Hemorrhagic Strokes

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Epidemiology

Intracerebral hemorrhages (ICHs) are most often caused by the rupture of small, penetrating arteries due to hypertensive changes or other vascular abnormalities [1, 2]. Although the incidence of hypertensive ICH has decreased with the improvement in blood pressure control in developed countries, [3] it still accounts for approximately 10–20% of all strokes: [4, 5] 8–15% in Western countries (e.g., the USA, the UK, and Australia) [6, 7] and 18–24% in Japan and Korea [3, 8]. However, the incidence of ICH may be higher in less-well-developed countries.

The incidence of ICH involving posterior circulation is unclear due to lack of data and adequate definitions for categorizing ICH [9]. However, hospital studies have reported that thalamic ICHs account for 10–15% of ICH cases, cerebellar ICHs for 5–15%, and pontine ICHs for approximately 10% [10]. Therefore, ICHs involving posterior circulation are not rare.

Etiology and Pathophysiology

Primary ICH

Hypertensive ICH

Hypertension is the most important risk factor for ICH. It contributes to the decreased elasticity of arteries, thereby increasing the likelihood of rupture in response to acute elevations in intravascular pressure [11]. Chronic hypertension is responsible for the degeneration of the tunica media and smooth muscle in cerebral arteries [2]. Vascular wall resistance to the stress due to elevated blood pressure in hypertension is weakened by the presence of hyaline, and this material in the cerebral vasculature has been linked to minimal resistance of the surrounding cerebral parenchyma. This may explain why the cerebral parenchyma is the only tissue in which increased blood pressure can lead to vascular rupture and hemorrhage [12].

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Amyloid Angiopathy

Cerebral amyloid angiopathy-related ICH accounts for 10–30% of primary ICH in older patients [13, 14]. It is characterized by the deposition of amyloid-β peptide in capillaries, arterioles, and small- and medium-sized arteries in the cerebral cortex, leptomeninges, and cerebellum [15]. The secondary pathological changes associated with advanced cerebral amyloid angiopathy include loss of vascular smooth muscle cells, microaneurysms, concentric splitting of the vessel wall, chronic perivascular or transmural inflammation, and fibrinoid necrosis [16–18]. Cerebral amyloid angiopathy-related hemorrhages occur preferentially in lobular areas, especially in the posterior brain regions (e.g., occipital and temporal lobes), reflecting the distribution of vascular amyloid deposits [19–21].

Secondary ICH

Arteriovenous Malformation

Vascular malformations are an important cause of intracranial hemorrhage, especially in younger patients. Among vascular malformations, arteriovenous malformations are the most frequent causes of ICH. These malformations are often found in border zone regions shared by the distal anterior, middle, and posterior cerebral arteries [22]. Potential risk factors for these malformation-related hemorrhages include (1) malformations with exclusively deep venous drainage (typically defined as drainage through the periventricular, galenic, or cerebellar pathways), (2) malformations associated with aneurysms, (3) malformations located deep within the brain, and (4) infratentorial malformations [23, 24] (Fig. 8.1).

Cavernous Malformation

Cerebral cavernous malformations, the second most common type of central nervous system vascular lesion, constitute abnormally enlarged capillary cavities without intervening brain parenchyma [25, 26]. These lesions may occur anywhere, including the cortical surface, white matter pathways, basal ganglia, brainstem, or the cerebellum. (Fig. 8.2) For patients who initially presented without both an overt intracranial hemorrhage and a brainstem cavernous

