History of Vertebrobasilar Territory Stroke and TIA

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Early Anatomical and Clinical–Pathological Studies

The first important attention to disease of the posterior circulation was likely by a Swiss pathologist and physician: Johan Jacob Wepfer. He followed the example of Vesalius and performed meticulous necropsy examinations. He described the results of his dissections in his magnum opus on apoplexy published in 1658 [1]. Wepfer distinguished two types of apoplexy: in one form, the supply of blood to the brain was obstructed or precluded, and in the other, animal spirits escaped and hemorrhage occurred. He described the appearance and the course of the intracranial arteries and recognized blockage of the carotid and vertebral arteries caused by disease of the arterial walls as a cause of apoplexy, the obstruction preventing entry of sufficient blood into a portion of the brain. He described the anatomy of the intracranial vertebral arteries as follows: "As regards the vertebral arteries, they emerge from the nearest foramen, that great orifice through which the spinal marrow descends. They advance to the sides of the medulla oblongata…. When they reach that place where the sixth pair of nerves (IX, X, XI, XII) arises, the right and left branches are joined and form a single channel (basilar artery) and remain united along the whole marrow tract."

The next attention to the posterior circulation was by clinicians and researchers in Europe during the second half of the nineteenth century and early twentieth century. These observers were mostly interested in brain and vascular anatomy and in anatomical–physiologic correlations. The so-called classic brainstem syndromes, all eponymic and named after the original describers of the syndromes, were stimulated by a fascination of the authors with the anatomy and functions of the brainstem. Recognized still today are these various constellations of findings as the syndromes of Benedikt, Claude, Millard–Gubler, Babinski–Nageotte, Foville, and Wallenberg, among others [2]. Retrospective reviews of these reports showed that many lesions were not vascular in etiology; the underlying arterial lesions and vascular pathology were very seldom studied or commented upon. More modern studies of series of patients with brainstem and cerebellar ischemia indicate that all but Wallenberg's syndrome are rare. During that era, clinicians were mostly interested in how the brain and its nuclei and tracts worked. The brainstem with its dense, packed heterogeneous and complex anatomy was of particular interest. Focal lesions limited to one location in the midbrain, pons, or medulla provided great insight into the anatomy and physiology of the brainstem. Of special utility in localization were crossed syndromes in which cranial nerve abnormalities involved one side of

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the head while long tract motor or sensory or extrapyramidal-cerebellar abnormalities involved the limbs and trunk on the opposite side of the body. The Millard–Gubler syndrome of ipsilateral facial palsy and contralateral hemiparesis was an example. Since there was no way during that time to identify the causative vascular lesion during life, and no treatment was known or available even if the causes were known, there was no interest in stroke etiology or the mechanism of ischemia in patients with brainstem or cerebellar infarcts.

Posterior Circulation Ischemia

The first detailed study of the clinical, pathological, and etiological aspects of brainstem infarction was by a German physician Adolf Wallenberg. During a period of 27 years, Wallenberg published 4 reports on the topic of infarction of the lateral medulla: a detailed analysis of the clinical findings in one patient, the necropsy findings in that patient, a single case report of another patient, and the clinical and pathological findings in the 15th patient he had studied [3–6]. Wallenberg had first seen the original patient, a ropemaker in 1889, for appendicitis. In 1993, the patient developed severe vertigo, intense pain in the left eye, difficulty swallowing, and hoarseness. Wallenberg reported a detailed clinical neurological examination that showed horizontal and vertical nystagmus, loss of pain and temperature sensation in the left face and right face and body, weakness of the left palate, paralysis of the left vocal cord, and left limb ataxia. Wallenberg wrote, "We are dealing with an insult on the left side of the medulla. It begins just above the pyramidal decussation. It passes through the accessory olive and the inferior olive more rostrally. Laterally it destroys the entire medulla to the pia mater. Rostrally and medially it reaches the ascending lemniscus damages the restiform body and ultimately also the cerebellum."

Six years after the initial report, the patient had another acute stroke and died. Wallenberg performed the autopsy himself and described and illustrated the location and extent of the medullary infarct. The vertebral arteries were severely diseased, and the left posterior inferior cerebellar artery was occluded.

