nimodipine is recommended to be administered to all patients with SAH according to the ASA guideline [95].

Transcranial Doppler ultrasonography is widely used as a noninvasive screening for vasospasm after aneurysmal SAH [95]. Perfusion CT or MRI or diffusion MRI can also be used for patients who have a new neurologic deficit. One vasospasm is detected in major cerebral arteries which are not improved by intravenous nimodipine infusion or induced hypertension, selective intraarterial chemical balloon angioplasty under fluoroscope can be considered as a treatment of choice [95]. In addition, balloon angioplasty before the development of vasospasm is not recommended [95].

Hydrocephalus

Both acute and delayed hydrocephalus can develop in patients with aneurysmal SAH. Acute hydrocephalus occurs due to extravasated blood to subarachnoid cistern or ventricles which arrest the normal cerebrospinal fluid circulation. The incidence of hydrocephalus varies from 15% to 85% in patients with subarachnoid SAH [95]. If the hydrocephalus causes encephalopathy which presents in neurologic impairment, a placement of an external ventricular drainage can be performed. Lumbar drainage can be an alternative treatment for acute hydrocephalus. Both external ventricular drainage and lumbar drainage have the capability of removing some contents of the by-products from extravasated blood which could reduce the risk of vasospasm. However, lumbar drainage should not be used in patients with obstructive hydrocephalus and increased intracranial hypertension due to the intraparenchymal hematoma.

One-third of acute hydrocephalus patients caused by aneurysmal SAH suffer from chronic symptomatic hydrocephalus. The mechanism of the chronic symptomatic hydrocephalus is not clearly defined; however, it is generally believed that it is caused by damage of the arachnoid villi, which absorbs cerebrospinal fluid, by extravasated blood. [131]. Permanent diversion of cerebrospinal fluid generally ventriculoperitoneal shunt could be considered to improve neurological impairment including cognitive dysfunction, gait disturbance, and urinary incontinence.

Medical Complication

Multiple medical complications are common in aneurysmal SAH patients; therefore, they should be treated in a neurocritical care unit if possible [132]. There are various goals for aneurysmal SAH patients including euvolemia, normothermia, avoidance of hypoglycemia or marked hyperglycemia, electrolyte balance, and adequate ventilation to avoid exacerbating elevated intracranial pressure. Majority of these goals were described in prior paragraphs; other than these medical problems, deep venous thrombosis should be taken care of in patients with aneurysmal SAH, especially among immobilized patients due to low mental status. Routine prophylaxis with pneumatic compression is recommended. Under risk evaluation of patients with plan of multiple invasive procedures, unfractionated heparin can be considered, starting 24 h after securing the ruptured aneurysm and continuing until patient's mobilization [133].

14.2.5.4 Guidelines

The latest guideline is from a writing group of the American Heart Association and American Stroke Association guidelines published in 2012 for the management of aneurysmal SAH [95]. This chapter generally follows this guideline; however, data from recent systemic reviews, clinical studies were added for further discussion in the management of aneurysmal SAH. Half a

decade has already passed in the current situation; therefore, a new guideline is expected in near future.

14.3 Cerebral Arteriovenous Malformation

Arteriovenous malformations (AVMs) are vascular abnormalities consisting of fistulous connections of arteries and veins without normal intervening capillary beds. Three morphologic features are typical of these lesions: feeding arteries, draining veins, and a dysplastic vascular nidus composed of a tangle of abnormal vessels that acts as a shunt from the arterial to venous system [134]. There is a direct transmission of arterial pressure to venous structures, leading to increased cerebrovascular blood flow, dilatation and tortuous growth of vessels [135]. As a result of this anatomic cerebrovascular changes, this process may bring about significant hemodynamic changes in the brain, such as reversal of venous flow, venous hypertension, and low-resistance AVM shunt "stealing" blood away from surrounding tissue [136]. The most common presentation symptom is intracerebral hemorrhage, followed by a seizure. And the current treatment of AVMs includes microsurgical resection, stereotactic radiosurgery alone, preoperative endovascular embolization followed by microsurgery or radiosurgery, or observation only.

14.3.1 Etiology

Although the pathogenesis of AVMs remains unknown, their angioarchitectural characteristics and presentation at any age indicate that they are probably either embryonic or acquired. Although most AVMs do not occur hereditarily, rare cases of familial occurrence have been reported [137]. AVMs which are related to the genetic disease are very rare. There are no clinically distinguishable features found between acquired and congenital AVMs, but the acquired type tends to be diagnosed or occurred at in their earlier age [137, 138].

Usually, AVMs are found to be a single lesion in the vast majority of the cases, clinical series reported 1~9% incidence of multiple AVMs. Multiple AVMs can occur without apparent cause or in association with syndromic conditions, such as hereditary hemorrhagic telangiectasia (Osler–Weber–Rendu syndrome), Wyburn–Mason syndrome, or soft tissue vascular malformations [139, 140].

14.3.2 Epidemiology and Presentation

The exact incidence of AVMs is an unclear and rather rare disease. The incidence rate of AVMs is estimated from 0.89 to 1.34 cases per 100,000 person-years in different population-based studies [141–143], and the prevalence of AVMs is presumed about 0.2% [135]. AVMs are accounted for 38% of all intracranial hemorrhage in patients between 15 and 45 years of age [144] and patients are usually initially seen in the third or fourth decade in life [145].

The most common presenting symptom of symptomatic AVMs is cerebral hemorrhage followed by seizure, headache, and focal neurological deficit due to mass effect or hemodynamic disturbance [135]. Hemorrhagic presentation of AVMs accounts for 30–72% of patients [146]. Intraparenchymal hemorrhage is the most common type, and it can also present intraventricular hemorrhage or subarachnoid hemorrhage [147]. The second most common symptom AVMs is symptomatic epilepsy, which is present in about 15–35% of patients [143].

14.3.3 Risk of Hemorrhage of Untreated AVMs

Because of the hemorrhagic stroke of cerebral AVMs could result in a serious complication, it is important to identify risk factors which are related to AVM rupture. The average annual hemorrhagic risk of untreated AVMs is about 2–4%,

but it differs from various risk factors and can be as low as 0.9% without any associated risk factors [140, 146, 148]. Cumulative hemorrhage rate was 2% in the first year, 14% at fifth year, and 31% at tenth year follow-up [149].

History of previous AVM hemorrhage, deep-seated location or infratentorial location or AVM and a deep venous draining system are typical risk factors which increase the bleeding risk of AVM [145, 146, 150]. Recent meta-analysis study of future hemorrhage risk of AVM showed that the annual rate of hemorrhage risk of unruptured AVM was 2.2%, meanwhile 4.5% in previously ruptured AVM [151]. Other risk factors are an intranidal or an extranidal aneurysm associated with AVMs and narrowing or occlusion of draining vein [151].

However, cautions are needed in interpreting these results, as the increased risk associated with these characteristics was inconsistent among various studies; the subgroup analysis was performed with a low event rate, and the number at risk for each of these subgroups was small after a short period [152].

Clinical outcome of ruptured cerebral AVMs differs from the extent of injury to adjacent brain structures. Hemorrhage which occurred in near eloquent area, deep white matter pathway, and basal ganglia can be associated with poor clinical outcomes.

14.3.4 Radiologic Findings

The first diagnostic examination which is performed in patients with suspected cerebral AVMs is usually CT and MRI, as the most common presentations, are not specific for AVM (hemorrhage, seizure, headache, and focal neurological deficit) [153].

Non-contrast brain CT is usually the initial imaging tool based on the clinical presentation, to evaluate for any hemorrhage. The AVM usually does not cause mass effect, unless in case of hemorrhage. Instead, there may be hypoattenuation and volume loss in the brain parenchyma surrounding the nidus, relating to gliosis or hemosiderin deposition from previous hemorrhage or chronic hypoperfusion [154]. For evaluation of possible underlying vascular malformation, CT angiography is chosen for next step, which is relatively noninvasive, only requiring an injection of contrast material into a vein. Enhancing nidus, flow-related aneurysms, or prominent draining veins will be well identified in CT angiography, but not as well depicted as on DSA.

On conventional MRI, dilated arterial feeding arteries, the nidus, and draining veins appear as flow voids. Hyperintensity in T2 and FLAIR involving the adjacent brain parenchyma frequently relates to gliosis [154] (Fig. 14.6a, b). MRI with MR angiography could be a useful noninvasive follow-up imaging tool after treatment of cerebral AVM with radiosurgery, which showed 80% of sensitivity and 100% of specificity compared with conventional DSA [155].

Despite of improvement of accuracy in noninvasive imaging modalities, DSA is the gold standard for evaluation of cerebral AVMs (Fig. 14.6c, d). DSA can evaluate image characteristic mentioned above, it can also find very small flow-related aneurysms, which makes it possible for the planning of endovascular embolization and evaluation of precise nidal extent for preradiosurgical planning. However, CT and MRI are required to recognize the relation between vascular structure and brain parenchyma, and it has a risk of permanent neurological deficit accounted for 0.1–1.0% [156].

14.3.5 Classification

For prediction of treatment outcome, several grading systems have been used for cerebral AVMs usually based on anatomical features. The Spetzler–Martin grading system is the most widely used scale for this purpose, which was originally developed not only to predict the outcome of microsurgical treatment of the cerebral AVMs but can also be used to predict the radiosurgical treatment outcome [157]. This scale includes major factors important in determining the difficulty of AVM resection: the size of the AVM, the pattern of venous drainage, and

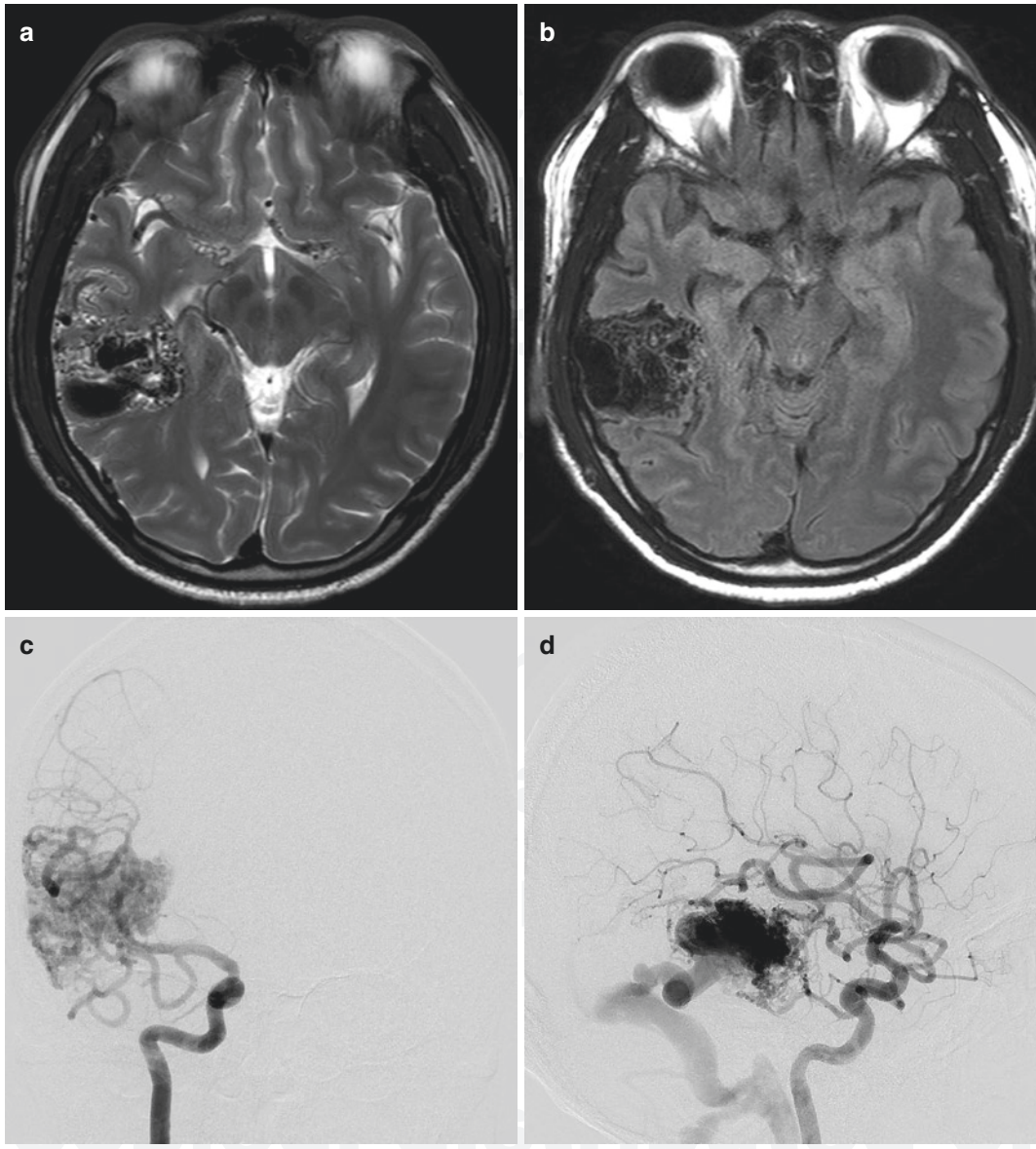


Fig. 14.6 A 29-year-old male presented with a headache and dizziness. About 5 cm entangled vascular mass with signal voids in right temporal lobe (**a** T1 weighted MRI, **b** FLAIR MRI). DSA revealed engorged feeding arteries from right MCA and PCA branches supplying nidus and engorged draining vein into right transverse sinus via vein of Labbe was noted (**c**, **d**)

