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CNS Manifestations of Hereditary Hemorrhagic Telangiectasia

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Hereditary hemorrhagic telangiectasia (HHT) is a familial angiodysplastic disorder. Dermal, mucosal, and visceral vascular lesions of this disorder are well known. However, central nervous system (CNS) manifestations, occurring in as many as one-third of patients, have not been well appreciated until recently. The etiology of neurologic symptomatology includes hypoxemia or ischemia secondary to pulmonary arteriovenous shunting, vascular lesions of the brain and spinal cord ranging from aneurysms to arteriovenous malformations, brain abscesses secondary to pulmonary arteriovenous fistulas, and portal systemic encephalopathy. Angiographic and computed tomographic findings in four patients with CNS involvement in HHT are reported.

Hereditary hemorrhagic telangiectasia (HHT), or Rendu-Osler-Weber disease, is an uncommon genetic angiodysplastic disorder transmitted as a simple mendelian dominant character. Characteristic findings first become evident at puberty and include widely scattered dermal and mucosal telangiectases, most common on the skin of the face and neck and on buccal and nasopharyngeal mucous membranes; diffuse visceral vascular lesions; recurrent bleeding; and absence of hematologic disorders other than those secondary to bleeding and/or arteriovenous fistulas (AVFs) [1, 2]. The most common presenting symptom is epistaxis from nasomucosal lesions. Gastrointestinal, genitourinary, pulmonary, and cerebral hemorrhage may all occur. More than 300 families with HHT have been recorded in the literature. Pulmonary AVFs have been reported in 15.4% of patients [4] and are the most frequent visceral lesions. Fifty percent of patients with pulmonary AVFs are cited as having HHT [5].

Vascular malformations of the brain in HHT are much less common and have rarely been documented either angiographically or pathologically [6]. Computed tomographic (CT) brain findings in HHT have not been illustrated previously in the English-language radiologic literature. Central nervous system (CNS) symptomatology has been estimated to occur in 27%–29% of patients [1], but the etiology has often remained obscure. We report the angiographic and CT findings of four patients with CNS involvement and review the pathogenesis of CNS symptoms in patients with HHT.

Case Reports

Case 1

A 32-year-old man had acute subarachnoid hemorrhage (SAH). Medical history included SAH 3 and 6 years before admission and gastrointestinal (GI) bleeding 3 years before. Myasthenia gravis diagnosed 1 year before admission was treated with thymectomy. The patient was also noted to have frequent severe nosebleeds, multiple episodes of stiff neck and headache, and "spells" with associated memory loss. Family history included a father with SAH and paternal grandfather with HHT. Physical examination demonstrated telangiectasia of the lips. Precontrast CT showed foci of increased density in the right frontal and

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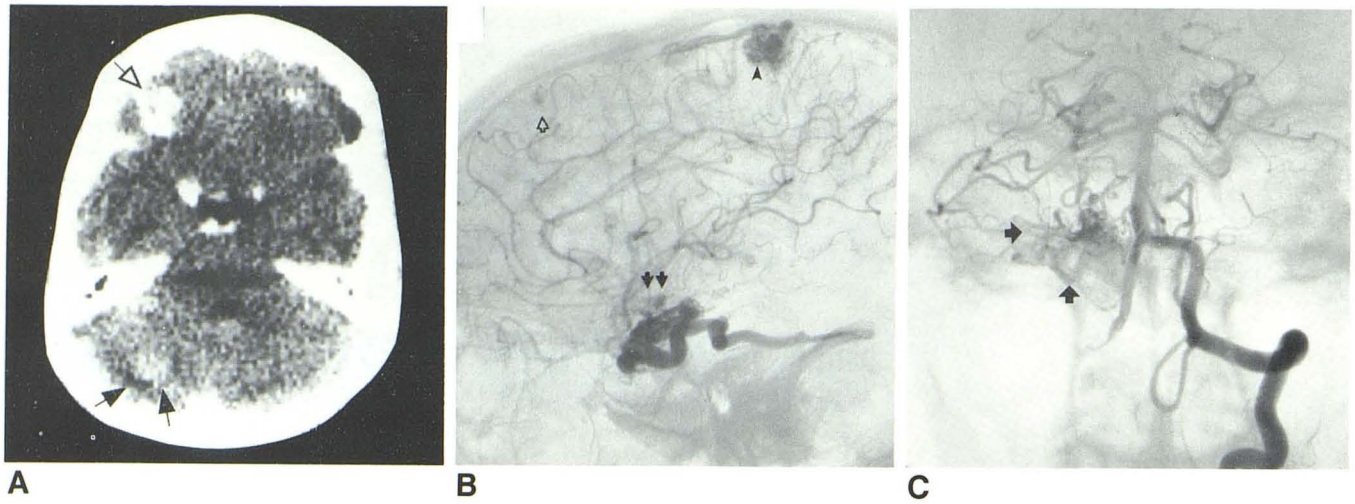