Anatomists and researchers working during the early part of the twentieth century became interested in the blood vessels that supply the brain including the brainstem and cerebellum. Duret [7, 8] in France and Stopford [9] in England meticulously dissected the arteries that supply the brainstem. Particularly prolific in performing studies that clarified arterial anatomy was Charles Foix who worked in the clinics and pathology laboratories at the Salpetriere hospital in Paris [10]. Foix and his colleagues defined the distribution and localization of brain infarcts ("ramollissements") and the corresponding neurological abnormalities that they caused during life. They also sought to clarify the anatomical distribution of the arterial supply to these areas. During 4 short years, between 1923 and 1927, Foix and his colleagues defined the arterial distribution of the posterior cerebral artery including the branches to the thalamus, and the supply of the pons, and the medulla oblongata [11–15]. Most importantly, Foix noted the common pattern of irrigation of all parts of the brainstem by paramedian, short circumferential, and long circumferential arteries. This schema is illustrated in Fig. 1.1.

Probably the single most important and influential communication regarding posterior circulation ischemia was the report on basilar artery occlusion by Kubik and Adams published in 1946 [16]. This report was one of the most complete and most detailed clinical–pathological studies of any vascular syndrome. Kubik and Adams did not publish the very first report of occlusion of the basilar artery; there had been prior reports. Hayem had described the pathological findings in a necropsy specimen from a single patient with basilar artery occlusion but did not describe the clinical findings [17]. Leyden had reported 2 patients with syphilitic arteritis of the basilar artery [18]. Marburg wrote a review of pontine and medullary infarcts in 1911 [19]. Lhermitte and Trelles reported a number of

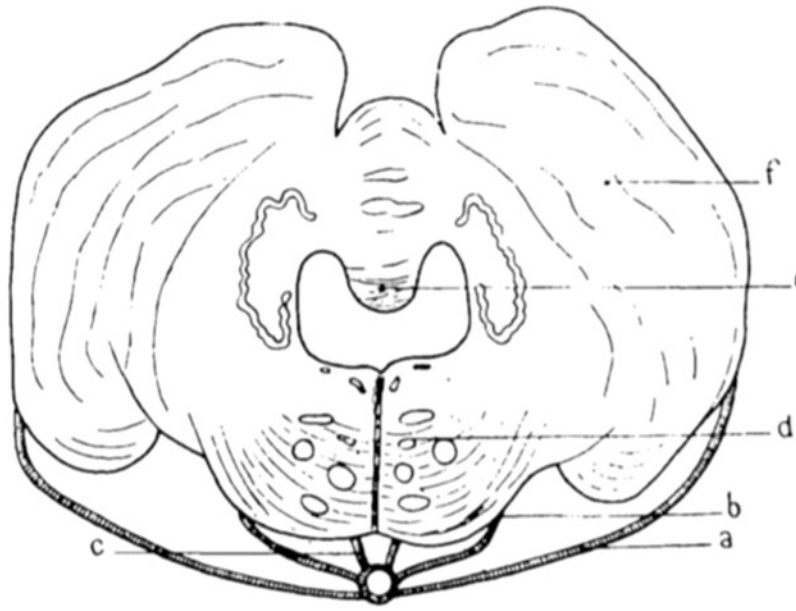

Fig. 1.1 Foix diagram of pontine supply. (a) Long circumferential artery, (b) short circumferential artery, (c) paramedian artery, (d) pons, (e) cerebellar vermis, and (f) lateral lobe of the cerebellum. (From Caplan, L.R. Charles Foix - The first modern stroke neurologist. Stroke 1990;21:348-356 with permission)

patients with pontine infarcts, some of whom had thrombosis within the basilar artery or its branches [20]. Pines and Gilinsky described a single patient with a likely embolic occlusion of the rostral basilar artery in which the brainstem had been serially sectioned and the infarcts well defined [21]. The report of Kubik and Adams was very important and influential because of the large size of the series (18 patients), the meticulous dissection and illustration of the brain lesions at the various brainstem levels, as well as delineation of the vascular occlusion (Figs. 1.1 and 1.2), and the details of the clinical findings.

At the time of their report, Kubik and Adams were both neuropathologists working in the necropsy laboratories at the Massachusetts General Hospital and the Boston City Hospital in Boston, as well as being active on the neurology wards of the hospitals. The authors examined some of the patients during life and later reviewed their clinical charts. The extent and location of the thrombosis correlated well with the areas of brainstem infarction, and usually, only a portion of the basilar artery was occluded. Figure 1.2 is a redrawing of a diagram of the location and extent of the basilar artery occlusion and the resultant infarcts in the pons. The infarcts were mostly confined to the territories of the paramedian and short circumferential pontine arteries. The authors discussed the pathological distinctions between thrombosis that formed in situ and embolism and concluded that 7 of the 18 basilar artery occlusions were embolic. The symptoms in most patients began abruptly, and all cases were fatal (or else the patient would not have reached their laboratory in the morgue). Each patient was described in detail, and the brain and vascular lesions were diagrammed. The clinical symptoms and signs during life such as dizziness, altered consciousness, dysarthria, paresthesias, pseudobulbar palsy, hemiplegia or quadriplegia, pupillary and oculomotor abnormalities, facial paralysis, and visual loss correlated well with the brainstem and posterior hemispheral structures involved. The authors emphasized that recognition of these signs should allow for accurate antemortem diagnosis of basilar artery occlusion. In fact, at the conclusion of the article, the author reported the clinical findings that led them to suspect basilar artery thrombosis in 7 patients who were still alive. Unfortunately, with the limited technology available at the time, there was no safe way to document the nature of the vascular lesion.