the eloquence of adjacent brain. A numerical value is assigned for each of the factors (Table 14.2): the diameter, <3 cm (1 point), 3–6 cm (2 points), or >6 cm (3 points), presence of deep venous drainage (1 point), and involvement of an eloquent location such as the motor, sensory, language, and visual cortex or basal ganglia (1 point). Complete resection of grade I lesion would require relatively minor technical difficulties and resulted in no or minor mortality and morbidity. But the highest grade (grade V) lesion would be associated with poor outcome of surgical morbidity and mortality. The authors defined grade VI as "inoperable"

Table 14.2 Spetzler–Martin Grade and Supplementary grade

Spetzler–Martin Grade	Points	Supplementary grade
Size (cm)		Age (year)
<3	1	<20
3–6	2	20–40
>6	3	>40
Venous drainage patterns		Bleeding
Superficial	0	Yes
Deep	1	No
Eloquence		Compactness of the Nidus
No	0	Yes
Yes	1	No

This table is from Lawton MT, Kim H, McCulloch CE, Mikhak B, Young WL. A supplementary grading scale for selecting patients with brain arteriovenous malformations for surgery. Neurosurgery. 2010;66(4):702–13; discussion 13 [158]

lesion because of surgical resection wound almost inevitably resulted in totally disabling deficit or death.

Recently, some clinicians use simplified Spetzler–Martin grading system. Class A includes grades I and II, class B includes grade III, and finally class C includes IV and V. The advantages of this modification include simplification, a larger sample size for each group for analysis of clinical series, and a system that reflects current decision-making [159]. In addition, supplementary grading system which is added to Spetzler–Martin grading system is also introduced to stratify surgical risk more evenly [158] (Table 14.2).

For the prediction of treatment outcome of radiosurgery for cerebral AVMs, the Virginia Radiosurgery AVM scale (VRAS) and the radiation-based AVM score (RBAS) have been introduced [160, 161].

14.3.6 Treatment

The main goal of AVM treatment is the prevention of intracranial hemorrhage and further brain injury. Treatment planning for AVM depends on the risk of subsequent hemorrhage, which is determined by the demographic, historical, and angiographic features of individual patients. History of hemorrhage, deep venous drainage, stenosis or occlusion of venous outflow, and flow-related aneurysms make subsequent hemorrhage more likely. Four therapeutic approaches have evolved to treat AVMs: surgery, radiosurgery, embolization, and conservative treatment. There is a lack of consensus about the choice of treatment, and the specialty of the physician who first sees a patient with an AVM often determines management [162].

14.3.6.1 Observation

There was no widely accepted consensus whether observation or performing invasive treatment to whom diagnosed unruptured cerebral AVMs. Because some clinicians take into account patients diagnosed with an unruptured cerebral AVMs who were also considered candidates for invasive treatment due to the possibility of hemorrhage. Otherwise, the opposite side insists an observation policy because of the low incidence of annual hemorrhage risk of unruptured cerebral AVMs [140].

Therefore, the multicenter randomized clinical trial of unruptured brain AVMs trial (ARUBA) was conducted [163]. The patients with an unruptured cerebral AVMs were randomized to observation or invasive therapy (endovascular, surgical, or radiosurgery), which was stopped because of superiority of the observation. But this study has been criticized on many points. Generally grade 1 or 2 are good candidates for surgical resection, skillful surgeons have reported success rate of microsurgery up to 95% which were confirmed on MRI or angiography [164]. The data were not analyzed according to the type of invasive treatment, specific characteristics of the lesion's location, and patient's risk factor which can affect the outcome of treatment [165]. In addition, it generally takes 2–5 years to assess treatment outcome of stereotactic radiosurgery (SRS) due to a characteristic of the treatment process. However, the ARUBA study terminated at 33 months which considered too short for determining the outcome of SRS.

14.3.6.2 Embolization

Embolization involves occluding blood flow by introducing occlusive materials into feeding

arteries and nidus of an AVM. There are two main types of liquid embolic materials, *N*-butyl-2-cyanoacrylate (NBCA) and Onyx [166]. NBCA is a classical liquid embolic material. However, it is difficult to handle and highly adhesive resulting in some complications such as gluing of the microcatheter to the vessels. Recently, Onyx is widely used as an alternative to NBCA for treatment of DAVFs and AVM.

The purpose of embolization in AVMs can either be curative or adjuvant therapy. Curative embolization can be performed in selective cases if the size of the AVM is small and have one or two feeding arteries. And it can be performed prior to the microsurgical resection or stereotactic radiosurgery (SRS) to reduce the blood flow and shrink the size of the nidus of the AVM. During the embolization, it is important not to violate the draining veins as it can result in devastating outcomes. Complications of embolization of the AVM have been reported in up to 14% of cases [167–169]. Majority of the complications are minor complications which are related to endovascular procedures; however, severe complications including major hemorrhage, major stroke, and death have also been reported.

14.3.6.3 Microsurgical Resection

Since the first reported craniotomy was done for resection of cerebral AVMs, surgical skill was developed incredibly with the introduction of operating microscope, brain navigation, and development of surgical instruments [170]. After craniotomy is done, arterial feeders are isolated and ligated. After gentle dissection around the nidus with complete resection, ligation of the draining vein is the last step in surgery. When doing dissection or cauterization, damage to surrounding structures (basal ganglia, deep white matter tract, functional cortex) or massive bleeding from incomplete ligation results in the poor clinical outcome or even death.

For assessment of postoperative surgical outcome and risk, the Spetzler–Martin grade has been used. Surgical resection is usually strongly recommended to the treatment of low-grade cerebral AVMs if surgically accessible with low risk [171] because when experienced surgeons conducted microsurgical resection of low-grade cerebral AVMs, high cure rate with low complication rate has been reported [164]. Grade III AVMs are heterogeneous entity, which is size <3 cm with superficial venous drainage in the eloquent area have a similar risk of low-grade cerebral AVMs. Otherwise cerebral AVMs in size of 3–6 cm with superficial draining vein located in the eloquent area have similar operative risk as that of high-grade cerebral AVMs [172]. High-grade cerebral AVMs are often not amenable to surgical treatment alone because of high surgical morbidity and mortality rate. These AVMs can be approached by a combined multimodal approach of a combination of embolization, radiosurgery, or surgery [171].

14.3.6.4 Stereotactic Radiosurgery

Over the past 40 years, SRS has been accepted as an appropriate management option for treatment of cerebral AVMs and shown to be effective even for small AVMs located in critical areas of the brain where the surgical risk would be considered unacceptable [173, 174]. The complete obliteration rate of the cerebral AVM usually depends on the volume of the lesion and the delivered radiation dose to the margins of the lesion. Lesions which respond most favorably to SRS were AVM with a volume less than 4 cm^3 treated radiation dose of 18 Gy or more (77.3%). Whereas larger lesion with less marginal dose (<18 Gy) achieved less successful rate (48.3%) [161].

The limitation of the SRS of cerebral AVMs area complete obliteration could take a long time, even for several years, the patients are exposed continuously to ongoing hemorrhagic risk, and patients can experience radiation-induced complications [161]. Also, SRS is not therapeutically effective for all lesions, large, high-grade Spetzler–Martin, VRAS, RBAS showed poor response to SRS; physicians should consider alternative treatment methods for overcoming the weakness [175]. Other factors related to poor treatment response of AVM to SRS are changes of nidal morphology after SRS due to resection of hemorrhage, treatment planning error [176, 177].

To improve treatment success rate of SRS for large or high-grade AVMs, a neoadjuvant endovascular embolization of nidus and feeding vessels with materials such as *N*-butyl-2-cyanoacrylate or ethylene vinyl alcohol copolymer, has been developed [175]. As a result volume reduction of a large AVM nidus may improve the obliteration rate after SRS of the residual AVM. Neoadjuvant embolization also reduces surgical morbidity by occluding deep arterial feeding vessels, minimizing the need for extensive dissection into deep white matter pathways adjacent to the AVM [178].

14.4 Cerebral Dural Arteriovenous Fistula

14.4.1 Epidemiology and Pathophysiology

Intracranial dural arteriovenous fistulas (DAVFs) are abnormal arteriovenous shunts between dural arterial feeders and dural venous sinus or cortical veins. DAVF is distinguished from AVM in that an abnormal shunt is made in dura mater and that there is no parenchymal nidus. DAVFs are rare diseases, accounting for 10–15% of all intracranial malformation [179–182]. In addition, DAVFs constitute approximately 6% of supratentorial and 35% of infratentorial vascular malformation [180, 182]. These abnormal shunts are mainly located at the dural leaflets around venous sinus, especially at the transverse–sigmoid sinus (50%) (Fig. 14.7), cavernous sinus (16%) (Fig. 14.8), tentorium (12%), superior sagittal sinus (8%), anterior cranial fossa (Fig. 14.9), foramen magnum (Fig. 14.10) and other locations [183]. DAVFs do not show a clear difference in sex ratio and mainly occur in the age of 50s and 60s, and rarely occur at younger ages including children [179]. In addition, there is no clear evidence that DAVFs are associated with genetic factors.

Most DAVFs are presumed to be idiopathic, but some cases of DAVFs occur secondary to concomitant disease including head trauma, previous brain surgery, infection, cancers, or dural venous sinus thrombosis [179, 184, 185]. The pathophysiological mechanism of DAVF formation is not fully understood. However, DAVF is thought to be caused by progressive steno-occlusion of a dural venous sinus and be a dynamic disease. The fistulous connection between meningeal arteries and venous sinus or cortical veins may develop as the result of the elevation of the venous sinus pressure. This pathological process is presumed to progress via the opening up of preexisting micro-shunt or de novo formation of fistula from neoangiogenesis [166, 179, 186, 187]. As a result, the venous sinus and the venous tributaries related to the affected sinus are exposed to arterial pressure. With an elevation of the pressure within the venous sinus, the normal venous outflow is affected. Therefore, the normal antegrade venous outflow is converted to the retrograde flow through cortical veins that cause venous hypertension. However, DAVF is not a static disease and can be changed dynamically over time; additional recruitment of additional feeders from external carotid arteries (ECA), recanalization of thrombosed sinus and spontaneous resolution of the fistula due to thrombosis may occur.