Fig. 1.—Case 1. **A**, Axial CT contrast scan demonstrates enhancing high-density foci in right frontal lobe (*open arrow*) and right cerebellar hemisphere (*closed arrows*) representing vascular lesions. **B**, Right internal carotid arteriogram reveals frontal cavernous angioma (*open arrow*), parietal AVM (*arrowhead*) draining into superior sagittal sinus, and temporal AVM (*closed arrows*) draining into cavernous and superior petrosal sinuses. Right frontal enhancing lesion on CT is not visualized angiographically but most likely is cavernous angioma. **C**, Left vertebral arteriogram demonstrates right cerebellar AVM (*arrows*).

temporal lobes and right cerebellar hemisphere without associated edema or mass effect. Postcontrast CT demonstrated marked enhancement in the same foci, consistent with vascular malformations (fig. 1A). Right internal carotid arteriography demonstrated a right frontal cavernous angioma, a right parietal arteriovenous malformation (AVM), and a right temporal AVM (fig. 1B). The right frontal enhancing lesion seen on CT was not visualized angiographically but was thought to probably represent a cavernous angioma. Left vertebral angiography revealed a large right cerebellar AVM with markedly enlarged draining veins (fig. 1C).

Case 2

A 51-year-old man had diminished sensations to touch and pain, disorientation, headache, and fever. Medical history included multiple severe nosebleeds and family history of HHT on the paternal side. Physical examination revealed decreased level of consciousness and multiple dermal telangiectases. Culture of the cerebrospinal fluid (CSF) grew *Streptococcus mutans*. A chest film showed a left-lower-lobe AVM. Precontrast CT demonstrated an old left basal ganglia infarct and abnormal low density in the left occipital lobe. On the postcontrast scan there was a rim of enhancement with surrounding edema in the left occipital lobe consistent with a pyogenic abscess (fig. 2). Cerebral arteriography was normal. At surgery 25 ml of pus was aspirated from the left occipital lobe.

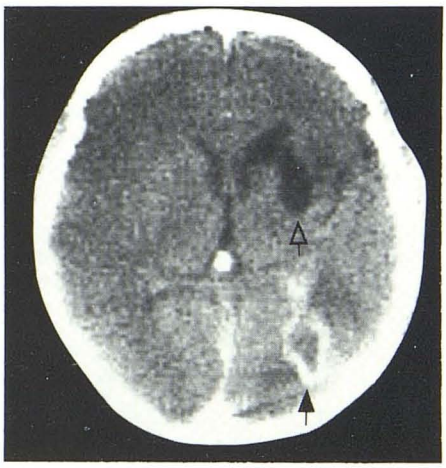

Fig. 2.—Case 2. Contrast-enhanced axial CT scan shows old left basal ganglia infarct (*open arrow*) with compensatory dilatation of left frontal horn and left occipital ring-enhancing lesion (*closed arrow*) with surrounding edema consistent with pyogenic abscess.

Case 3

A 42-year-old woman was admitted with signs and symptoms of meningitis of 3 weeks duration. On physical examination she was neurologically intact but was found to have cutaneous lesions of HHT and a left chest bruit.

CT brain scan revealed abnormal enhancement in the left occipital lobe extending into the parietal lobe with a rim component with surrounding edema and mass effect (figs. 3A and 3B). Vertebral angiography demonstrated an AVM immediately superior to an occipital lobe mass found at surgery to represent an actinomycotic brain abscess (fig. 3C). A pulmonary angiogram demonstrated multiple AVMs of the left lower lobe (fig. 3D).