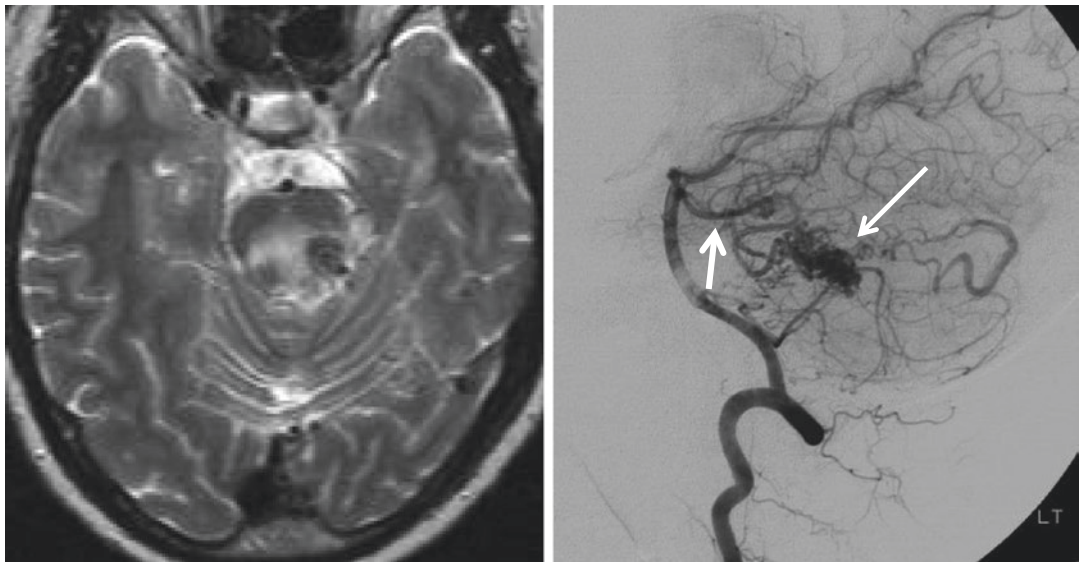

Fig. 8.1 A 42-year-old woman developed dizziness and tingling sensation in the right extremities. Left image: T2-weighted Brain MRI showed a round, dark signal intensity with adjacent high signal intensity signals consistent with acute hemorrhage surrounded by edema. Right image: Angiogram showed arteriovenous malformation (long arrow) that is mainly supplied by enlarged superior cerebellar artery (short arrow). The patient was treated with embolization

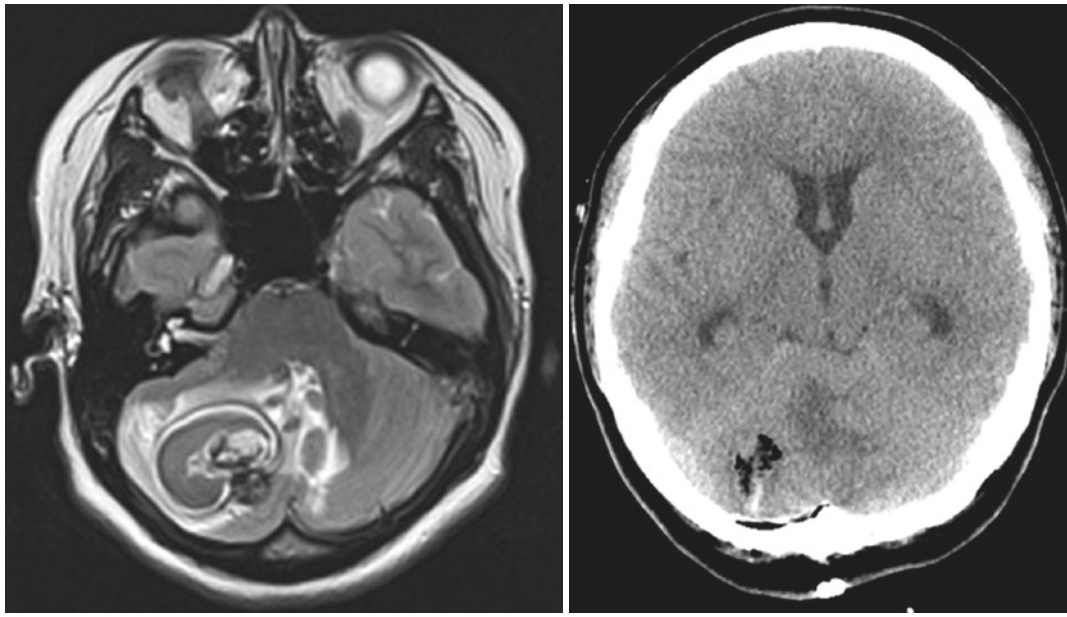

Fig. 8.2 An 18-year-old girl developed sudden dizziness, headache, and gait ataxia. Left image: T2-weighted MRI showed heterogeneous (dark, iso, high) lobulated signals suggesting multistage hemorrhages that were surrounded by edema. Angiogram findings were normal. These findings were consistent with repeated bleeding from cavernous hemangioma. Right image: Follow-up CT showed that the hemorrhages and mass were surgically resected

malformation, the initial 5-year risk of hemorrhage was 3.8%, and the recurrent 5-year hemorrhage risk was 18.4%. In contrast, patients with brainstem cavernous malformations were reported to have significantly higher 5-year rates of initial (8%) and recurrent (30.8%) hemorrhage [27].

Dural Arteriovenous Fistula

Dural arteriovenous fistulae constitute arteriovenous shunts at the level of the meninges that are usually supplied by branches of the external carotid or vertebral arteries. Hemorrhages due to these fistulae show more benign clinical courses than those with other vascular lesions (e.g., intracranial aneurysms) due to the bleeding site being a venous rather than a direct arterial source [28].