Cavernous sinus DAVF (CSDAVF), which is a unique subtype of DAVF, means the abnormal fistulas between internal carotid artery (ICA) and/or ECA and cavernous sinus (CS) and is also called cavernous carotid fistula (CCF) (Fig.14.8). CSDAVF is divided into direct type and indirect type. Direct CSDAVFs that are defined as a high-flow direct shunt between the ICA and CS are usually developed at the cavernous segment of ICA due to skull base fracture, rupture of an aneurysm at the cavernous segment ICA, and iatrogenic causes. Indirect CSDAVFs that may develop spontaneously are usually low-flow shunt between meningeal branches of ICA and/or ECA and CS. Several medical comorbidities, such as postmenopausal status, pregnancy, diabetes mellitus, connective tissue diseases, and hypertension may affect the formation of indirect CSDAVFs [179].

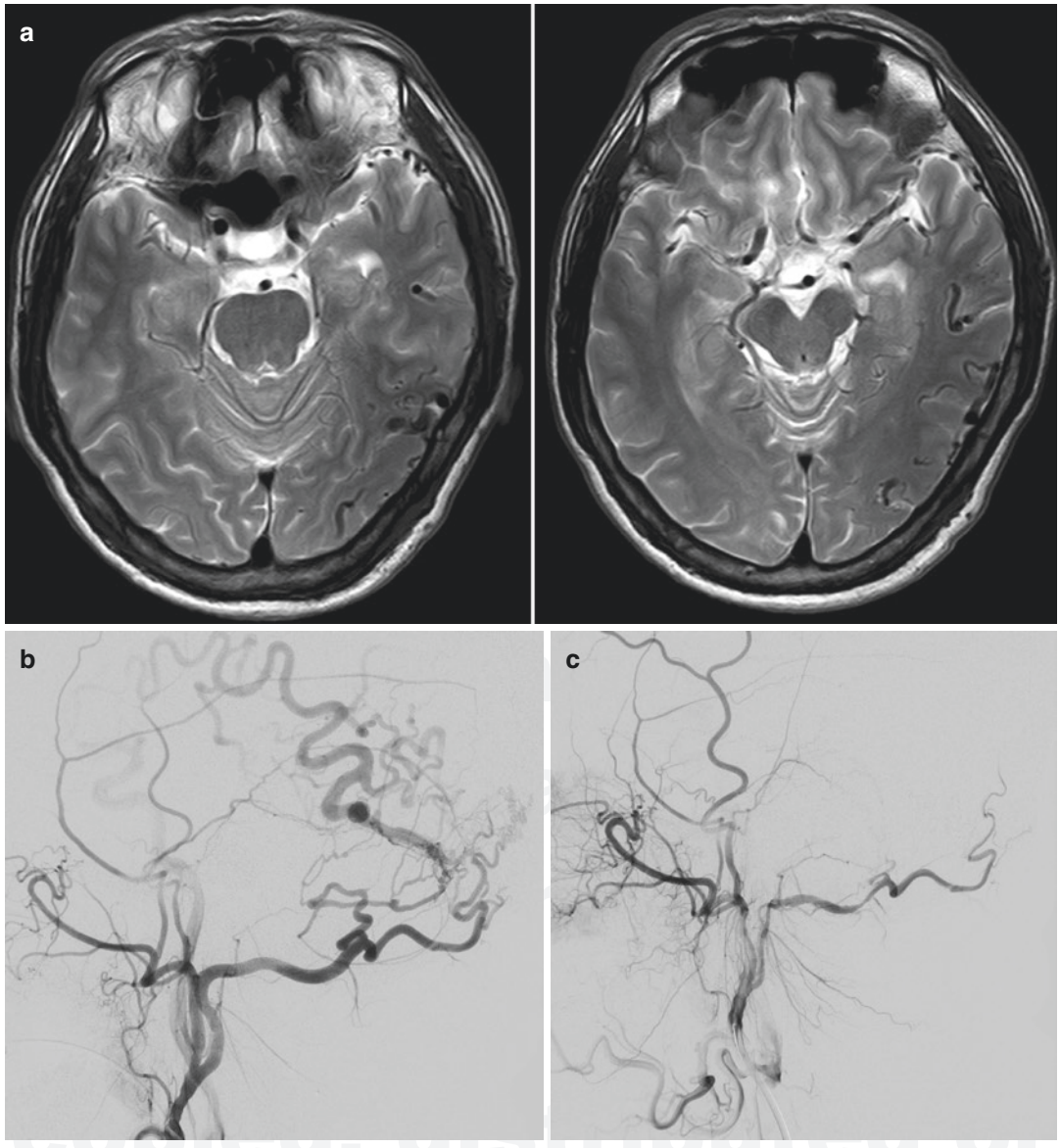
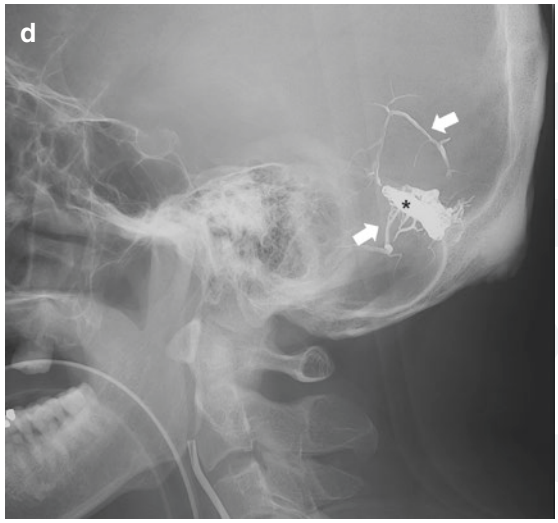


Fig. 14.7 A 43-year-old woman presented with a seizure. (**a**) T2-weighted magnetic resonance images show the flow voids from large arterialized draining veins. (**b**) Digital subtraction angiography (DSA) shows the dural arteriovenous fistula (DAVF) at the left transverse sinus. Main feeding arteries are the stylomastoid branch and transmastoid branch of occipital artery and the middle meningeal artery. DSA also shows that the DAVF has retrograde cortical venous reflux without antegrade flow and trapped segment of left transverse sinus with reflux into the arterialized and enlarged subarachnoid veins (Borden type III 2). (**c**, **d**) The DAVF was obliterated with transarterial embolization using Onyx and transvenous embolization using coils. White arrow, Onyx cast; Asterisk, Coils



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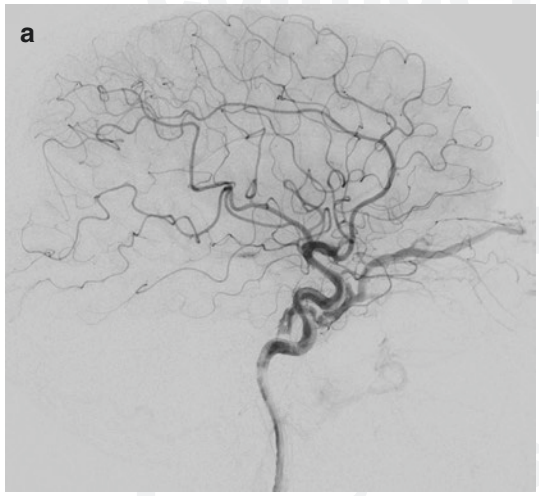


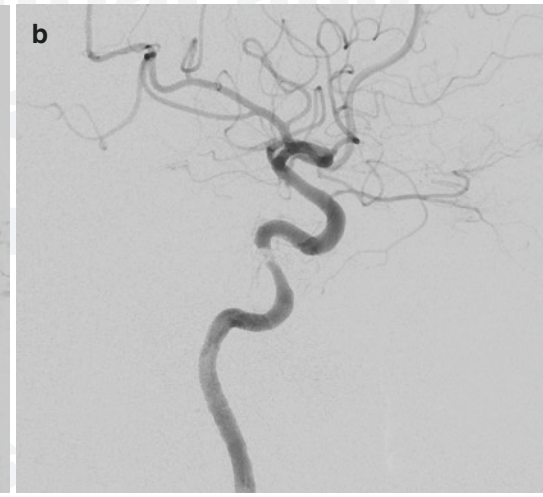
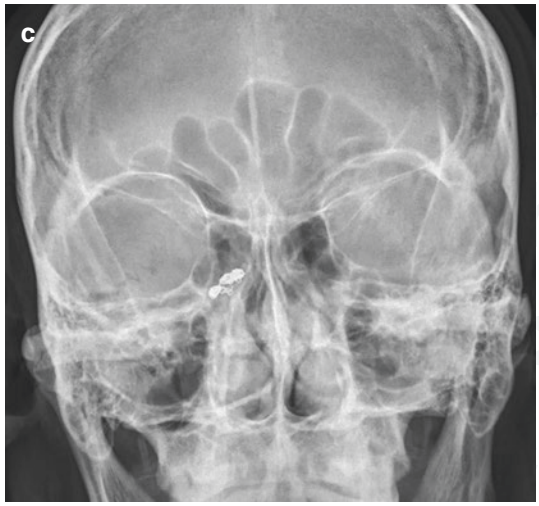


Fig. 14.8 A 53-year-old man presented with right eyeball pain, proptosis, chemosis, and limitation of right extraocular muscle movement. (**a**) Digital subtraction angiography shows a cavernous sinus dural arteriovenous fistula and the fistula between meningeal branches of internal carotid artery and cavernous sinus. In addition, there is a retrograde blood flow into the superior ophthalmic vein that causes the presenting symptoms. (**b**, **c**) The fistula was obliterated with transvenous embolization using coils



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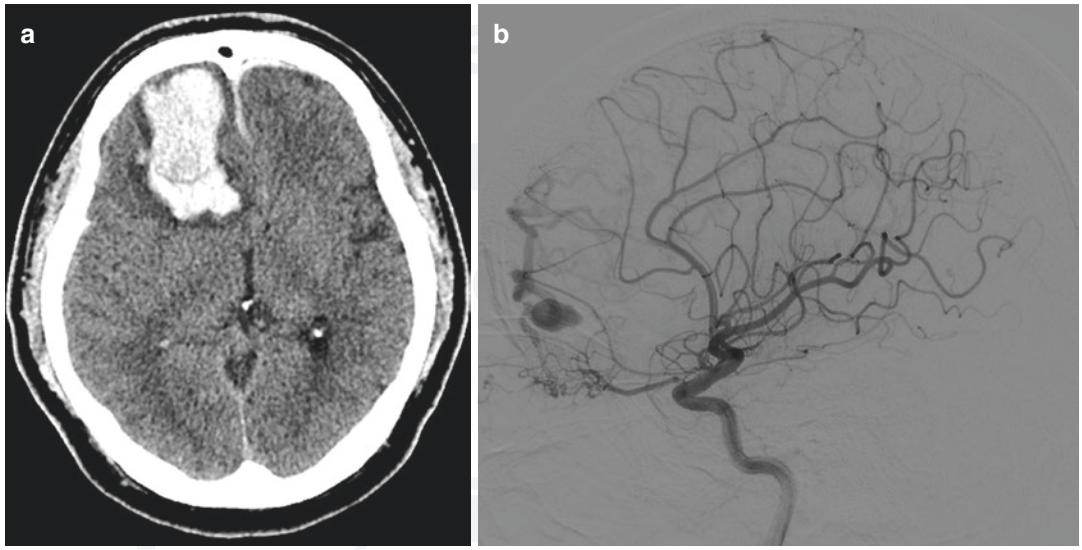
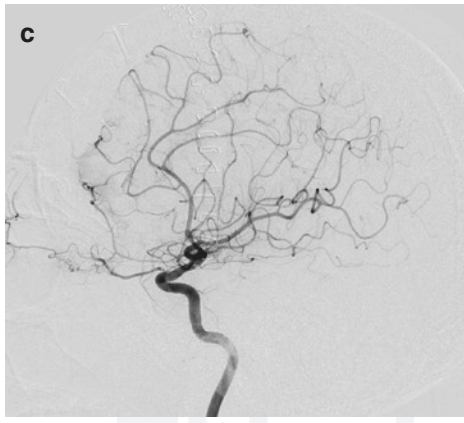


Fig. 14.9 A 48-year-old man presented with consciousness degradation. (**a**) Computed tomography shows a large amount intracerebral hemorrhage at right frontal lobe and subdural hemorrhage around falx. (**b**) Digital subtraction angiography shows a dural arteriovenous fistula (DAVF) at anterior cranial fossa. The arterial feeders are ethmoidal branches of the right ophthalmic artery and direct cortical venous reflux with venous ectasia (Borden type III 3 and Cognard type IV). (**c**) The DAVF at anterior cranial fossa was treated safely and effectively using microsurgery