Case 4

A 61-year-old woman presented with sudden onset of mild right hemiparesis and aphasia preceded by a 2 week history of several episodes of momentary loss of consciousness. The patient was found to have multiple AVFs on chest films. Family history included a daughter and grandmother with pulmonary AVFs. Physical examination revealed angiomas on the lips, paraphasic speech, and increased deep tendon reflexes on the right. CT technology was not yet available. A left internal carotid arteriogram revealed several small

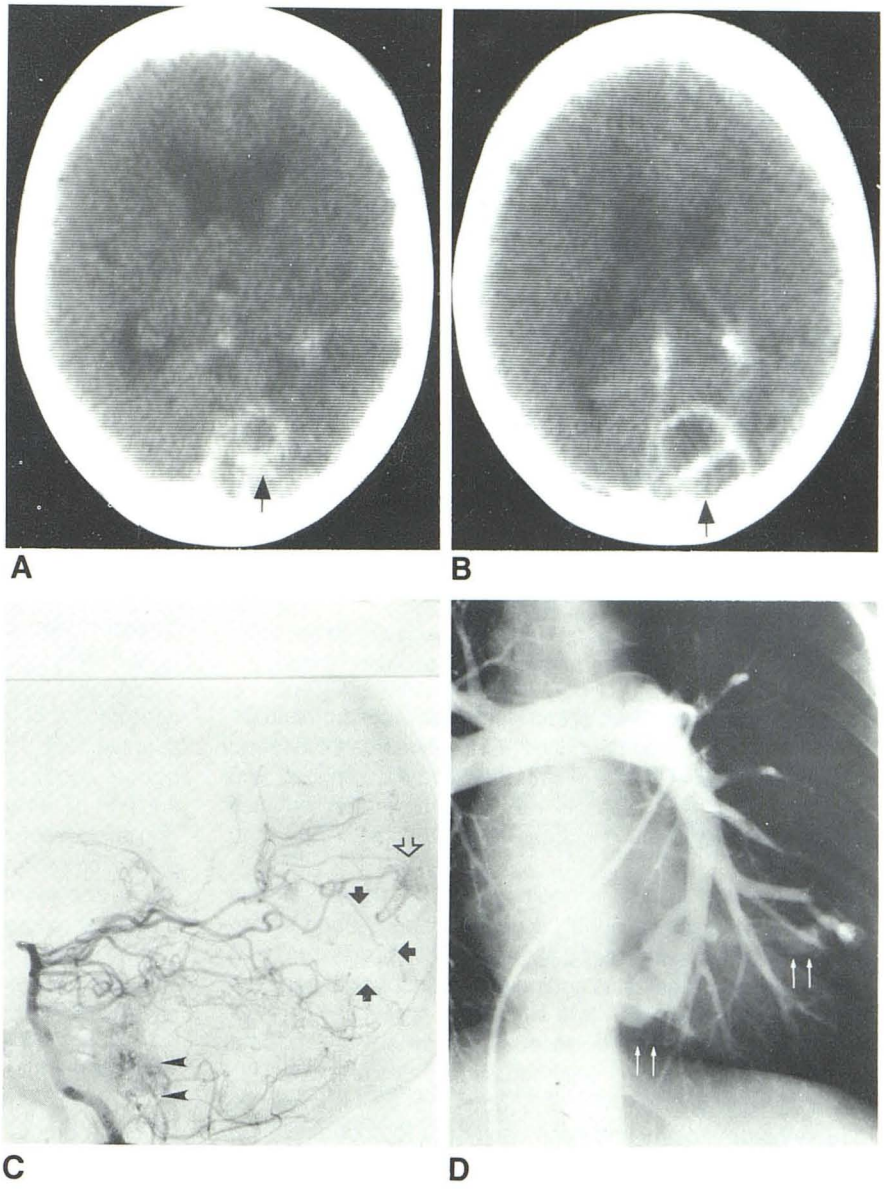

Fig. 3.—Case 3. Contrast-enhanced axial CT scans demonstrate complex, partly ring-enhancing lesion in left occipital lobe (**A**, *arrow*) with bilobular rim of enhancement more superiorly in occipital and inferior parietal lobes (**B**, *arrow*). At surgery, enhancing lesion on CT was actinomycosis abscess inferiorly with AVM superiorly. (Parietal AVM in **C** was not distinguished by CT.) **C**, Left vertebral angiogram shows left parietooccipital AVM (*open arrow*), left occipital mass effect (*closed arrows*), and right cerebellar AVM (*arrowheads*). Veins draining malformations visualized in later arterial phase are not seen. **D**, Pulmonary arteriogram demonstrates two left-lower-lobe AVMs (*arrows*).

cavernous angiomas of the left anterior and middle cerebral arteries and a posterior cerebral AVM (fig. 4). Ten days after admission the patient developed pleuritic chest pain and fever. A pulmonary arteriogram showed a right-lower-lobe embolus proximal to an AVF.