Cerebral Venous Thrombosis

Cerebral venous thrombosis is a well-established cause of ICH. Elevated cerebral venous pressure due to venous occlusion results in a spectrum of pathophysiological changes, including dilated venous and capillary beds, development of interstitial brain edema, increased CSF production, decreased CSF absorption, and rupture of cerebral veins leading to hemorrhagic lesions [29]. It is crucial to recognize ICH caused by cerebral venous thrombosis because it is the only variety of ICH that should be treated with anticoagulants.

ICHs Associated with Antithrombotics

Coagulopathy caused by oral anticoagulation therapy is also an important pathophysiology of ICH. Oral anticoagulants can directly interfere with the synthesis of vitamin K-dependent clotting factors, resulting in dysfunctional prothrombin and factors VII, IX, and Xa [30–32]. Oral anticoagulants can trigger preexisting subclinical intracerebral bleeding, especially in patients with underlying hypertension and cerebrovascular disease [33]. Subdural hematoma has also been reported to be a rare complication of anticoagulation therapy [34, 35].

ICHs Associated with Cancer

Cancer-related intracerebral bleeding is an uncommon cause of ICH. The incidence of tumoral hemorrhages has been estimated to be 0.8–4.4% of all ICHs [36]. However, intracere-

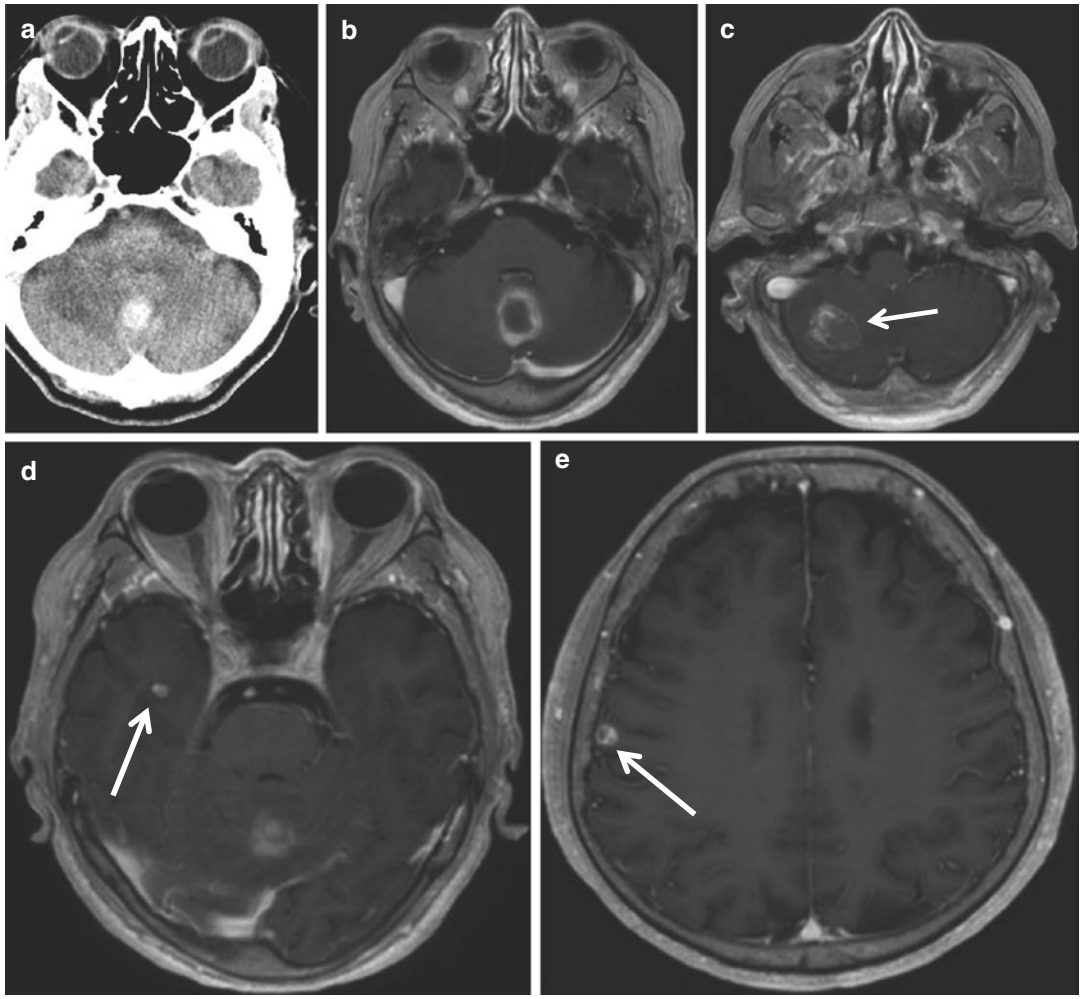

Fig. 8.3 An 88-year-old woman developed dizziness and gait difficulty. She had malignant papillary thyroid carcinoma with multiple lung and bone metastasis. Brain CT showed an acute hemorrhage in the midline cerebellum (**a**), which was identified by MRI (**b**). Gadolinium-enhanced MRI showed additional enhancing hemorrhagic lesion in the right cerebellum (**c**) and small enhancing lesions in the right temporal (**d**) and frontal lobe (**e**). It is likely that the current cerebellar hemorrhage was bleeding from the metastatic cancer