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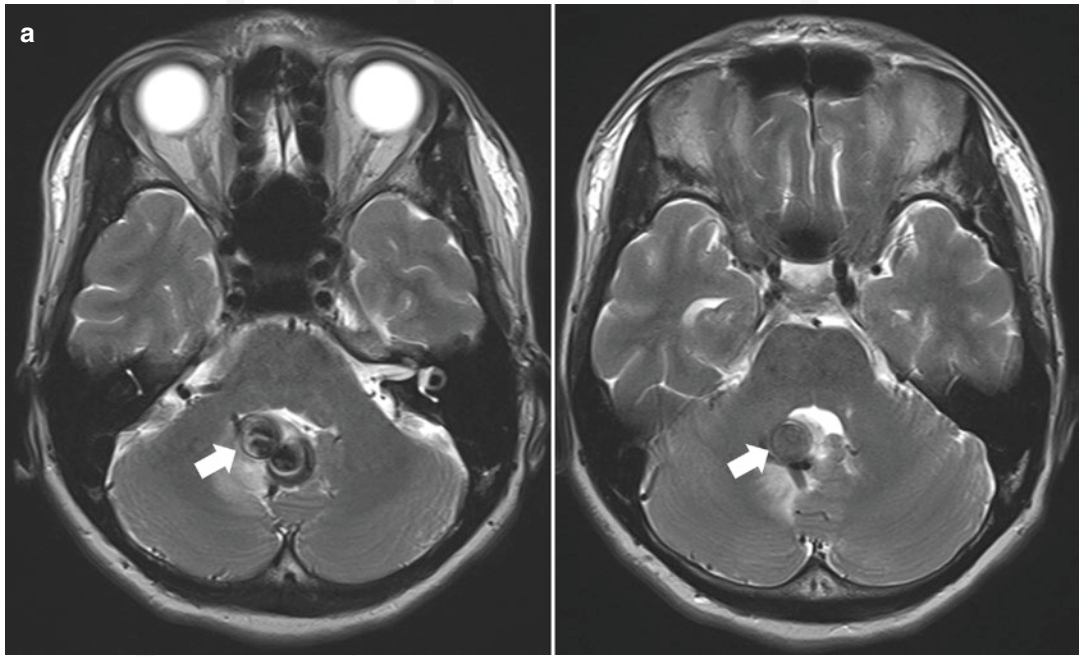

Fig. 14.10 A 41-year-old woman presented with a severe headache and ataxic gait. (**a**) T2-weighted magnetic resonance images show the vasogenic edema at right cerebellar peduncle and hemisphere and venous ectasia. (**b**) Digital subtraction angiography (DSA) shows a dural arteriovenous fistula (DAVF) at the foramen magnum. The arterial feeders are a stylomastoid branch of the right occipital artery, neuromeningeal trunk of right ascending pharyngeal artery and meningeal branch of the right vertebral artery. DSA also show retrograde venous reflux into the cortical and perimedullary vein, venous ectasia and venous aneurysm. (Borden classification III 3) (**c**) Endovascular treatment failed to obliterate the DAVF. Therefore, microsurgery was performed to obliterate the fistula. (**d**) The fistula was completely obliterated after microsurgery. White arrow, venous aneurysm; White circle, fistula point; Asterisk. Posterior inferior cerebellar artery

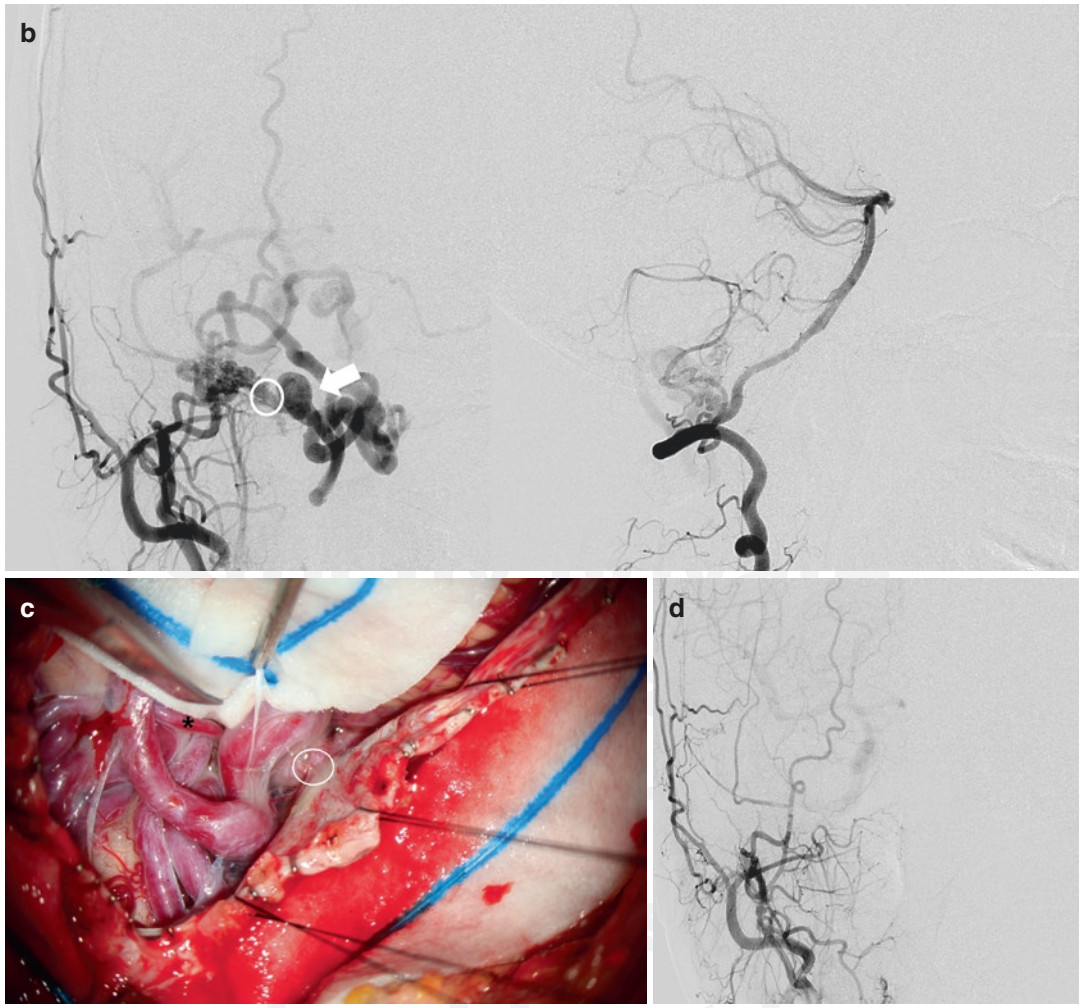

Fig. 14.10 (continued)

14.4.2 Imaging and Classification

When patients show symptoms related to intracranial lesions or test for health screening, CT or MRI is usually taken first. CT alone cannot confirm the presence of DAVFs but can detect intracranial hemorrhage and vasogenic edema caused by venous hypertension. MRI can detect not only intracranial hemorrhage and vasogenic edema, but also the flow voids from large arterialized draining veins, venous ectasia, dilated leptomeningeal and medullary vessels, parenchymal enhancement and venous sinus occlusion or thrombosis (Figs. 14.7a and 14.10a) [179]. Digital subtraction angiography (DSA) remains the gold standard for the diagnosis of DAVFs. The aim of DSA is not only to diagnose DAVFs but also to identify the arterial feeders, the site of the fistula, the presence of venous ectasia, and the pattern of venous drainage. DSAs for ECAs, ICAs, and VAs should be acquired because one DAVF can have various arterial feeders. The acquisition of DSA images should begin at the early arterial phase and proceed to the late venous phase. Superselective angiography of all potential arterial feeders is also very helpful to understand the anatomic structure of DAVFs and to establish a treatment plan.

DAVFs except CSDAVFs are usually classified based on their venous drainage characteris-

tics that determine the natural history and treatment recommendations. Borden classification (Table 14.3) and Cognard classification (Table 14.4) are most commonly used for classification of DAVFs [188, 189]. CSDAVFs that are also called CCFs are usually classified based on their shunt flow (high-flow and low-flow fistula) and their angiographic characteristics. Barrow classification is most widely used for classification of CSDAVFs [190]. Barrow et al. classified CSDAVF into four types: Type A fistulas are direct high-flow shunt between the ICA and the CS; Type B, C, and D fistulas are indirect, low-flow dural shunts. Type B is a fistula between meningeal branches from the ICA and the CS (Fig. 14.8), Type C is a fistula between meningeal branches of the ECA and the CS and Type D is a fistula between meningeal branches of both ICA and CEA and the CS [190].

Table 14.3 Borden classification

Type I	Drainage into meningeal veins, spinal epidural veins or into a dural venous sinus
	Normal anterograde flow in both the draining veins and other veins draining into the system
	Equivalent to Cognard type I and IIa, with a favorable natural history
Type II	Drainage into meningeal veins, spinal epidural veins or into a dural venous sinus
	Retrograde flow into the normal subarachnoid veins
	Equivalent to Cognard type IIb and IIa + b
Type III	Direct drainage into subarachnoid veins or into an isolated segment of the venous sinus (which results from a thrombosis on either side of the dural sinus segment)
	Equivalent to Cognard type III, IV and V

The content of table is from Borden JA, Wu JK, Shucart WA. A proposed classification for spinal and cranial dural arteriovenous fistulous malformations and implications for treatment. Journal of neurosurgery. 1995;82(2):166–79 [188]

Table 14.4 Cognard classification

Type I	Confined to sinus
	Antegrade flow
	No cortical venous drainage/reflux
Type II	IIa
	Confined to sinus
	Retrograde flow (reflux) into sinus
	No cortical venous drainage/reflux
	IIb
	Drains into sinus with reflux into cortical veins
	Antegrade flow
	IIa + b
	Drains into sinus with reflux into cortical veins
	Retrograde flow
Type III	Drains directly into cortical veins (not into sinus) drainage (40% hemorrhage)
Type IV	Drains directly into cortical veins (not into sinus) drainage with venous ectasia (65% hemorrhage)
Type V	Spinal perimedullary venous drainage, associated with progressive myelopathy

The content of table is from Cognard C, Gobin YP, Pierot L, Bailly A-L, Houdart E, Casasco A, et al. Cerebral dural arteriovenous fistulas: clinical and angiographic correlation with a revised classification of venous drainage. Radiology. 1995;194 (3):671–80 [189]

14.4.3 Clinical Manifestations

DAVFs in some patients are often diagnosed without any symptoms, but symptoms, when present, raged from mild symptoms such as tinnitus to fatal intracranial hemorrhage. The symptoms depend on the location of the fistula and venous drainage pattern. DAVFs that drain into the transverse sinus or sigmoid sinus often accompany pulsatile tinnitus. In addition, headache and cranial bruit are also common symptoms. Patients with these symptoms can undergo conservative management according to the venous drainage pattern, and DAVFs may occlude spontaneously.

However, patients with DAVFs also present with intracranial hemorrhages such as ICH, SAH, and/or SDH (Fig. 14.9a) and non-hemorrhagic neurologic deficits including seizures, focal cortical dysfunction, cranial nerve dysfunction, dementia, Parkinsonism, cerebellar dysfunction (Fig. 14.10a), myelopathy, quadriparesis, dysphasia, aphasia, and symptoms related to increased intracranial pressure. Intracranial hemorrhages are caused by the rupture of a fragile arterialized vein or hemorrhage transformation of cerebral venous congestion [179]. Non-hemorrhagic neurologic deficits are usually caused by focal or global cortical venous congestion and these symptoms usually develop more gradually over several days to weeks [179, 188].

In cases of DAVFs that cause these aggressive symptoms, neurosurgical treatments may be required to prevent further neurological deterioration.