Results

Cerebral angiography was performed in all four patients. It showed both AVMs and cavernous angiomas in two patients and an AVM without associated demonstrable cavernous or capillary angioma in one patient. In one patient, angiography was normal, and in one, it failed to visualize one of several vascular malformations shown by CT. This missed lesion probably was a cavernous angioma. CT was performed in three of the four patients, and vascular malformations were detected in one of the two patients with cerebral vascular lesions. The third patient with a cerebral vascular malformation was studied before the availability of CT. CT demonstrated brain abscesses in two patients, one of whom also had a cerebral AVM and the other a brain infarction.

Discussion

Sutton [7] is credited with reporting the first case of HHT in 1864. He described a patient with recurrent epistaxis, skin telangiectasias, and internal hemorrhage. Rendu described a patient with "pseudohemophilia" in 1896 (cited in [8]). In 1901, Osler [8] was the first to recognize the familial nature of the disease. Weber [9] characterized the differences between this disease and hemophilia. *Hereditary hemorrhagic telangiectasia* was first used by Hanes [10] in 1909.

The diffuse multisystem involvement of vascular dysplasia in this disorder is now well recognized. Vascular lesions of

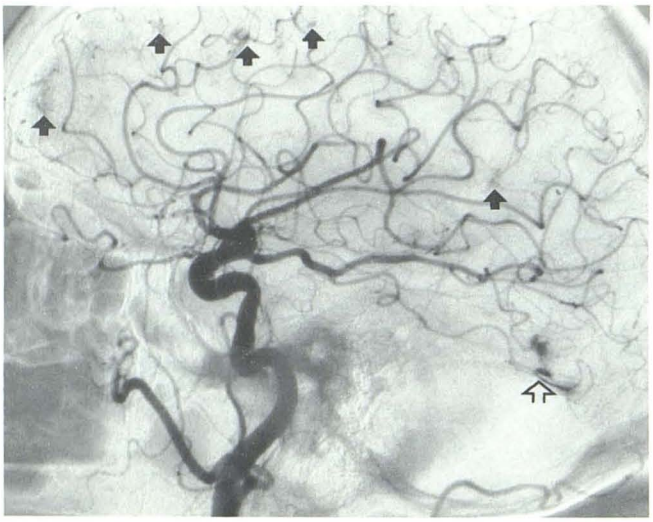

Fig. 4.—Case 4. Left internal carotid arteriogram shows multiple small cavernous angiomas of left anterior and middle cerebral artery branches (*closed arrows*) with posterior cerebral AVM (*open arrow*). Later arterial film (not illustrated) showed early opacification of left lateral sinus.

the lungs, intestines, liver, spleen, pancreas, cervix, bladder, urethra, brain, spinal cord, and vertebrae have been described [11] as well as aneurysms of the aorta and iliac, splenic, and hepatic arteries [12]. Lesions vary from tiny telangiectases and nodular cavernous angiomas to aneurysms, AFVs, and AVMs.

The fundamental vascular lesion in HHT is described as a dysplasia of vessel walls with deficient muscular and elastic tissue primarily on the capillary and venous side but with associated arterial ectasias and development of arteriovenous communications [6, 13].

Goldstein [14] is credited with reporting in 1921 the first patient with HHT to manifest neurologic dysfunction. This was a 42-year-old woman with sudden onset of hemiplegia. CNS symptomatology has been estimated to occur in 27%–29% of patients with HHT [1], but neuroradiologic and pathologic documentation has been sparse. Disagreement exists in the literature as to the etiology of the CNS dysfunction in this disorder. One author [4] cites telangiectases of the brain as the most common etiology, whereas another [15] claims hypoxia and/or ischemic infarction secondary to polycythemia and embolism, as well as brain abscesses, as the more common causes.

As recently as 1964, Van Bogaert [16] stated that cerebral involvement in HHT was almost unknown. A literature review in 1964 by Boczko [1] found 36 patients with HHT and CNS symptoms. Cerebral arteriography was performed in three of these patients, revealing only a small AVM in one case. Three patients underwent surgery with findings of a spinal cord venous angioma, intracerebral blood clot, and brain abscess, respectively. Boczko found another eight cases of HHT in the literature in which the brains were examined pathologically. Six of these patients had telangiectases of the brain or meninges, but none had neurologic symptoms. It would thus appear that smaller lesions tend to remain clinically silent, whereas the larger lesions are more likely to be symptomatic. Two of our patients had both small cavernous angiomas and AVMs and one had an AVM and a brain abscess. One presented with SAH, one with hemiparesis, and one with symptoms secondary to infection.