bral hemorrhage is relatively common in cancer patients and has been demonstrated in 3.0–14.6% patients at autopsy [37–39]. There are multiple causes of hemorrhage in cancer patients, including intratumoral bleeding, coagulation disorders, and complications of anticancer treatment (Fig. 8.3).

Reversible Cerebral Vasoconstriction

Reversible cerebral vasoconstriction syndrome is a group of conditions typically preceded by severe thunderclap headaches associated with reversible, segmental, multifocal cerebral artery vasoconstriction. In a large cohort of patients with this syndrome, brain hemorrhages were reported to be frequent (43%) [40].

Aneurysm

Rupture of intracranial arteries causes subarachnoid hemorrhages. Dissecting aneurysms involving intracranial posterior circulation are unusual lesions that affect otherwise healthy young adults. The dissection usually occurs between the intima or internal elastic lamina and the media;

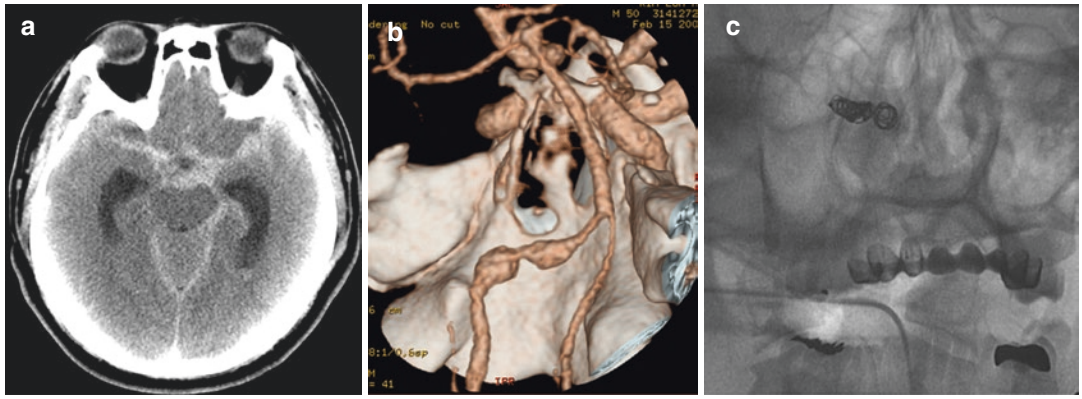

Fig. 8.4 A 45-year-old man developed sudden severe headache after baseball playing. CT showed subarachnoid hemorrhage (**a**). CT angiogram showed dissecting aneurysm in the left distal vertebral artery (**b**), which was treated with coil embolization (**c**)

subadventitial dissection can also occur and accounts for the infrequent finding of subarachnoid hemorrhage [41].

Hemorrhagic stroke due to dissection seems to involve posterior circulation more commonly than anterior circulation. Pathology studies have shown that subadventitial dissections are more frequent in the vertebral artery than in the middle cerebral artery; [42, 43] this could explain the relatively high frequency of hemorrhages in patients with posterior circulation dissection (Fig. 8.4).

Diagnosis

Computed tomography (CT) has excellent sensitivity and specificity (nearly 100%) for the detection of acute hemorrhage [44]. Acute hematomas appear as hyperdense areas on a noncontrast CT scan owing to their high protein concentration and high mass density. The density seen on a CT scan varies according to the timing of the scan. CT angiography is used to detect underlying vascular abnormalities and conditions, such as intracranial aneurysms and the "spot sign," an early predictor of hematoma expansion [45]. Traditionally, magnetic resonance imaging (MRI) has been considered to be insensitive to the presence of acute intraparenchymal blood and has been used to detect ischemia. With the use of gradient-echo imaging and susceptible weighted imaging, MRI has a diagnostic accuracy similar to that of noncontrast CT for acute blood and is markedly superior in the detection of chronic hemorrhage [46]. High-resolution vessel wall MRI is being increasingly used to assess vascular wall pathology (see Chap. 9).