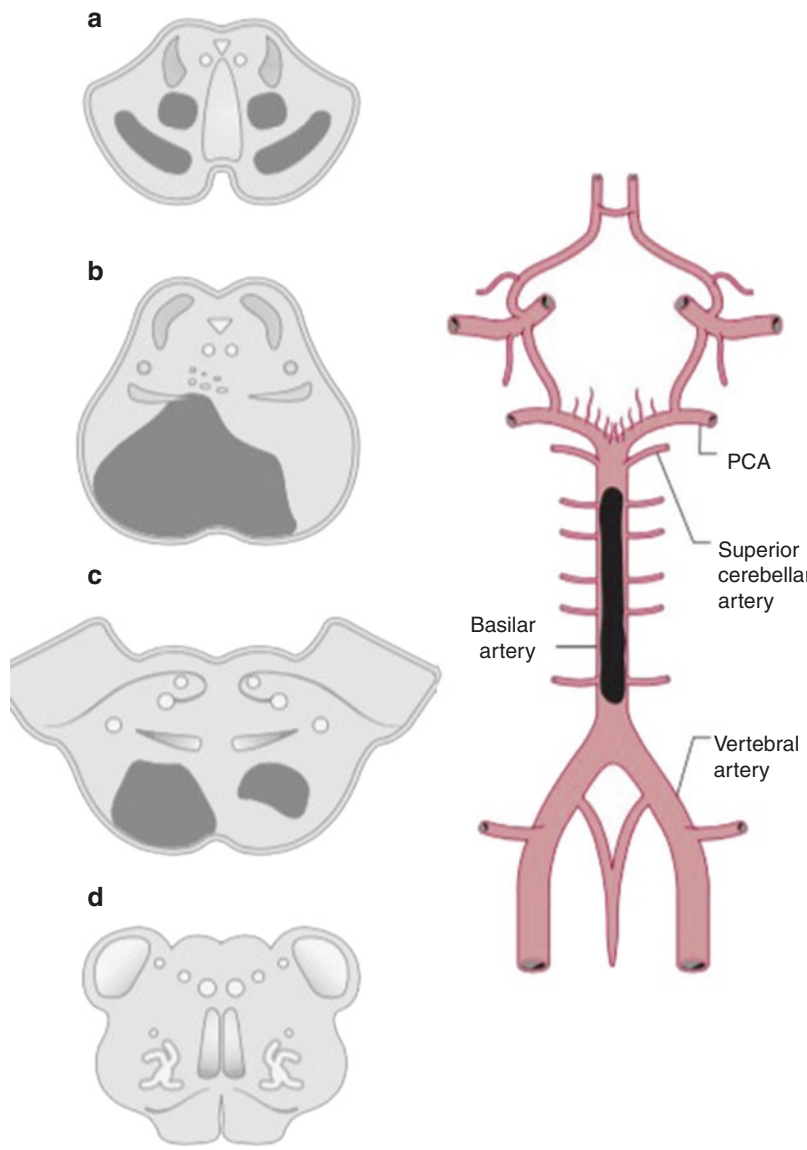

Fig. 1.2 Cartoon showing the pons with an infarct caused by occlusion of the basilar artery. (**a**) midbrain, (**b**) upper pons, (**c**) lower pons, and (**d**) medulla. (From Caplan, L.R.: Caplan's Stroke: A Clinical Approach, 4th edition. Philadelphia: Elsevier, 2009 redrawn from Kubik C, Adams R. Occlusion of the basilar artery: a clinical and pathologic study. Brain 1946; 69:73-121)

Early Clinical Studies

During the first half of the twentieth century and before that time, most brain infarcts were attributed to occlusion of intracranial arteries. In the report of Kubik and Adams, the occlusion involved the basilar artery, an important intracranial artery, and most anterior circulation infarcts were attributed to occlusion of the middle cerebral artery. As in Kubik and Adams's report, clinicians of that era thought that strokes generally came abruptly without warning but often progressed after the onset of ischemia.