In 1971, Reagan and Bloom [6] described four more cases, including one of their own, of pathologically documented cerebral vascular anomalies associated with HHT [6]. Three of the four patients had neurologic symptoms. Lesions in these patients included an AVM in a patient with seizures, a capillary angioma not visible angiographically in a patient with SAH, and a venous angioma in a patient with seizures. The one asymptomatic patient had dilated capillaries and veins in the right frontal lobe.

In 1978, Roman et al. [11] collected reports of more than 200 patients with HHT with CNS symptoms, including two of their own and those reported by Boczko [1] and Reagan and Bloom [6]. In 36% of these patients, vascular lesions in the brain or spinal cord were documented surgically, pathologically, or radiologically: 16.7% of patients had cerebral AVMs, 2.8% had aneurysms, 0.5% (one patient) had a spontaneous carotid-cavernous fistula, and 7.9% (17 patients) had spinal cord AVMs.

We have found three more case reports of documented cerebral vascular lesions in HHT. These cases include a telangiectatic lesion found at autopsy in a patient with a normal cerebral arteriogram [17]; a patient with radiologic findings of tentorial, orbital, and calvarial vascular malformation angiographically, and mention of abnormal choroid plexus enhancement on CT [18]; and a patient with a middle cerebral artery aneurysm and posterior cerebral artery AVM demonstrated angiographically and by CT [19].

We report three more patients with radiologic findings of CNS vascular malformations, including two patients with both cavernous angiomas and AVMs and one patient with an AVM. This is the first English-language illustration of CT findings in these patients.

A pulmonary AVF is reported to be the etiology of neurologic symptoms in 61% of patients [11]. Symptomatology is related to decreased systemic arterial oxygen saturation and resultant cerebral anoxia, secondary polycythemia vera with associated propensity to thrombus formation and infarction, passage of emboli through the fistula, air embolism to the brain occurring during hemoptysis, and brain abscess [2]. Air has been postulated to gain entrance to the systemic circulation via a defect in the wall of a pulmonary AVF.

Brain abscesses were responsible for neurologic symptoms in 13% of more than 200 patients with CNS involvement of HHT [11]. Five percent of a series of 350 patients with pulmonary AVFs were reported to have developed brain abscesses [20]. The abscesses have been thought to be from silent septic emboli bypassing the pulmonary filter with resultant infarction and infection or sterile emboli lodging in the brain and becoming secondarily infected in a hypoxic setting [15, 21].

Two of our four patients with HHT had brain abscesses and pulmonary AVFs. One of these patients also had a cerebral AVM. The CT brain scan was helpful in preoperative diagnosis of the abscess as well as in showing its extent. The

AVM was not distinguishable from the abscess by CT, probably because of its adjacent location. This distinction was made angiographically. Rarely, an AVM, by demonstrating on CT a cystic appearance with partial rim enhancement, may simulate an abscess [22], but clinical differentiation is usually possible.

Brain infarction or ischemia related to pulmonary AVFs is the most common cause of neurologic symptoms in HHT, accounting for more than 40% of patients with CNS findings [11]. An old infarct of the basal ganglia was demonstrated by CT in one of our patients also found to have a brain abscess.

Portal systemic encephalopathy as the cause of neurologic symptoms is reported in 2.8% of patients [11]. Fibrovascular lesions of the liver are described to result in cirrhosis with portal hypertension and portal systemic shunting.

In summary, as many as one-third of patients with HHT have CNS symptoms. The etiology in decreasing order of incidence includes hypoxemia and/or ischemia secondary to pulmonary arteriovenous shunting through an AVF, vascular lesions of the brain and spinal cord ranging from aneurysms to AVMs, brain abscess secondary to pulmonary AVF, and, finally, portal systemic encephalopathy secondary to liver cirrhosis and resultant portal systemic shunting. CT is an important screening and diagnostic test when neurologic symptoms are present. Sometimes angiography may be required. A carefully interpreted chest radiograph will often suggest the diagnosis and the etiology of the pathologic CNS changes.

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