Clinical Features

Thalamic Hemorrhage

At the beginning of the nineteenth century, Dejerine and Roussy provided a detailed description of thalamic syndrome [47]. Recent advances in neuroimaging have provided accurate diagnoses and have enabled clinicians to correlate clinical findings with neuroimaging findings. The clinical features of thalamic ICH vary with hematoma location and volume. The classic symptoms include the following: (1) contralateral hemiparesis, as the thalamus is close to the posterior limb of the internal capsule; hemiparesis was reported in 95% of cases; [48, 49] (2) hemisensory syndrome; approximately 85% of patients with thalamic ICH develop prominent sensory loss in the face, limb, and trunk [48] (Fig. 8.5); and (3) ophthalmologic symptoms such as paresis of upward gaze ("peering at the tip of the nose"), miotic

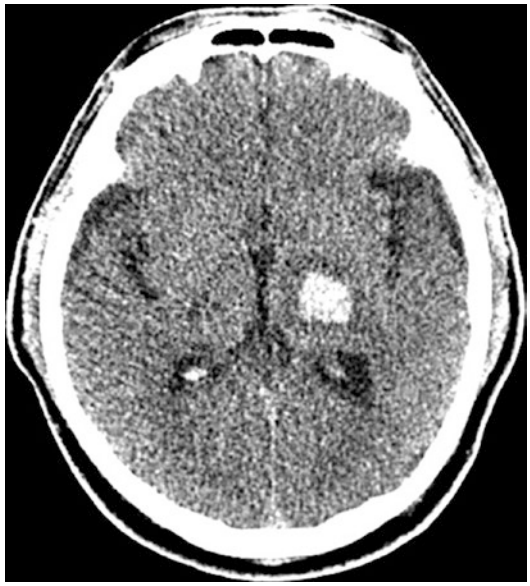

Fig. 8.5 A 60-year-old hypertensive man developed dysarthria, right hemiparesis, and severe sensory deficits. CT showed a thalamic hemorrhage of posterolateral type (Fig. 8.6c)

and unreactive pupils caused by ICH-induced pressure on the dorsal midbrain, [50] and skew deviation and horizontal gaze disturbances accompanied by involvement of the oculomotor tracts at the midbrain level [51].

The clinical syndromes associated with thalamic ICH differ according to the location of the hematoma and are subclassified based on the ruptured arterioles supplying specific thalamic areas (Table 8.1 and Fig. 8.6) [49, 52].

Midbrain Hemorrhage

A nontraumatic, spontaneous, primary midbrain hemorrhage is extremely rare. Midbrain hemorrhages mostly result from secondary extensions of hematomas from thalamic or pontine ICHs. The most frequent cause of an isolated midbrain hemorrhage is an arteriovenous malformation; rarely, it can also be caused by hypertension [53].

Table 8.1 Clinical syndromes of thalamic intracerebral hemorrhage

	Anterior type	Posteromedial type	Posterolateral type	Dorsal type	Global type
Ruptured artery	Branches of the "polar" or tuberothalamic artery	Thalamo-perforating arteries	Thalamo-geniculate arteries	Branches of the posterior choroidal artery	Nonspecific
Consciousness	Alert	Usually acute stupor or coma	Consciousness level parallels hematoma size	Usually alert	Stupor or coma in 3/4 of patients
Behavioral changes	Acute confusion, language dysfunctions, memory impairment, and apathy	Prominent memory dysfunction in case of hematoma limited to the medial thalamus; decorticate posture in the early stage with concomitant midbrain involvement	Hemi-neglect in right-sided lesions and simulating lesions; dysphasia in left-sided lacunar syndrome (sensorimotor stroke > pure motor stroke > pure sensory stroke)	None	Frequent decerebrate postures in the early stage; very similar to the posterolateral type in less severe cases
Sensory manifestation	Rare	Uncommon	Frequent; preceding paresthetic episodes at onset, contralateral hypesthesia, and late thalamic pain syndrome	Preceding paresthesia in 1/3 of patients; frequent sensory dysfunction	Almost always; severe

Table 8.1 (continued)

	Anterior type	Posteromedial type	Posterolateral type	Dorsal type	Global type
Motor manifestation	Usually absent and only slight, if any	Moderate-to-marked contralateral hemiparesis	Frequent moderate-to-marked contralateral hemiparesis mainly due to compression of the cerebral peduncle	Mild-to-moderate contralateral hemiparesis due to compression of the posterior limb of the internal capsule	Severe contralateral hemiparesis
Ocular findings	None	Very frequent	Infrequent extraocular muscle dysfunctions; occasional Horner's syndrome	None	Frequent classic ocular features
Prognosis	Excellent	High fatality	High fatality and morbidity	Very good	Very high fatality