Miller Fisher's reports on the clinical features of carotid artery disease appeared just 5 and 8 years after Kubik and Adams's report [22, 23]. Fisher made two key observations that had an important influence on the approach of clinicians to posterior circulation ischemia. Fisher's patients with carotid artery disease often had warning spells, TIAs, that preceded and warned of an impending stroke. The occlusive disease was in

the neck where it was potentially reachable by surgery. This was the first emphasis on occlusive disease in the neck. Several years after Fisher's report, Hutchinson and Yates began to systematically dissect and examine the cervicocranial arteries in the neck [24]. They found a high frequency of occlusive disease in the cervical vertebral arteries near their origins from the subclavian arteries. Vertebral artery occlusive disease in the neck seemed to parallel carotid occlusive disease leading Hutchinson and Yates to coin the term "carotico-vertebral" stenosis [25]. Later, Miller Fisher also emphasized the importance of occlusive disease involving the vertebral arteries in the neck, which often involved these vessels bilaterally [26].

In the ensuing years, description of the so-called subclavian steal syndrome added more weight to the growing evidence that extracranial occlusive disease was common. The report by Reivich and colleagues called attention to patients with periodic attacks of dizziness and vertigo, sometimes precipitated by arm exercise, who had occlusive lesions involving the subclavian artery proximal to the vertebral artery origin [27, 28]. Angiography and blood flow studies showed that blood coursed from the contralateral subclavian artery up the vertebral artery to reach the cranium and then traveled retrograde down the vertebral artery ipsilateral to the subclavian artery stenosis or occlusion. Ultimately, the retrograde vertebral artery flow went into the ischemic arm. Later, Hennerici and colleagues showed that reversed vertebral artery flow was common in patients with subclavian artery occlusive disease but rarely produced important neurological symptoms or signs [29].

During the 1950s and 1960s, arteriography of the aortic arch and its cervicocranial branches became feasible. A great advance in angiography was made when Seldinger, in Sweden in 1953, introduced angiography by catheterization of the femoral artery, allowing selective catheterization of all the vessels to be studied [30]. During the 1970s, there were improvements in angiography performance, namely that trained experienced full-time neuroradiologists began to perform the procedure; newer safer dyes were developed and introduced; and biplane filming techniques were perfected. These advances led to safer, more useful angiography. Impressed by the lesson from the subclavian steal syndrome that the occlusive lesion could be at a distance from the ischemia, physicians advocated full opacification of the aortic arch and all 4 main arteries supplying the brain. Routine "arch and 4" angiography was performed. Arch angiography, a cumbersome procedure necessitating lots of dye, was used in the very large Joint Study of Extracranial Arterial Occlusions begun in the middle years of the twentieth century. This study corroborated the high frequency of extracranial occlusive disease in the carotid, subclavian, and vertebral arteries in the neck [31].

During the 1950s, clinicians had become alerted to the presence of TIAs by Fisher [22, 23]. They had also become aware of the usual symptoms and signs in patients who were later proven to have fatal basilar artery occlusions by Kubik and Adams [16]. During the late 1950s and early 1960s, a series of articles written by American and British clinicians concerned patients with TIAs that indicated involvement of brain structures fed by posterior circulation arteries. When studied during life by angiography, there was a high frequency of severe vertebrobasilar occlusive lesions. The lesions involved mostly the basilar artery, but the cervical and intracranial portions of the vertebral arteries were also often stenosed or occluded. The syndrome of intermittent TIAs involving the posterior circulation was dubbed "vertebrobasilar insufficiency" (VBI) by neurologists at the Mayo Clinic in Rochester, Minnesota: Clark Millikan, Robert Siekert, and Jack Whisnant [32]. The so-called VBI was not at all rare; in fact, Bradshaw and McQuaid conclude their article on VBI by stating that "the syndrome is one of the most common causes of neurological illness [33]."

Influenced greatly by the report of Kubik and Adams on necropsy-proven cases of basilar artery occlusion, clinicians during the middle of the twentieth century widely believed that severe occlusive disease of the intracranial posterior circulation arteries was a very serious, often mortal disease. During this era, the popular drug that was being used for occlusive vascular disease

was warfarin. Anticoagulation had been used in patients with thrombophlebitis and pulmonary embolism, myocardial infarction, and rheumatic valve disease with systemic and brain embolism. Warfarin seemed to be worth trying for occlusive vascular disease. Using this reasoning, Millikan, Siekert, and Shick from the Mayo Clinic published an important and very influential paper on the use of warfarin anticoagulation to treat patients with VBI [34]. Patients with the clinical symptoms and signs of VBI (angiography was not often used) were given warfarin in an uncontrolled observational study. Many patients stopped having attacks, and many had no or minimal strokes. Believing that the disease was usually fatal or disabling without treatment, the authors reasoned and believed that warfarin was clearly effective and indicated to treat patients with symptoms suggesting VBI.