The patients with CSDAVFs often present with the classical clinical symptoms such as eyeball pain, proptosis, chemosis, bruit, and limitation of extraocular muscle movement. These symptoms are related to ischemic dysfunction of cranial nerve, mechanical compression of the cranial nerves, and eyeball component due to retrograde blood flow into the superior ophthalmic vein and venous engorgement of the orbital contents. Epistaxis, even fatal epistaxis is not uncommon with Type A, direct high-flow fistula [191]. Intracranial hemorrhage can develop with any type of CSDAVF associated with retrograde cortical venous drainage.

14.4.4 Natural History

Previous studies reported that the natural history of DAVFs depends on the venous drainage pattern. DAVFs without retrograde cortical venous reflux including Borden type I and Cognard type I and IIa usually have a benign natural history and rarely cause intracranial hemorrhage and non-hemorrhagic neurologic deficits. The annual rate of newly developed neurological deterioration related to intracranial hemorrhage and/or non-hemorrhagic neurologic deficits ranges from 0% to 0.6% and the annual mortality rate is 0% in the cases of DAVFs without retrograde cortical venous reflux during conservative management or after only partially palliative endovascular therapy [192–194]. These types of DAVFs may improve spontaneously. A previous study reported that 81% of patients with DAVFs without retrograde cortical venous reflex experienced symptom improvement or complete occlusion [166]. However, DAVFs without retrograde cortical venous reflux can be converted to DAVFs with cortical venous reflux over time [189, 192, 193]. This phenomenon may be caused by the progression of stenosis of venous outlets, increased arterial flow, recruitment of arterial feeder, or extension of the fistulous connection [179]. Shah et al. reported that the annual rate of conversion from DAVFs without retrograde cortical venous reflux to DVAFs with cortical venous reflux after only partial palliative endovascular treatment was 0.8% [193].

DAVFs with cortical venous reflux including Borden type II and III, and Cognard type IIb, III, IV, and V have an unfavorable prognosis and can develop intracranial hemorrhage or non-hemorrhagic neurologic deficit if they are not treated. van Dijk et al. reported their long-term follow-up results of the patients with Borden type II and III dAVFs who did not undergo treatment [195]; excluding events at presentation, the annual risk of intracranial hemorrhage was 8.1% and the annual risk of the non-hemorrhagic neurologic deficit was 6.9%. In addition, they reported an annual mortality rate of 10.4%. Cognard et al. also reported intracranial hemorrhage in 40% of patients with Cognard type III DAVFs and in 65% of patients with Cognard type IV DAVFs [189]. If the patients with Borden type II and III were initially present with intracranial hemorrhage and non-hemorrhagic neurologic deficit, there may be a high probability that these symptoms will occur again.

The annual risk of the new non-hemorrhagic neurologic deficit and annual risk of intracranial hemorrhage were 0.07 and 0.03% in Borden type II and III DAVFs without no previous hemorrhage and were 0 and 0.02% in Borden type II and III DAVFs with asymptomatic or minimal symptomatic but no previous hemorrhage [194]. However, the annual risk of non-hemorrhagic neurologic deficit annual risk of intracranial hemorrhage was 20 and 10% in Borden type II and III DAVFs that initially presented with the non-hemorrhagic neurologic deficit [194]. In addition, the annual rebleeding rate was 46% in Borden type II and III DAVFs with previous intracranial hemorrhage [194]. Another study also reported that natural history of DAVFs with retrograde cortical venous reflux that initially presents with intracranial hemorrhage or non-hemorrhagic neurologic deficit is poor; annual risk of intracranial hemorrhage and non-hemorrhagic neurologic deficit range from 7.4% to 19.0% and the annual mortality rate is 3.8% [196].

DAVFs with venous ectasia (Cognard type IV) are well known to cause more intracranial hemorrhages than DAVFs without venous ectasia. Bulters et al. reported that there was a significant difference in annual risk of intracranial hemorrhage between DAVFs with venous ectasia and without venous ectasia; 19.0 and 1.4% [185]. Gross et al. also reported that the annual bleeding rate of Borden type III without venous ectasia was 10%, but the annual bleeding rate of Borden type III with venous ectasia was 21%.

CSDAVFs also show various natural histories. In some cases, the symptoms and signs, especially ocular symptoms, resolve within several days to several weeks after symptom develops. 20%–50% of CSDAVFs close spontaneously even if the patients had significant congestive orbital signs [197]. However, intracranial hemorrhage can also occur with both direct and indirect CSDAVFs associated with retrograde cortical venous reflux. Especially, direct CSDAVFs that initially presented with intracranial hemorrhage usually have a poor prognosis with a high risk of short-term rebleeding if not treated.

14.4.5 Treatment

DAVFs without retrograde cortical venous reflux can be managed conservatively because the natural history of these DAVFs is usually benign and these DAVF may be occluded spontaneously. However, these DAVFs should be carefully and periodically monitored with neurologic and radiologic examinations because DAVFs without retrograde cortical venous reflux may be converted to DAVFs with cortical venous reflux over time. Advanced DAVFs with retrograde cortical venous reflux should be considered for neurosurgical treatment to prevent intracranial hemorrhage and non-hemorrhagic neurologic deficit.

With the development of endovascular treatment techniques, devices, and materials, endovascular treatments are usually considered as the first-line treatment method of DAVFs for curative purposes. Endovascular treatment is divided into two categories: transarterial embolization and transvenous embolization (Figs. 14.7 and 14.8). The transarterial approach is a technique of embolization of arterial feeders and fistula using liquid embolic agents (NBCA or ONYX) via microcatheterization of arterial feeders. The transvenous approach is a technique of embolization of the fistula, cortical venous drainage and sinus itself using liquid embolic materials and/or detachable coils. This approach is particularly effective in the treatment of CSDAVF [179].

Microsurgery with craniotomy is often necessary when lesions are very difficult to be obliterated successfully or safely using endovascular treatments. DAVFs of anterior cranial fossa can be treated safely and effectively using microsurgery [166, 179]. In cases of DAVFs located in anterior cranial fossa, the primary arterial feeders are ethmoidal branches of the ophthalmic artery (Fig. 14.9). During endovascular treatments, arterial and/or venous access of DAVFs located anterior cranial fossa is very difficult and these techniques may result in unintentional injury or occlusion of the ophthalmic artery and central retinal artery that cause visual loss. For DAVFs that located superior sagittal sinus, microsurgical disconnection of the fistula is useful in the cases of difficulties with endovascular access to the fistula and/or cases of impossibility to safely sacrifice of the sinus. Microsurgery with craniotomy may be also considered for other sites of DAVFs in cases of high-risk of complications associated with the endovascular procedures, incomplete treatment or failure to access during endovascular treatment (Fig. 14.10).

Radiosurgery is also a viable alternative for treatment of DAVFs. However, the usefulness and effectiveness of radiosurgery for DAVFs remain controversial, because there is a lack of large case-control studies to support the routine used of radiosurgery for DAVFs. In addition, it is estimated that it would take 1–3 years for symptom resolution and obliteration of the fistula after radiosurgery [166, 179]. Therefore, it is not recommended to treat DAVFs using radiosurgery as the first-line treatment, especially for DAVFs with retrograde cortical venous reflux, intracranial hemorrhage, and non-hemorrhagic neurologic deficit.

Radiosurgery can be used as an adjuvant treatment method for complex DAVFs that preclude endovascular or microsurgical treatment.

References

1. Sacco S, Marini C, Toni D, Olivieri L, Carolei A. Incidence and 10-year survival of intracerebral hemorrhage in a population-based registry. Stroke. 2009;40(2):394–9.
2. Fogelholm R, Murros K, Rissanen A, Avikainen S. Long term survival after primary intracerebral haemorrhage: a retrospective population based study. J Neurol Neurosurg Psychiatry. 2005;76(11):1534–8.
3. Kuramatsu JB, Huttner HB, Schwab S. Advances in the management of intracerebral hemorrhage. J Neural Transm (Vienna). 2013;120(Suppl 1):S35–41.
4. Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo H, Hanley DF. Spontaneous intracerebral hemorrhage. N Engl J Med. 2001;344(19):1450–60.
5. Garcia JH, Ho KL. Pathology of hypertensive arteriopathy. Neurosurg Clin N Am. 1992;3(3):497–507.
6. Hong KS, Bang OY, Kang DW, Yu KH, Bae HJ, Lee JS, et al. Stroke statistics in Korea: part I. Epidemiology and risk factors: a report from the Korean stroke society and clinical research center for stroke. J Stroke. 2013;15(1):2–20.
7. Krishnamurthi RV, Moran AE, Forouzanfar MH, Bennett DA, Mensah GA, Lawes CM, et al. The global burden of hemorrhagic stroke: a summary of findings from the GBD 2010 study. Glob Heart. 2014;9(1):101–6.
8. Hemphill JC 3rd, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. Stroke. 2001;32(4):891–7.
9. Broderick J, Connolly S, Feldmann E, Hanley D, Kase C, Krieger D, et al. Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: a guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. Stroke. 2007;38(6):2001–23.
10. Toyoda K. Epidemiology and registry studies of stroke in Japan. J Stroke. 2013;15(1):21–6.
11. Krishnamurthi RV, Feigin VL, Forouzanfar MH, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet Glob Health. 2013;1(5):e259–81.
12. Broderick JP, Brott T, Tomsick T, Miller R, Huster G. Intracerebral hemorrhage more than twice as common as subarachnoid hemorrhage. J Neurosurg. 1993;78(2):188–91.
13. Jolink WM, Klijn CJ, Brouwers PJ, Kappelle LJ, Vaartjes I. Time trends in incidence, case fatality, and mortality of intracerebral hemorrhage. Neurology. 2015;85(15):1318–24.
14. van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A, Klijn CJ. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. Lancet Neurol. 2010;9(2):167–76.
15. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol. 2009;8(4):355–69.
16. An SJ, Kim TJ, Yoon BW. Epidemiology, risk factors, and clinical features of intracerebral hemorrhage: an update. J Stroke. 2017;19(1):3–10.
17. Chan S, Hemphill JC 3rd. Critical care management of intracerebral hemorrhage. Crit Care Clin. 2014;30(4):699–717.
18. Martini SR, Flaherty ML, Brown WM, Haverbusch M, Comeau ME, Sauerbeck LR, et al. Risk factors for intracerebral hemorrhage differ according to hemorrhage location. Neurology. 2012;79(23):2275–82.
19. Rosenblum WI. Amyloid angiopathy. Neurology. 1997;48(1):291.
20. Rosand J, Hylek EM, O'Donnell HC, Greenberg SM. Warfarin-associated hemorrhage and cerebral amyloid angiopathy: a genetic and pathologic study. Neurology. 2000;55(7):947–51.
21. Rost NS, Greenberg SM, Rosand J. The genetic architecture of intracerebral hemorrhage. Stroke. 2008;39(7):2166–73.
22. Sturgeon JD, Folsom AR, Longstreth WT Jr, Shahar E, Rosamond WD, Cushman M. Risk factors for intracerebral hemorrhage in a pooled prospective study. Stroke. 2007;38(10):2718–25.
23. Garcia-Rodriguez LA, Gaist D, Morton J, Cookson C, Gonzalez-Perez A. Antithrombotic drugs and risk of hemorrhagic stroke in the general population. Neurology. 2013;81(6):566–74.
24. Goos JD, Henneman WJ, Sluimer JD, Vrenken H, Sluimer IC, Barkhof F, et al. Incidence of cerebral microbleeds: a longitudinal study in a memory clinic population. Neurology. 2010;74(24):1954–60.
25. Yakushiji Y, Yokota C, Yamada N, Kuroda Y, Minematsu K. Clinical characteristics by topographical distribution of brain microbleeds, with a particular emphasis on diffuse microbleeds. J Stroke Cerebrovasc Dis. 2011;20(3):214–21.
26. Rosand J, Muzikansky A, Kumar A, Wisco JJ, Smith EE, Betensky RA, et al. Spatial clustering of hemorrhages in probable cerebral amyloid angiopathy. Ann Neurol. 2005;58(3):459–62.
27. Fan JS, Huang HH, Chen YC, Yen DH, Kao WF, Huang MS, et al. Emergency department neurologic deterioration in patients with spontaneous intracerebral hemorrhage: incidence, predictors, and prognostic significance. Acad Emerg Med. 2012;19(2):133–8.