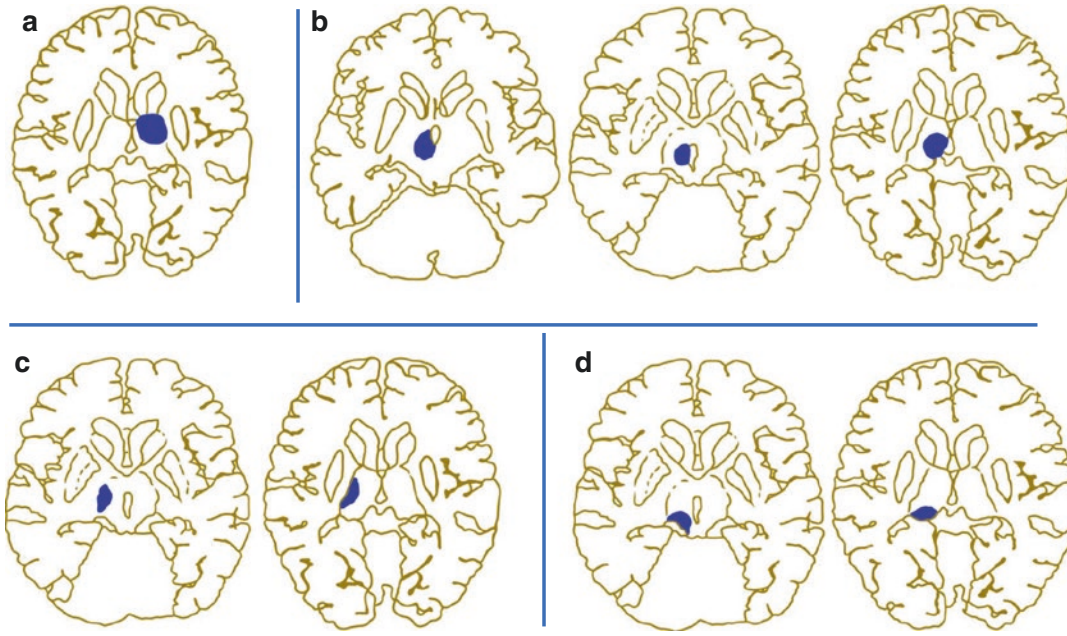

Fig. 8.6 Hemorrhage location according to the vascular supply of the thalamus. (**a**) Anterior type: Thalamo-tuberal arteries of posterior communicating arteries. (**b**) Posteromedial type: Posterior thalamo-subthalamic para-median arteries, thalamo-perforate. (**c**) Posterolateral type: Infero-lateral arteries, thalamo-geniculate. (**d**) Dorsal type: Posterior choroidal arteries

Midbrain ICHs present with progressive symptoms of ipsilateral ataxia or contralateral hemiparesis in combination with ophthalmoplegia (typically an ipsilateral partial/complete third cranial nerve palsy). In rare cases, isolated syndromes can also occur (Table 8.2).

Pontine Hemorrhage

Pontine hemorrhaging accounts for 10% of ICHs [59, 60] and shows a wide spectrum of clinical symptoms and prognosis, with its mortality ranging widely from 30% to 90% [61–63]. This wide

Table 8.2 Clinical syndromes of midbrain intracerebral hemorrhage

Syndromes	Symptoms
Dorsal midbrain syndrome [54]	Vertical gaze palsy, nystagmus retractorius, eyelid retraction, and light-near pupillary dissociation
Dorsal midbrain syndrome + [55]	Dorsal midbrain syndrome with associated bilateral fourth nerve palsy
Weber's syndrome [56]	Ipsilateral third nerve palsy and contralateral hemiparesis
Fascicular third nerve palsy syndrome [57]	Isolated ipsilateral third nerve palsy without hemiparesis
Movement disorder [58]	Contralateral limb dystonia and tremors with "rubral" characteristics

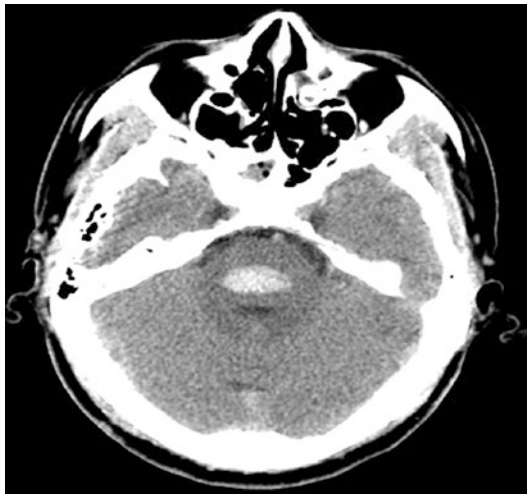

Fig. 8.7 A hypertensive, 53-year-old man suddenly became drowsy. Neurologic examination showed severe dysarthria, quadriparesis, and sensory deficits bilaterally. CT showed a pontine hemorrhage (bilateral-tegmental type, Fig. 8.8C)

range is mainly attributed to the size and location of the hematoma; thus, pontine ICH is classified as either small unilateral-tegmental, basal- or bilateral-tegmental, or massive (Figs. 8.7 and 8.8 and Table 8.3) [63].