By the middle of the 1960s, there was widespread belief in the medical and neurological community that posterior circulation TIAs and ischemic strokes could be readily diagnosed clinically; transient attacks and insufficiency states were explained by hemodynamic factors; and anticoagulation with heparin-warfarin therapy was an effective treatment. Angiography was generally considered not to be indicated although a few anecdotal studies later showed the ability of angiography to clarify the nature of the underlying vascular causes and prognosis in isolated instances. Patients with posterior circulation ischemia were usually given heparin and warfarin unless contraindicated. Little investigations were performed. This situation remained until modern brain and vascular imaging, including MRI, MRA, and CTA, became widely available during the last years of the twentieth century.

Many years later, in the Warfarin–Aspirin for Symptomatic Intracranial Disease (WASID) trial of patients with severe intracranial atherosclerosis, there was no significant difference in the prevention of new strokes between aspirin and warfarin [35]. The study drugs were initiated often weeks after the last ischemic event. Warfarin was difficult to control; patients maintained within the target therapeutic INR range of warfarin performed better than patients treated with 1300 mg aspirin per day. In those treated with warfarin whose INR levels were below the target range, more infarcts developed, and more hemorrhages developed in those above the target INR range. There were too few patients with severe (>80%) intracranial vertebral (107 patients) or basilar artery stenosis (112 patients) to render meaningful conclusions about the treatment of these specific occlusive lesions.

Although the mechanism of TIAs involving the anterior and posterior circulations was uncertain, opinion during the middle years of the twentieth century favored hemodynamic, general circulatory mechanisms. In a series of influential papers, Derek Denny-Brown put forth the hypothesis that intermittent spells of ischemia were explained by circulatory perturbations, and he called the temporarily inadequate blood flow "insufficiency." Denny-Brown hypothesized that carotid and vertebrobasilar insufficiency was a "physiological, potential hemodynamic state in which reversible hemodynamic crises could be elicited by any factor that impaired the collateral circulation." [36] Hemodynamic crises could be transient, or partially or completely reversible depending on the length and severity of the pathophysiological cause. Denny-Brown reviewed the anatomical, physiological, and experimental data that favored his hypothesis. However, his own tilt table experiments, performed with Dr. John Sterling Meyer, one of his chief assistants at that time, using EEG monitoring of patients with clinical "insufficiency," more often than not failed to provoke attacks or EEG changes.

Clinicopathologic and Clinical-Imaging Studies During the Second Half of the Twentieth Century

The advent of modern brain and vascular imaging (MRI, MRA, and CTA) facilitated the study of various clinical posterior circulation syndromes. Clinicians and researchers in the USA, Europe, and Asia studied and reported various clinical syndromes related to involvement of specific locations within the posterior circulation-supplied brain regions and caused by various stroke sub-

types. These studies included reports about lateral medullary infarcts [37, 38]; medial medullary infarcts [39, 40]; cerebellar infarcts [41–45]; top of the basilar syndrome [46]; basilar artery occlusion [47]; thalamic infarcts [48–52]; pure motor hemiparesis, ataxic hemiparesis, and dysarthria-clumsy hand syndrome explained by pontine lacunar infarcts [53–56]; lateral tegmental pontine syndrome [57, 58]; basilar branch occlusion [59]; intracranial atheromatous branch disease [60]; midbrain infarcts [61]; and posterior cerebral artery territory infarcts [62, 63]. The distribution of brain and vascular lesions and clinical symptoms and signs and stroke outcomes were also studied in detail [64–67]. Nonatherosclerotic vascular lesions were also described [67, 68].

By the end of the first quarter of the twenty-first century, clinicians had become aware of the major stroke syndromes involving the posterior circulation and the frequency of various vascular lesions and various stroke subtypes.

Pathophysiology of infarction was also investigated. Clinicians and researchers began to question the importance of hypoperfusion alone in explaining most brain infarcts. Transcranial Doppler emboli monitoring of patients with vascular lesions showed the frequency and importance of intra-arterial emboli. Diffusion-weighted MRI scans documented small "rosary"-shaped arcs of tissue injury in border-zone regions related to microembolism. Stenotic vascular lesions generated fibrin-platelet and cholesterol crystal emboli, which often broke loose and traveled intracranially. When the donor vascular lesions became flow-reducing, the decreased perfusion inspired washout and clearance of these emboli. Hypoperfusion and embolism interacted and complemented each other to promote and enhance brain infarction in both the anterior and the posterior circulations [69–71].