28. Claassen J, Jette N, Chum F, Green R, Schmidt M, Choi H, et al. Electrographic seizures and periodic discharges after intracerebral hemorrhage. Neurology. 2007;69(13):1356–65.
29. Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. Lancet Neurol. 2009;8(11):1006–18.
30. Moon JS, Janjua N, Ahmed S, Kirmani JF, Harris-Lane P, Jacob M, et al. Prehospital neurologic deterioration in patients with intracerebral hemorrhage. Crit Care Med. 2008;36(1):172–5.
31. Veltkamp R, Purrucker J. Management of spontaneous intracerebral hemorrhage. Curr Neurol Neurosci Rep. 2017;17(10):80.
32. Willmot M, Leonardi-Bee J, Bath PM. High blood pressure in acute stroke and subsequent outcome: a systematic review. Hypertension. 2004;43(1):18–24.
33. Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med. 2013;368(25):2355–65.
34. Hemphill JC 3rd, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2015;46(7):2032–60.
35. Qureshi AI, Palesch YY, Barsan WG, Hanley DF, Hsu CY, Martin RL, et al. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. N Engl J Med. 2016;375(11):1033–43.
36. Steiner T, Al-Shahi Salman R, Beer R, Christensen H, Cordonnier C, Csiba L, et al. European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. Int J Stroke. 2014;9(7):840–55.
37. Pollack CV, Varon J, Garrison NA, Ebrahimi R, Dunbar L, Peacock WF. Clevidipine, an intravenous dihydropyridine calcium channel blocker, is safe and effective for the treatment of patients with acute severe hypertension. Ann Emerg Med. 2009;53(3):329–38.
38. Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet (London, England). 2015;386(10008):2059–68.
39. Dastur CK, Yu W. Current management of spontaneous intracerebral haemorrhage. Stroke Vasc Neurol. 2017;2(1):21–9.
40. Schulman S, Beyth RJ, Kearon C, Levine MN. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133(6 Suppl):257S–98S.
41. Pabinger I, Brenner B, Kalina U, Knaub S, Nagy A, Ostermann H. Prothrombin complex concentrate (Beriplex P/N) for emergency anticoagulation reversal: a prospective multinational clinical trial. J Thromb Haemost. 2008;6(4):622–31.
42. Connolly SJ, Milling TJ Jr, Eikelboom JW, Gibson CM, Curnutte JT, Gold A, et al. Andexanet Alfa for acute major bleeding associated with factor Xa inhibitors. N Engl J Med. 2016;375(12):1131–41.
43. Pollack CV Jr, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, et al. Idarucizumab for dabigatran reversal. N Engl J Med. 2015;373(6):511–20.
44. Lindahl TL, Baghaei F, Blixter IF, Gustafsson KM, Stigendal L, Sten-Linder M, et al. Effects of the oral, direct thrombin inhibitor dabigatran on five common coagulation assays. Thromb Haemost. 2011;105(2):371–8.
45. Baharoglu MI, Cordonnier C, Al-Shahi Salman R, de Gans K, Koopman MM, Brand A, et al. Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial. Lancet. 2016;387(10038):2605–13.
46. Becker KJ, Baxter AB, Bybee HM, Tirschwell DL, Abouelsaad T, Cohen WA. Extravasation of radiographic contrast is an independent predictor of death in primary intracerebral hemorrhage. Stroke. 1999;30(10):2025–32.
47. Hanley DF, Lane K, McBee N, Ziai W, Tuhrim S, Lees KR, et al. Thrombolytic removal of intraventricular haemorrhage in treatment of severe stroke: results of the randomised, multicentre, multiregion, placebo-controlled CLEAR III trial. Lancet. 2017;389(10069):603–11.
48. Mendelow AD, Gregson BA, Fernandes HM, Murray GD, Teasdale GM, Hope DT, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. Lancet. 2005;365(9457):387–97.
49. Mendelow AD, Gregson BA, Rowan EN, Murray GD, Gholkar A, Mitchell PM. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial. Lancet (London, England). 2013;382(9890):397–408.
50. Sakamoto Y, Koga M, Yamagami H, Okuda S, Okada Y, Kimura K, et al. Systolic blood pressure after intravenous antihypertensive treatment and clinical outcomes in hyperacute intracerebral hemorrhage: the stroke acute management with urgent risk-factor assessment and improvement-intracerebral hemorrhage study. Stroke. 2013;44(7):1846–51.
51. Mould WA, Carhuapoma JR, Muschelli J, Lane K, Morgan TC, McBee NA, et al. Minimally invasive surgery plus recombinant tissue-type plasminogen activator for intracerebral hemorrhage evacuation decreases perihematomal edema. Stroke. 2013;44(3):627–34.

52. Mendelow AD. Surgical craniotomy for intracerebral haemorrhage. Front Neurol Neurosci. 2015;37:148–54.
53. De Herdt V, Dumont F, Henon H, Derambure P, Vonck K, Leys D, et al. Early seizures in intracerebral hemorrhage: incidence, associated factors, and outcome. Neurology. 2011;77(20):1794–800.
54. Passero S, Rocchi R, Rossi S, Ulivelli M, Vatti G. Seizures after spontaneous supratentorial intracerebral hemorrhage. Epilepsia. 2002;43(10):1175–80.
55. Rossi C, De Herdt V, Dequatre-Ponchelle N, Henon H, Leys D, Cordonnier C. Incidence and predictors of late seizures in intracerebral hemorrhages. Stroke. 2013;44(6):1723–5.
56. Honig A, Michael S, Eliahou R, Leker RR. Central fever in patients with spontaneous intracerebral hemorrhage: predicting factors and impact on outcome. BMC Neurol. 2015;15:6.
57. Greer DM, Funk SE, Reaven NL, Ouzounelli M, Uman GC. Impact of fever on outcome in patients with stroke and neurologic injury: a comprehensive meta-analysis. Stroke. 2008;39(11):3029–35.
58. Qureshi AI, Palesch YY, Martin R, Novitzke J, Cruz-Flores S, Ehtisham A, et al. Association of serum glucose concentrations during acute hospitalization with hematoma expansion, perihematomal edema, and three month outcome among patients with intracerebral hemorrhage. Neurocrit Care. 2011;15(3):428–35.
59. Diringer MN, Skolnick BE, Mayer SA, Steiner T, Davis SM, Brun NC, et al. Thromboembolic events with recombinant activated factor VII in spontaneous intracerebral hemorrhage: results from the factor seven for acute hemorrhagic stroke (FAST) trial. Stroke. 2010;41(1):48–53.
60. Dennis M, Sandercock PA, Reid J, Graham C, Murray G, Venables G, et al. Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial. Lancet. 2009;373(9679):1958–65.
61. CLOTS (Clots in Legs Or sTockings after Stroke) Trials Collaboration. Effect of intermittent pneumatic compression on disability, living circumstances, quality of life, and hospital costs after stroke: secondary analyses from CLOTS 3, a randomised trial. Lancet Neurol. 2014;13(12):1186–92.
62. Nyquist P, Bautista C, Jichici D, Burns J, Chhangani S, DeFilippis M, et al. Prophylaxis of venous thrombosis in neurocritical care patients: an evidence-based guideline: a statement for healthcare professionals from the Neurocritical Care Society. Neurocrit Care. 2016;24(1):47–60.
63. Zahuranec DB, Brown DL, Lisabeth LD, Gonzales NR, Longwell PJ, Smith MA, et al. Early care limitations independently predict mortality after intracerebral hemorrhage. Neurology. 2007;68(20):1651–7.
64. Kassell NF, Torner JC, Haley EC Jr, Jane JA, Adams HP, Kongable GL. The international cooperative study on the timing of aneurysm surgery. Part 1: overall management results. J Neurosurg. 1990;73(1):18–36.
65. Brown RD Jr, Broderick JP. Unruptured intracranial aneurysms: epidemiology, natural history, management options, and familial screening. Lancet Neurol. 2014;13(4):393–404.
66. Morita A, Kirino T, Hashi K, Aoki N, Fukuhara S, Hashimoto N, et al. The natural course of unruptured cerebral aneurysms in a Japanese cohort. N Engl J Med. 2012;366(26):2474–82.
67. Ingall T, Asplund K, Mahonen M, Bonita R. A multinational comparison of subarachnoid hemorrhage epidemiology in the WHO MONICA stroke study. Stroke. 2000;31(5):1054–61.
68. Rincon F, Rossenwasser RH, Dumont A. The epidemiology of admissions of nontraumatic subarachnoid hemorrhage in the United States. Neurosurgery. 2013;73(2):217–22.. discussion 2-3
69. Johnston SC, Selvin S, Gress DR. The burden, trends, and demographics of mortality from subarachnoid hemorrhage. Neurology. 1998;50(5):1413–8.
70. Hop JW, Rinkel GJ, Algra A, van Gijn J. Case-fatality rates and functional outcome after subarachnoid hemorrhage: a systematic review. Stroke. 1997;28(3):660–4.
71. Bor AS, Koffijberg H, Wermer MJ, Rinkel GJ. Optimal screening strategy for familial intracranial aneurysms: a cost-effectiveness analysis. Neurology. 2010;74(21):1671–9.
72. Broderick JP, Brown RD Jr, Sauerbeck L, Hornung R, Huston J 3rd, Woo D, et al. Greater rupture risk for familial as compared to sporadic unruptured intracranial aneurysms. Stroke. 2009;40(6):1952–7.
73. Lall RR, Eddleman CS, Bendok BR, Batjer HH. Unruptured intracranial aneurysms and the assessment of rupture risk based on anatomical and morphological factors: sifting through the sands of data. Neurosurg Focus. 2009;26(5) https://doi.org/10.3171/2009.2.FOCUS0921.
74. Abraham MK, Chang WW. Subarachnoid hemorrhage. Emerg Med Clin North Am. 2016;34(4):901–16.
75. Bassi P, Bandera R, Loiero M, Tognoni G, Mangoni A. Warning signs in subarachnoid hemorrhage: a cooperative study. Acta Neurol Scand. 1991;84(4):277–81.
76. Fine B, Singh N, Aviv R, Macdonald RL. Does a patient with a thunderclap headache need a lumbar puncture? Can Med Assoc J. 2012;184(5):555–6.
77. Polmear A. Sentinel headaches in aneurysmal subarachnoid haemorrhage: what is the true incidence? A systematic review. Cephalalgia. 2003;23(10):935–41.
78. Edlow JA. Diagnosing headache in the emergency department: what is more important? Being right, or not being wrong? Eur J Neurol. 2008;15(12):1257–8.
79. Kowalski RG, Claassen J, Kreiter KT, Bates JE, Ostapkovich ND, Connolly ES, et al. Initial misdiagnosis and outcome after subarachnoid hemorrhage. JAMA. 2004;291(7):866–9.