Medullary Hemorrhage

Isolated medulla oblongata ICH has rarely been reported in the literature [64, 65]. The common symptoms of medullary ICH are vertigo, headache, and diplopia. Various neuro-otological symptoms, including spontaneous nystagmus, ocular lateropulsion, and apogeotropic positional nystagmus, have been reported [66].

Cerebellar Hemorrhage

Regarding cerebellar hemorrhage, over 75% of patients complain of dizziness with headache being common at onset, while dysarthria, tinnitus, and hiccups can occur but less frequently [67]. Neurological exam findings differ depending on the involvement of the dentate nucleus, hemispheric white matter, and tegmental pons. Ipsilateral ataxia is found in 70% of all patients and also in patients with peripheral facial palsy, ipsilateral horizontal gaze palsy, sixth cranial nerve palsy, depressed corneal reflex, and miosis. In noncomatose patients, a characteristic triad of ipsilateral appendicular ataxia, horizontal gaze palsy, and peripheral facial palsy appear together when the ipsilateral pontine tegmentum is involved [67]. Ocular bobbing has occasionally been reported after cerebellar hemorrhage, [68] and the overall clinical course during the acute period of cerebellar hemorrhage is reported to be unpredictable [69–71].

Cortical Hemorrhage

The occipital lobe is a relatively rare site for hypertensive hematomas. Occipital hemorrhages are reported to be caused by arteriovenous angioma and cerebral angiopathy [72]. These hemorrhages can cause severe headaches, usually at or around the ipsilateral eye, contralateral homonymous hemianopia, contralateral extinction, dysgraphia, and dyslexia.

Management

Blood Pressure Control

Hypertension is the most common cause of ICH, and its early management is extremely important. Current evidence indicates that early and intensive lowering of blood pressure (BP) is safe and

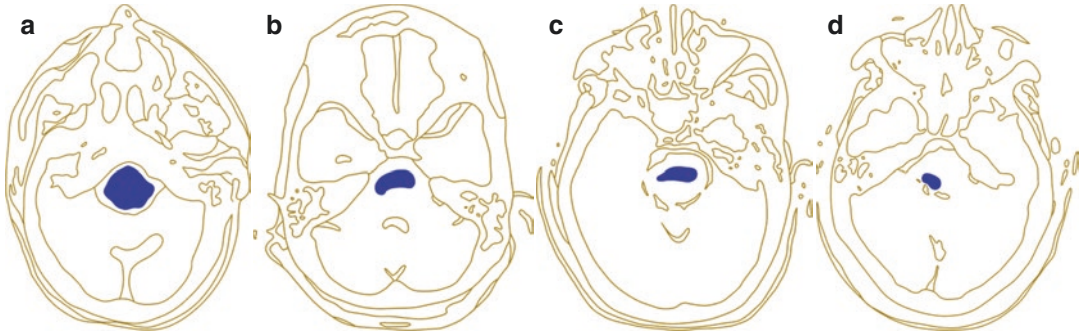

Fig. 8.8 Hemorrhage locations in the pons. (**a**) Massive type, (**b**) basal-tegmental type, (**c**) bilateral-tegmental type, and (**d**) unilateral-tegmental type

Table 8.3 Clinical syndromes of pontine intracerebral hemorrhage

	Small unilateral-tegmental type	Basal-tegmental/ bilateral-tegmental type	Massive type
Ruptured artery	Penetrating branches of the long circumferential arteries	Perforators of the basilar artery	Perforators of the basilar artery
Consciousness	Alert	Usually acute stupor or coma	Coma
Behavioral changes	Uncommon	Uncommon	Uncommon
Sensory manifestation	Facial numbness	Uncommon; hypesthesia	Bilateral hypesthesia
Motor manifestation	Frequent hemiparesis and palatal myoclonus	Pure motor stroke and ataxic hemiparesis	Progressive hemiparesis
Ocular findings	Ipsilateral miosis, "one-and-a-half syndrome," horizontal gaze palsy, internuclear ophthalmoplegia, partial involvement of vertical eye movements, ocular bobbing, and ocular ataxia	Rare; isolated abducens nerve palsy	Miotic pinpoint pupils, absent horizontal eye movements, and ocular bobbing
Prognosis	Excellent	Moderate to high fatality	Very high fatality

feasible and that surviving patients show modestly better functional recovery, with a favorable trend toward a reduction in the mortality and major disability endpoints. However, two large clinical trials, INTERACT II and ATACH II, failed to demonstrate an improved functional outcome with intensive reduction of systolic BP to <140 mmHg, compared to the standard goal of <180 mmHg, in acute primary ICH [73, 74]. Based on currently available data, for ICH patients presenting with a systolic BP between 150 and 220 mmHg and without any contraindications for acute BP treatment, acute lowering to 140 mmHg is safe. For ICH patients presenting with a systolic BP >220 mmHg, it may be reasonable to consider an aggressive reduction of BP using a continuous intravenous infusion and frequent BP monitoring [75].