Treatment of Patients with Posterior Circulation Ischemia

After publication of the NIHSS study of intravenous tPA thrombolytic study in 1995 [72], much data began to accumulate about the results of intravenous and intra-arterial administration of tPA and later tenecteplase. Most randomized trials involved either patients whose vascular lesion was not studied or included only patients with anterior circulation infarction. Anecdotal results showed that treatment with thrombolytics in patients with brainstem ischemia could be effective over a longer time window than in anterior circulation disease. Most posterior circulation patients in whom the vascular lesion was studied had basilar artery occlusions, and results were, in general, poor [73].

Angioplasty and stenting began to be applied in patients with posterior circulation occlusive lesions to prevent further infarction. In one major trial that studied stenting versus aggressive closely monitored medical treatment, stenting of intracranial arteries was less effective than medical treatment [74, 75]. Stenting of the basilar artery was often complicated by perforator territory brainstem infarcts, and hemorrhage was an important complication [74, 75].

Trained and experienced interventionalists also began to explore nonchemical means of opening blocked arteries. The strategies included aspirating the clot by creating a vacuum effect using a simple syringe, using a power-driven apparatus to create more of a vacuum to suck back the clot, and using a corkscrew-like device to try to hook the clot and then extract it. After these initial explorations, device-makers designed "stent retrievers" that proved more effective than previous devices in opening arteries. Interventionalists could manipulate these devices to and then through the occluding clots and, in doing so, quickly restore flow. The clot could be trapped within the stent and then pulled back down the catheter into a receptacle outside of the body. Randomized trials that used stent retrievers proved their effectiveness, even up to a full 24 h after stroke symptom onset [76, 77]. The randomized trials of mechanical clot retrieval included only patients with anterior circulation vascular disease, but mechanical vascular opening was also frequently applied to individuals with basilar artery occlusion. The success rates of mechanical manipulation were much higher than with chemical thrombolysis [78].

Vertebrobasilar Territory Brain Hemorrhages

The first recognition and description of a posterior circulation hemorrhage was contained in an influential treatise on apoplexy published in 1812 by an Irish physician John Cheyne [79]. Cheyne included in his treatise detailed clinical descriptions of patients, as they would be encountered socially in their usual attire, and the appearance of their brains at necropsy. Cheyne described brain softening and intracerebral and subarachnoid hemorrhages. In some patients who survived their apoplectic attack for some time, Cheyne found cavities filled with rusty yellowish serum within the brain at necropsy. Cheyne surmised that the cavities were lined by a membrane, which was able to absorb red blood cells, and that the lesion represented an old hemorrhage. One patient described by Cheyne had a pontine hematoma. Case 14 was a "carpenter, 35 years of age, phlegmatic, pale, muscular, not habitually intemperate." He had severe headaches and, after one such headache, he vomited and soon after "became insensible." About an hour later, his breathing became irregular, and he was deeply comatose and soon dead. Cheyne described this man's brain as follows: "In dissecting the base of the brain, there was discovered, formed by rupture in the substance of the pons varolii, a collection of dark clotted blood, in an irregular cavity, having a ragged surface and communicating with the fourth ventricle which was full of blood [79]."

Although accounting for only 8–10% of intracerebral hemorrhages, pontine hematomas attracted attention because the clinical findings were dramatic and distinctive. After Cheyne's description of a pontine hematoma, single case reports and series of cases were reported during the nineteenth century. In 1903, Charles Dana, then Professor of Neurology at Cornell University in New York, reviewed prior reports and his own personal experience and summarized the clinical aspects of pontine hemorrhages and infarcts [80]. Dana reviewed the brain and vascular anatomy of the pons. Among 2288 hematomas found at necropsy, 205 (9%) were pontine [80]. Dana described the typical patient: "Some prodromal headache and malaise for a few days … then he falls suddenly as if by a lightning stroke, into a coma, usually very profound. There are twitching of the face or of the limbs or both … the pupils are contracted to a pinpoint … there is convergent strabismus or conjugate deviation of the eyes. The limbs are at first stiff but tone may be reduced later and the reflexes increased. The patient can not be aroused but can be made to vomit … the patient dies in 6 to 20 hours usually with paralysis of respiration [80]." Dana listed the "syndrome of the pons" as (1) headache, malaise, vomiting; (2) sudden profound coma; (3) face and limb twitching; (4) small pupils, convergent strabismus, or conjugate eye deviation; (5) slow irregular respirations; (6) irregular pulse; (7) dysphagia; (8) paralysis of all limbs, or crossed paralysis; (9) gradual rise of temperature; and (10) death within 24 h.