80. Lawton MT, Vates GE. Subarachnoid hemorrhage. N Engl J Med. 2017;377(3):257–66.
81. Butzkueven H, Evans AH, Pitman A, Leopold C, Jolley DJ, Kaye AH, et al. Onset seizures independently predict poor outcome after subarachnoid hemorrhage. Neurology. 2000;55(9):1315–20.
82. Hart RG, Byer JA, Slaughter JR, Hewett JE, Easton JD. Occurrence and implications of seizures in subarachnoid hemorrhage due to ruptured intracranial aneurysms. Neurosurgery. 1981;8(4):417–21.
83. Pinto AN, Canhao P, Ferro JM. Seizures at the onset of subarachnoid haemorrhage. J Neurol. 1996;243(2):161–4.
84. Rhoney DH, Tipps LB, Murry KR, Basham MC, Michael DB, Coplin WM. Anticonvulsant prophylaxis and timing of seizures after aneurysmal subarachnoid hemorrhage. Neurology. 2000;55(2):258–65.
85. Choi KS, Chun HJ, Yi HJ, Ko Y, Kim YS, Kim JM. Seizures and epilepsy following aneurysmal subarachnoid hemorrhage: incidence and risk factors. J Korean Neurosurg Soc. 2009;46(2):93–8.
86. Suwatcharangkoon S, Meyers E, Falo C, Schmidt JM, Agarwal S, Claassen J, et al. Loss of consciousness at onset of subarachnoid hemorrhage as an important marker of early brain injury. JAMA Neurol. 2016;73(1):28–35.
87. Meurer WJ, Walsh B, Vilke GM, Coyne CJ. Clinical guidelines for the emergency department evaluation of subarachnoid hemorrhage. J Emerg Med. 2016;50(4):696–701.
88. Report of World Federation of Neurological Surgeons Committee on a Universal Subarachnoid Hemorrhage Grading Scale. J Neurosurg. 1988;68(6):985–6.
89. Hunt WE, Hess RM. Surgical risk as related to time of intervention in the repair of intracranial aneurysms. J Neurosurg. 1968;28(1):14–20.
90. Macdonald RL, Pluta RM, Zhang JH. Cerebral vasospasm after subarachnoid hemorrhage: the emerging revolution. Nat Clin Pract Neurol. 2007;3(5):256–63.
91. Rowland MJ, Hadjipavlou G, Kelly M, Westbrook J, Pattinson KT. Delayed cerebral ischaemia after subarachnoid haemorrhage: looking beyond vasospasm. Br J Anaesth. 2012;109(3):315–29.
92. Fisher CM, Kistler JP, Davis JM. Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. Neurosurgery. 1980;6(1):1–9.
93. Frontera JA, Claassen J, Schmidt JM, Wartenberg KE, Temes R, Connolly ES Jr, et al. Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified fisher scale. Neurosurgery. 2006;59(1):21–7.. discussion 21-7
94. Greving JP, Wermer MJ, Brown RD Jr, Morita A, Juvela S, Yonekura M, et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. Lancet Neurol. 2014;13(1):59–66.
95. Connolly ES Jr, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2012;43(6):1711–37.
96. Cortnum S, Sorensen P, Jorgensen J. Determining the sensitivity of computed tomography scanning in early detection of subarachnoid hemorrhage. Neurosurgery. 2010;66(5):900–2.. discussion 3
97. Sayer D, Bloom B, Fernando K, Jones S, Benton S, Dev S, et al. An observational study of 2,248 patients presenting with headache, suggestive of subarachnoid hemorrhage, who received lumbar punctures following normal computed tomography of the head. Acad Emerg Med. 2015;22(11):1267–73.
98. Leblanc R. The minor leak preceding subarachnoid hemorrhage. J Neurosurg. 1987;66(1):35–9.
99. Schriger DL, Kalafut M, Starkman S, Krueger M, Saver JL. Cranial computed tomography interpretation in acute stroke: physician accuracy in determining eligibility for thrombolytic therapy. JAMA. 1998;279(16):1293–7.
100. van der Wee N, Rinkel GJ, Hasan D, van Gijn J. Detection of subarachnoid haemorrhage on early CT: is lumbar puncture still needed after a negative scan? J Neurol Neurosurg Psychiatry. 1995;58(3):357–9.
101. Shimoda M, Hoshikawa K, Shiramizu H, Oda S, Matsumae M. Problems with diagnosis by fluid-attenuated inversion recovery magnetic resonance imaging in patients with acute aneurysmal subarachnoid hemorrhage. Neurol Med Chir. 2010;50(7):530–7.
102. Czuczman AD, Thomas LE, Boulanger AB, Peak DA, Senecal EL, Brown DF, et al. Interpreting red blood cells in lumbar puncture: distinguishing true subarachnoid hemorrhage from traumatic tap. Acad Emerg Med. 2013;20(3):247–56.
103. Dubosh NM, Bellolio MF, Rabinstein AA, Edlow JA. Sensitivity of early brain computed tomography to exclude aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. Stroke. 2016;47(3):750–5.
104. Brunell A, Ridefelt P, Zelano J. Differential diagnostic yield of lumbar puncture in investigation of suspected subarachnoid haemorrhage: a retrospective study. J Neurol. 2013;260(6):1631–6.
105. Agid R, Andersson T, Almqvist H, Willinsky RA, Lee SK, terBrugge KG, et al. Negative CT angiography findings in patients with spontaneous subarachnoid hemorrhage: when is digital subtraction angiography still needed? AJNR Am J Neuroradiol. 2010;31(4):696–705.
106. Li MH, Cheng YS, Li YD, Fang C, Chen SW, Wang W, et al. Large-cohort comparison between three-dimensional time-of-flight magnetic resonance and rotational digital subtraction angiographies in intracranial aneurysm detection. Stroke. 2009;40(9):3127–9.

107. Cha KC, Kim JH, Kang HI, Moon BG, Lee SJ, Kim JS. Aneurysmal rebleeding: factors associated with clinical outcome in the rebleeding patients. J Korean Neurosurg Soc. 2010;47(2):119–23.
108. Ohkuma H, Shimamura N, Naraoka M, Katagai T. Aneurysmal subarachnoid hemorrhage in the elderly over age 75: a systematic review. Neurol Med Chir. 2017;57(11):575–83.
109. Schievink WI, Wijdicks EF, Parisi JE, Piepgras DG, Whisnant JP. Sudden death from aneurysmal subarachnoid hemorrhage. Neurology. 1995;45(5):871–4.
110. Starke RM, Connolly ES Jr. Rebleeding after aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2011;15(2):241–6.
111. Edlow JA, Panagos PD, Godwin SA, Thomas TL, Decker WW. Clinical policy: critical issues in the evaluation and management of adult patients presenting to the emergency department with acute headache. Ann Emerg Med. 2008;52(4):407–36.
112. Lanzino G, D'Urso PI, Suarez J. Seizures and anticonvulsants after aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2011;15(2):247–56.
113. Hillman J, Fridriksson S, Nilsson O, Yu Z, Saveland H, Jakobsson KE. Immediate administration of tranexamic acid and reduced incidence of early rebleeding after aneurysmal subarachnoid hemorrhage: a prospective randomized study. J Neurosurg. 2002;97(4):771–8.
114. Starke RM, Kim GH, Fernandez A, Komotar RJ, Hickman ZL, Otten ML, et al. Impact of a protocol for acute antifibrinolytic therapy on aneurysm rebleeding after subarachnoid hemorrhage. Stroke. 2008;39(9):2617–21.
115. Diringer MN, Reaven NL, Funk SE, Uman GC. Elevated body temperature independently contributes to increased length of stay in neurologic intensive care unit patients. Crit Care Med. 2004;32(7):1489–95.
116. Todd MM, Hindman BJ, Clarke WR, Torner JC, Weeks JB, Bayman EO, et al. Perioperative fever and outcome in surgical patients with aneurysmal subarachnoid hemorrhage. Neurosurgery. 2009;64(5):897–908.. discussion 908
117. Oddo M, Frangos S, Milby A, Chen I, Maloney-Wilensky E, Murtrie EM, et al. Induced normothermia attenuates cerebral metabolic distress in patients with aneurysmal subarachnoid hemorrhage and refractory fever. Stroke. 2009;40(5):1913–6.
118. Commichau C, Scarmeas N, Mayer SA. Risk factors for fever in the neurologic intensive care unit. Neurology. 2003;60(5):837–41.
119. Cruz JP, O'Kelly C, Kelly M, Wong JH, Alshaya W, Martin A, et al. Pipeline embolization device in aneurysmal subarachnoid hemorrhage. AJNR Am J Neuroradiol. 2013;34(2):271–6.
120. Kulcsar Z, Wetzel SG, Augsburger L, Gruber A, Wanke I, Rufenacht DA. Effect of flow diversion treatment on very small ruptured aneurysms. Neurosurgery. 2010;67(3):789–93.
121. Rajah G, Narayanan S, Rangel-Castilla L. Update on flow diverters for the endovascular management of cerebral aneurysms. Neurosurg Focus. 2017;42(6):E2.
122. Claassen J, Carhuapoma JR, Kreiter KT, Du EY, Connolly ES, Mayer SA. Global cerebral edema after subarachnoid hemorrhage: frequency, predictors, and impact on outcome. Stroke. 2002;33(5):1225–32.
123. Mocco J, Prickett CS, Komotar RJ, Connolly ES, Mayer SA. Potential mechanisms and clinical significance of global cerebral edema following aneurysmal subarachnoid hemorrhage. Neurosurg Focus. 2007;22(5):E7.
124. Brilstra EH, Rinkel GJ, van der Graaf Y, van Rooij WJ, Algra A. Treatment of intracranial aneurysms by embolization with coils: a systematic review. Stroke. 1999;30(2):470–6.
125. Dorsch NW, King MT. A review of cerebral vasospasm in aneurysmal subarachnoid haemorrhage part I: incidence and effects. J Clin Neurosci. 1994;1(1):19–26.
126. Lucke-Wold BP, Logsdon AF, Manoranjan B, Turner RC, McConnell E, Vates GE, et al. Aneurysmal subarachnoid hemorrhage and neuroinflammation: a comprehensive review. Int J Mol Sci. 2016;17(4):497.
127. Sen J, Belli A, Albon H, Morgan L, Petzold A, Kitchen N. Triple-H therapy in the management of aneurysmal subarachnoid haemorrhage. Lancet Neurol. 2003;2(10):614–21.
128. Dankbaar JW, Slooter AJ, Rinkel GJ, Schaaf IC. Effect of different components of triple-H therapy on cerebral perfusion in patients with aneurysmal subarachnoid haemorrhage: a systematic review. Critical Care. 2010;14(1):R23.
129. Gathier CS, van den Bergh WM, van der Jagt M, Verweij BH, Dankbaar JW, Muller MC, et al. Induced hypertension for delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage: a randomized clinical trial. Stroke. 2018;49(1):76–83.
130. Dorhout Mees SM, Rinkel GJ, Feigin VL, Algra A, van den Bergh WM, Vermeulen M, et al. Calcium antagonists for aneurysmal subarachnoid haemorrhage. Cochrane Database Syst Rev. 2007;(3):CD000277.
131. Chen S, Luo J, Reis C, Manaenko A, Zhang J. Hydrocephalus after subarachnoid hemorrhage: pathophysiology, diagnosis, and treatment. Biomed Res Int. 2017;2017:8584753.
132. Samuels O, Webb A, Culler S, Martin K, Barrow D. Impact of a dedicated neurocritical care team in treating patients with aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2011;14(3):334–40.
133. Nyquist P, Jichici D, Bautista C, Burns J, Chhangani S, DeFilippis M, et al. Prophylaxis of venous thrombosis in neurocritical care patients: an executive summary of evidence-based guidelines: a statement for healthcare professionals from the Neurocritical Care Society and Society of Critical Care Medicine. Crit Care Med. 2017;45(3):476–9.