ICH Related to Antithrombotics

ICH related to anticoagulation therapy is a medical emergency and is associated with high mortality and an unfavorable outcome. In patients treated with vitamin K antagonists (VKAs), determination of anticoagulant status is performed by measuring the international normalized ratio (INR). Patients with ICH whose INR is elevated because of anticoagulation therapy

should have their VKA withheld, receive therapy to replace vitamin K-dependent factors and correct the INR, and receive intravenous vitamin K [75]. Three agents are capable of correcting an elevated INR: activated factor VII, fresh frozen plasma, and prothrombin complex concentrate [76].

In contrast to VKA-ICH, in which INR measurements allow the assessment of anticoagulation status, coagulation testing in patients treated with novel oral anticoagulants is not available. Data from experimental settings suggest that prothrombin complex concentrate, fresh frozen plasma, and activated factor VII are all effective in preventing hematoma expansion with rivaroxaban and dabigatran [77–79]. For specific antidotes, idarucizumab is recommended as frontline therapy in patients receiving dabigatran who present with major or life-threatening bleeding, and andexanet alfa is a first choice for reversing life-threatening bleeding under FXa-inhibitor therapy [80]. The PATCH trial randomized patients with spontaneous acute ICH taking antiplatelet therapy (aspirin, clopidogrel, and dipyridamole) to either receive platelet transfusion therapy or standard therapy and reported an increased likelihood of death or unfavorable outcomes in the platelet transfusion group [81]. For ICH-related coagulation therapy, cessation of antiplatelet therapy is considered sufficient.

Control of Increased Intracranial Pressure

Increased intracranial pressure (ICP) is associated with worse outcomes following ICH, suggesting that ICP monitoring may benefit high-risk patients [82]. Current AHA/ASA guidelines recommend ICP monitoring and treatment for patients with a Glasgow Coma Scale score of ≤8, those with clinical evidence of transtentorial herniation, and those with significant intraventricular hemorrhage or hydrocephalus. A cerebral perfusion pressure of 50–70 mmHg may be reasonable. Corticosteroids are not recommended for the treatment of increased ICP in ICH [75].

Surgical Management of ICH

Two large clinical trials, STICH and STICH II, were undertaken to determine whether early surgery reduces mortality and improves the neurological outcomes for supratentorial ICH compared to those with conservative management. Early hematoma evacuation was not found to be beneficial [83, 84]. Although a randomized clinical trial has not been performed, craniotomy for posterior fossa hemorrhage patients with cerebellar hemorrhages >3 cm in diameter is recommended for patients with neurological deterioration or with brainstem compression and/or hydrocephalus from ventricular obstruction. In contrast to cerebellar hemorrhage, evacuation of brainstem hemorrhages may be harmful [75].

Prognosis

ICH involving posterior cerebral circulation demonstrates diverse prognoses depending on the location of the ICH and size of the hematoma. Several studies have reported the factors associated with prognosis according to the location of the ICH (Table 8.4)

Table 8.4 Poor prognostic factors of ICH involving posterior circulation

Thalamic ICH [49, 85]	Pontine ICH [86]	Cerebellar ICH
Low level of consciousness at onset	Low level of consciousness at onset	Low level of consciousness at onset
Severe motor weakness and appearance of decerebrate posturing	Dilated pupils	Delayed surgical decompression
Systemic complications	Abnormal respiration	Severe hydrocephalus
Global and posteromedial types	Larger hematoma	Identifiable underlying causes, such as arteriovenous malformation and coagulopathy
Larger hematoma	Systolic blood pressure of <100 mmHg	Volume of cerebellar hematoma

Table 8.4 (continued)

Thalamic ICH [49, 85]	Pontine ICH [86]	Cerebellar ICH
Extension of hematoma, involving the midbrain and basal ganglia	Hydrocephalus	Obliteration of the quadrigeminal cistern
Markedly enlarged ventricles and severe mass effect, causing a midline shift		
Presence of dense blood clots in the third ventricle		

ICH intracerebral hemorrhage

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