Gowers, in his 1892 textbook of Neurology, described the location of pontine hematomas [81]. The bleeding usually involved the tegmentobasal junction near the rostral end of the pons. Hematomas often spread rostrally but rarely spread caudally to the medulla; often, the hematomas dissected into the fourth ventricle [81].

Oppenheim, in his popular Neurology textbook, first published in 1892, included a review of the clinical signs in patients with pontine hemorrhages [82]. Occasionally a hemiplegia or asymmetric bulbar paralysis was present, but more often, there was bilateral limb weakness and bilateral paralysis of the mouth, palate, pharynx, and larynx. The pupils were small but could be dilated. Eye movements were often lost. Coma, trismus, and high fever were common. Oppenheim emphasized that the disorder was invariably fatal [82].

Some pontine hematomas described in the nineteenth century were accompanied by supratentorial hemorrhages. Separation of primary pontine hematomas from secondary, pressure-related lesions did not occur until the twentieth century. Duret produced brainstem hemorrhages experimentally by injecting fluids into the supratentorial tissues of dogs [83, 84]. Duret noted that humans with fatal head trauma often had hematomas in the midbrain and pons

[83]. Attwater, in 1911, separated more definitively primary pontine hematomas from secondary brainstem hemorrhages [85]. Attwater reviewed 77 pontine hematomas examined at necropsy at Guys hospital in London. Some patients, especially those with head trauma, had supratentorial bleeding as well as brainstem hemorrhages. Attwater posited that some pontine hemorrhages were due to "an increase in intracranial tension produced by the rapid entry of blood into the cranial cavity [85]." Duret, in later research, showed that the secondary hemorrhages in the midbrain and pons, now referred to as Duret hemorrhages, were caused by sudden intracranial supratentorial pressure that distorted and compressed the brainstem and its vessels causing the latter to stretch and tear [86].

Although most authors continued to emphasize the abrupt onset of symptoms, Kornyey, in a remarkable single case report, described the gradual inexorable progression of symptoms and signs in a young man whose pontine hematoma occurred and developed under observation [87]. The patient was a 39-year-old man sent to the hospital in Hungary where Kornyey practiced for treatment of severe malignant hypertension. While his history was being taken, the patient reported numbness and tingling of the hands followed by restlessness, dysphagia, and loss of hearing. His blood pressure was found to be 245/170 mm Hg. While being observed, he developed bilateral sixth nerve palsies, dysarthria, deafness, and left hemiparesis. Then, small pupils, quadriplegia, and coma developed. Within 2 h after walking into the clinic, he had died of a pontine hematoma [87]. Not until 2 decades later did Miller Fisher emphasize the gradual evolution of signs and hematoma growth [88, 89].

In 1951, Steegman reported 17 patients with primary pontine hemorrhages and summarized the literature up to that time [90]. The hematomas in his 17 patients usually involved the center of the pons, and in 10, the blood ruptured into the 4th ventricle; 3 had asymmetrical lesions affecting the tegmentum and base more on one side. Most patients were quadriplegic, but 2 had hemiplegia, 1 with crossed face and limb weakness. Steegman opined that the shivering, shaking, twisting, and trembling were due to abnormalities of motor function and were likely not convulsive as had been previously thought [90]. Steegman emphasized abnormal respirations, which were often slow, labored, and gasping. Death was seldom instantaneous but usually occurred in 24–72 h.

CT and later MRI allowed for detection of smaller pontine hemorrhages that were previously not identified. The classic large central pontine hematomas were the result of the rupture of the large paramedian pontine artery penetrators. The next syndrome that was recognized was lateral tegmental hematomas, which arose from rupture of arteries penetrating into the lateral tegmentum as branches of long circumferential arteries, especially the superior cerebellar arteries [91–93]. These lesions cause a contralateral hemisensory loss due to the involvement of the sensory lemniscus formed in the pons from the merging of the lateral spinothalamic tract and the medial lemniscus. Ataxia and oculomotor abnormalities often were also present, but paresis was usually absent or minimal. Later smaller lateral tegmental hematomas were described that caused only contralateral sensory abnormalities. Small basal hematomas arising from small paramedian arteries and short circumferential penetrators could cause pure motor hemiparesis, or ataxic hemiparesis causing similar signs as patients with lacunar infarcts.