134. Martin NA, Vinters HV. Arteriovenous malformations. In: Carter LP, Spetzler RF, Hamilton MG, editors. Neurovascular surgery. New York: McGraw-Hill; 1995. p. 875–903.
135. Laakso A, Hernesniemi J. Arteriovenous malformations: epidemiology and clinical presentation. Neurosurg Clin N Am. 2012;23(1):1–6.
136. McCormick WF. The pathology of vascular ("arteriovenous") malformations. J Neurosurg. 1966;24(4):807–16.
137. van Beijnum J, van der Worp HB, Schippers HM, van Nieuwenhuizen O, Kappelle LJ, Rinkel GJ, et al. Familial occurrence of brain arteriovenous malformations: a systematic review. J Neurol Neurosurg Psychiatry. 2007;78(11):1213–7.
138. Yokoyama K, Asano Y, Murakawa T, Takada M, Ando T, Sakai N, et al. Familial occurrence of arteriovenous malformation of the brain. J Neurosurg. 1991;74(4):585–9.
139. Reddy K, West M, McClarty B. Multiple intracerebral arteriovenous malformations. A case report and literature review. Surg Neurol. 1987;27(5):495–9.
140. Willinsky RA, Lasjaunias P, Terbrugge K, Burrows P. Multiple cerebral arteriovenous malformations (AVMs). Review of our experience from 203 patients with cerebral vascular lesions. Neuroradiology. 1990;32(3):207–10.
141. ApSimon HT, Reef H, Phadke RV, Popovic EA. A population-based study of brain arteriovenous malformation: long-term treatment outcomes. Stroke. 2002;33(12):2794–800.
142. Al-Shahi R, Bhattacharya JJ, Currie DG, Papanastassiou V, Ritchie V, Roberts RC, et al. Prospective, population-based detection of intracranial vascular malformations in adults: the Scottish Intracranial Vascular Malformation Study (SIVMS). Stroke. 2003;34(5):1163–9.
143. Brown RD Jr, Wiebers DO, Forbes G, O'Fallon WM, Piepgras DG, Marsh WR, et al. The natural history of unruptured intracranial arteriovenous malformations. J Neurosurg. 1988;68(3):352–7.
144. Toffol GJ, Biller J, Adams HP Jr. Nontraumatic intracerebral hemorrhage in young adults. Arch Neurol. 1987;44(5):483–5.
145. Fults D, Kelly DL Jr. Natural history of arteriovenous malformations of the brain: a clinical study. Neurosurgery. 1984;15(5):658–62.
146. Stapf C, Mast H, Sciacca RR, Choi JH, Khaw AV, Connolly ES, et al. Predictors of hemorrhage in patients with untreated brain arteriovenous malformation. Neurology. 2006;66(9):1350–5.
147. Aoki N. Do intracranial arteriovenous malformations cause subarachnoid haemorrhage? Review of computed tomography features of ruptured arteriovenous malformations in the acute stage. Acta Neurochir. 1991;112(3–4):92–5.
148. Graf CJ, Perret GE, Torner JC. Bleeding from cerebral arteriovenous malformations as part of their natural history. J Neurosurg. 1983;58(3):331–7.
149. Crawford PM, West CR, Chadwick DW, Shaw MD. Arteriovenous malformations of the brain: natural history in unoperated patients. J Neurol Neurosurg Psychiatry. 1986;49(1):1–10.
150. Yamada S, Takagi Y, Nozaki K, Kikuta K, Hashimoto N. Risk factors for subsequent hemorrhage in patients with cerebral arteriovenous malformations. J Neurosurg. 2007;107(5):965–72.
151. Gross BA, Du R. Natural history of cerebral arteriovenous malformations: a meta-analysis. J Neurosurg. 2013;118(2):437–43.
152. Winn HR. Youmans & Winn neurological surgery. 7th ed. Philadelphia, PA: Elsevier; 2017.
153. Brown RD Jr, Flemming KD, Meyer FB, Cloft HJ, Pollock BE, Link ML. Natural history, evaluation, and management of intracranial vascular malformations. Mayo Clin Proc. 2005;80(2):269–81.
154. Mossa-Basha M, Chen J, Gandhi D. Imaging of cerebral arteriovenous malformations and dural arteriovenous fistulas. Neurosurg Clin N Am. 2012;23(1):27–42.
155. Pollock BE, Kondziolka D, Flickinger JC, Patel AK, Bissonette DJ, Lunsford LD. Magnetic resonance imaging: an accurate method to evaluate arteriovenous malformations after stereotactic radiosurgery. J Neurosurg. 1996;85(6):1044–9.
156. Griffiths PD, Hoggard N, Warren DJ, Wilkinson ID, Anderson B, Romanowski CA. Brain arteriovenous malformations: assessment with dynamic MR digital subtraction angiography. AJNR Am J Neuroradiol. 2000;21(10):1892–9.
157. Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. J Neurosurg. 1986;65(4):476–83.
158. Lawton MT, Kim H, McCulloch CE, Mikhak B, Young WL. A supplementary grading scale for selecting patients with brain arteriovenous malformations for surgery. Neurosurgery. 2010;66(4):702–13.. discussion 13
159. Spetzler RF, Ponce FA. A 3-tier classification of cerebral arteriovenous malformations. Clinical article. J Neurosurg. 2011;114(3):842–9.
160. Ajiboye N, Chalouhi N, Starke RM, Zanaty M, Bell R. Cerebral arteriovenous malformations: evaluation and management. Sci World J. 2014;2014:649036.
161. Starke RM, Kano H, Ding D, Lee JY, Mathieu D, Whitesell J, et al. Stereotactic radiosurgery for cerebral arteriovenous malformations: evaluation of long-term outcomes in a multicenter cohort. J Neurosurg. 2017;126(1):36–44.
162. Cockroft KM, Jayaraman MV, Amin-Hanjani S, Derdeyn CP, McDougall CG, Wilson JA. A perfect storm: how a randomized trial of unruptured brain arteriovenous malformations' (ARUBA's) trial design challenges notions of external validity. Stroke. 2012;43(7):1979–81.
163. Mohr JP, Parides MK, Stapf C, Moquete E, Moy CS, Overbey JR, et al. Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a

multicentre, non-blinded, randomised trial. Lancet. 2014;383(9917):614–21.
164. Morgan MK, Stoodley MA, Fuller JW. Letter to the editor: comparison between surgery and gamma knife radiosurgery for brain AVMs. J Neurosurg. 2017;126(1):338–41.
165. Sahlein DH, Mora P, Becske T, Huang P, Jafar JJ, Connolly ES, et al. Features predictive of brain arteriovenous malformation hemorrhage: extrapolation to a physiologic model. Stroke. 2014;45(7):1964–70.
166. Gupta A, Periakaruppan A. Intracranial dural arteriovenous fistulas: a review. Indian J Radiol Imaging. 2009;19(1):43.
167. Hartmann A, Pile-Spellman J, Stapf C, Sciacca RR, Faulstich A, Mohr JP, et al. Risk of endovascular treatment of brain arteriovenous malformations. Stroke. 2002;33(7):1816–20.
168. Taylor CL, Dutton K, Rappard G, Pride GL, Replogle R, Purdy PD, et al. Complications of preoperative embolization of cerebral arteriovenous malformations. J Neurosurg. 2004;100(5):810–2.
169. Weber W, Kis B, Siekmann R, Kuehne D. Endovascular treatment of intracranial arteriovenous malformations with onyx: technical aspects. AJNR Am J Neuroradiol. 2007;28(2):371–7.
170. Kretzer RM, Coon AL, Tamargo RJ, Walter E. Dand's contributions to vascular neurosurgery. J Neurosurg. 2010;112(6):1182–91.
171. Ogilvy CS, Stieg PE, Awad I, Brown RD Jr, Kondziolka D, Rosenwasser R, et al. AHA scientific statement: recommendations for the management of intracranial arteriovenous malformations: a statement for healthcare professionals from a special writing group of the Stroke Council, American Stroke Association. Stroke. 2001;32(6):1458–71.
172. Lawton MT, Project UBAMS. Spetzler-Martin Grade III arteriovenous malformations: surgical results and a modification of the grading scale. Neurosurgery. 2003;52(4):740–8.. discussion 8-9
173. Heros RC, Korosue K. Radiation treatment of cerebral arteriovenous malformations. N Engl J Med. 1990;323(2):127–9.
174. Sasaki T, Kurita H, Saito I, Kawamoto S, Nemoto S, Terahara A, et al. Arteriovenous malformations in the basal ganglia and thalamus: management and results in 101 cases. J Neurosurg. 1998;88(2):285–92.
175. Solomon RA, Connolly ES Jr. Arteriovenous malformations of the brain. N Engl J Med. 2017;377(5):498.
176. Friedman WA, Bova FJ. Linear accelerator radiosurgery for arteriovenous malformations. J Neurosurg. 1992;77(6):832–41.
177. Foote KD, Friedman WA, Ellis TL, Bova FJ, Buatti JM, Meeks SL. Salvage retreatment after failure of radiosurgery in patients with arteriovenous malformations. J Neurosurg. 2003;98(2):337–41.
178. Starke RM, Komotar RJ, Otten ML, Hahn DK, Fischer LE, Hwang BY, et al. Adjuvant embolization with N-butyl cyanoacrylate in the treatment of cerebral arteriovenous malformations: outcomes, complications, and predictors of neurologic deficits. Stroke. 2009;40(8):2783–90.
179. Reynolds MR, Lanzino G, Zipfel GJ. Intracranial dural arteriovenous fistulae. Stroke. 2017;48(5):1424–31.
180. Lawton MT, Chun J, Wilson CB, Halbach VV. Ethmoidal dural arteriovenous fistulae: an assessment of surgical and endovascular management. Neurosurgery. 1999;45(4):805–11.
181. Awad IA, Little JR, Akrawi WP, Ahl J. Intracranial dural arteriovenous malformations: factors predisposing to an aggressive neurological course. J Neurosurg. 1990;72(6):839–50.
182. Newton TH, Cronqvist S. Involvement of dural arteries in intracranial arteriovenous malformations. Radiology. 1969;93(5):1071–8.
183. Lasjaunias P, Chiu M, ter Brugge K, Tolia A, Hurth M, Bernstein M. Neurological manifestations of intracranial dural arteriovenous malformations. J Neurosurg. 1986;64(5):724–30.
184. Brown RD Jr, Wiebers DO, Nichols DA. Intracranial dural arteriovenous fistulae: angiographic predictors of intracranial hemorrhage and clinical outcome in nonsurgical patients. J Neurosurg. 1994;81(4):531–8.
185. Bulters DO, Mathad N, Culliford D, Millar J, Sparrow OC. The natural history of cranial dural arteriovenous fistulae with cortical venous reflux—the significance of venous ectasia. Neurosurgery. 2011;70(2):312–9.
186. Chung SJ, Kim JS, Kim JC, Lee SK, Kwon SU, Lee MC, et al. Intracranial dural arteriovenous fistulas: analysis of 60 patients. Cerebrovasc Dis. 2002;13(2):79–88.
187. Oh JT, Chung SY, Lanzino G, Park KS, Kim SM, Park MS, et al. Intracranial dural arteriovenous fistulas: clinical characteristics and management based on location and hemodynamics. J Cerebrovasc Endovasc Neurosurg. 2012;14(3):192–202.
188. Borden JA, Wu JK, Shucart WA. A proposed classification for spinal and cranial dural arteriovenous fistulous malformations and implications for treatment. J Neurosurg. 1995;82(2):166–79.
189. Cognard C, Gobin YP, Pierot L, Bailly A-L, Houdart E, Casasco A, et al. Cerebral dural arteriovenous fistulas: clinical and angiographic correlation with a revised classification of venous drainage. Radiology. 1995;194(3):671–80.
190. Barrow DL, Spector RH, Braun IF, Landman JA, Tindall SC, Tindall GT. Classification and treatment of spontaneous carotid-cavernous sinus fistulas. J Neurosurg. 1985;62(2):248–56.
191. Debrun GM, Viñuela F, Fox AJ, Davis KR, Ahn HS. Indications for treatment and classification of 132 carotid-cavernous fistulas. Neurosurgery. 1988;22(2):285–9.
192. Satomi J, van Dijk JMC, Terbrugge KG, Willinsky RA, Wallace MC. Benign cranial dural arteriovenous fistulas: outcome of conservative management based

on the natural history of the lesion. J Neurosurg. 2002;97(4):767–70.
193. Shah MN, Botros JA, Pilgram TK, Moran CJ, Cross DT III, Chicoine MR, et al. Borden-Shucart Type I dural arteriovenous fistulas: clinical course including risk of conversion to higher-grade fistulas. J Neurosurg. 2012;117(3):539–45.
194. Gross BA, Du R. The natural history of cerebral dural arteriovenous fistulae. Neurosurgery. 2012;71(3):594–603.
195. van Dijk JMC, Willinsky RA, Wallace MC. Clinical course of cranial dural arteriovenous fistulas with long-term persistent cortical venous reflux. Stroke. 2002;33(5):1233–6.
196. Zipfel GJ, Shah MN, Refai D, Dacey RG Jr, Derdeyn CP. Cranial dural arteriovenous fistulas: modification of angiographic classification scales based on new natural history data. Neurosurg Focus. 2009;26(5):E14.
197. Miller NR. Dural carotid-cavernous fistulas: epidemiology, clinical presentation, and management. Neurosurg Clin N Am. 2012;23(1):179–92.