Another common region of posterior circulation bleeding is in the cerebellum. The first cases of cerebellar hemorrhage were those of Morgagni and Lieutard, which were cited in a paper describing a fatal cerebellar hemorrhage written by Sedillot in 1813 [94]. Childs in 1858 reported the first American patient, a 19-year-old woman who developed a cerebellar hemorrhage while shaking her head vigorously to amuse a child [95]. Carion, in a doctoral thesis in 1875, reported 7 patients who had cerebellar hemorrhages [96]. Michael, in 1932, described 10 of his own patients and reviewed the literature up to that time [97]. He noted that headache, vertigo, and weakness developed very quickly and wrote that "in fulminating cases antemortem localization is practically impossible [97]." In 1942, Mitchell

and Angrist reported 15 of their own patients with spontaneous cerebellar hemorrhage and also reviewed the 109 cases reported to that time [98]. "Coma as a prominent symptom far overshadowed all other findings" and was present in 64 of the 124 patients (52%). The next most common symptoms were vomiting and headaches. Dizziness was present in only 16 patients (13%) and ataxia in 11 (9%) [98]. They concluded, as had Michael, that there was no consistent pattern of symptoms and signs in patients with cerebellar hemorrhage.

In 1960, Wylie McKissock and his London colleagues reported 34 patients with cerebellar hemorrhage who had been under the care of one surgeon (Mr. McKissock) [99]. Hypertension was the commonest cause, but 6 patients in the series had angiomas and 2 had aneurysms. In 18, the hematomas were confined to the cerebellum while in 10 hematomas spread into the brainstem and in 6 they ruptured into the 4th ventricle. All patients had some form of surgery except for 6 who died before surgery was possible; in 14, only ventriculography or ventricular drainage was performed [99]. The outcome was very poor since 19 of the 28 surgically treated patients died. The authors were pessimistic about the clinical recognition of cerebellar hemorrhage. "The neurological signs presented by these patients were in the main singularly unhelpful. Localizing signs could not be elicited in those patients who were unconscious except that most of them had constricted and non-reactive pupils and periodic respirations. In the conscious patients, signs of cerebellar dysfunction were present in less than half [99]."

Miller Fisher and colleagues, in a very important benchmark paper published in 1965, emphasized clinical findings that they thought would improve clinical recognition of cerebellar hemorrhage [100]. They described only 3 patients in detail. In an addendum, added after the paper had been accepted, the authors mentioned that they had since seen 8 other patients in whom the rules derived from the original 3 patients and outlined in the paper had allowed the diagnosis of cerebellar hematomas, which were confirmed at surgery [100]. Fisher and colleagues emphasized the importance of several clinical findings: *vomiting* was a very constant feature; inability to stand or walk especially unaided was a reliable and very consistent sign; ipsilateral 6th nerve palsy and *conjugate gaze palsy* were very common; and hemiparesis or hemiplegia was not observed, but often there was bilateral increased deep tendon reflexes and Babinski signs [100]. Headache, neck stiffness, limb ataxia, dysarthria, and dizziness were variable findings. The authors urged surgical exploration when the clinical signs were typical. Later, several large clinical series of patients with cerebellar hemorrhages corroborated the frequency of the symptoms and signs reported by Fisher et al. [101, 102].

More recently, CT and MRI have allowed for the diagnosis of smaller cerebellar hematomas. Most involve the cerebellar hemispheres, especially the white matter in the region of the dentate nucleus in the territory of the superior cerebellar arteries. Some also arise more caudally from PICA territory branches. Occasionally, hemorrhages arise in the vermis and compress the 4th ventricle and the medullary and pontine tegmentum, but the clinical findings in these patients with vermian cerebellar hematomas have not been fully clarified.

Although bleeding into the thalamus is another common site of posterior circulation hemorrhage, separation of the clinical symptoms and signs from those found in patients with putaminal and basal ganglionic hemorrhages did not occur until Fisher's discussion during a 1959 meeting of the Houston Neurological Society [88]. Fisher commented during his presentation, "The clinical and laboratory features of hemorrhage at most sites within the brain have been described in the past, but bleeding into the thalamus and subthalamus is rarely alluded to, and a comprehensive report on the subject has never been made [88]." Fisher emphasized the presence of vertical gaze paralysis, position of the eyes downward at rest as if the patient is peering at the tip of the nose, constricted pupils, and sensory signs on the contralateral limbs greater than hemiparesis. The thalamic hemorrhages that Fisher was able to diagnose clinically were large, and all were accompanied by blood in the CSF.

Smaller hemorrhages in the thalamus were not recognized until the advent of CT and later MRI scanning. Chung and colleagues in 1996 reviewed the findings in patients with thalamic hemorrhages in various loci in the thalamus according to the distribution of the bleeding artery: tuberothalamic, thalamo-geniculate, thalamic-subthalamic, and posterior choroidal [103]. Similarly, midbrain and medullary hemorrhages were not separated from ischemic lesions in those sites until the advent of CT and later MRI.

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