The Brain in Hereditary Hemorrhagic Telangiectasia

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Abstract: The Brain in Hereditary Hemorrhagic Telangiectasia

While neurological symptoms are often mentioned in reports of families with hereditary hemorrhagic telangiectasia (HHT) and are frequently assumed to be due to vascular anomalies of the central nervous system, documentation of such anomalies is surprisingly rare. Two cases of surgically treated symptomatic cerebral vascular malformations in HHT have been published previously. In addition, there are three descriptions of vascular anomalies discovered at autopsy in the brains of neurologically asymptomatic patients with HHT available in the literature. A complete postmortem examination of a patient with a symptomatic cerebral vascular anomaly associated with HHT has not been recorded previously.

The patient reported in this paper presented with seizures and underwent surgical resection of infarcted brain tissue associated with a venous angioma. He died six months later and, at autopsy, was found to have multiple "cryptic" venous angiommas of the brain. Hypoxic damage to brain tissue related to small venous angiommas is one mechanism whereby these lesions may become symptomatic. Hemorrhage may also occur. Neurological symptoms in patients with HHT cannot be assumed to be due to cerebral vascular anomalies, and consideration must be especially given to the complications of pulmonary arteriovenous fistula such as polycythemia, embolism, and abscess.

ADDITIONAL KEY WORDS

cerebral vascular malformation
Rendu-Osler-Weber syndrome
venous angioma

Introduction

Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome) is a dominantly inherited disorder whose cardinal manifestation is the appearance, usually around puberty, of telangiectasias distributed variably over the skin and mucous membranes of the body. The most common symptom of the disease is hemorrhage from lesions of the nasal mucosa, and the vast majority of patients first present clinically with epistaxis.

Over 300 families affected with the condition have been recorded in the literature. As experience with the clinical and pathological features of the disorder has grown, it has become apparent that the abnormalities are by no means confined to the small vessels of epithelial surfaces but may include major vascular anomalies in a variety of internal organs. The most frequently described visceral vascular anomaly is the arteriovenous fistula of the lung. Pulmonary arteriovenous fistulas occurred in 15.4% of individuals affected by the disease in the kinship reported by Hodgson et al. Conversely, about 50% of pulmonary arteriovenous fistulas are said to occur in patients with hereditary hemorrhagic telangiectasia.

Much less common, and certainly less well documented, are vascular malformations...
Pedigree of family with hereditary hemorrhagic telangiectasia. Arrow indicates patient.

**Figure 1**

of the central nervous system. There are only two reports in the literature of patients with hereditary hemorrhagic telangiectasia operated upon for clinically manifest cerebral vascular malformations. The purpose of this report is to present the third such patient, including the findings at autopsy performed six months following surgery, and to review the frequency, pathology, and pathogenesis of the cerebrovascular lesions in this condition.

**Case Report**

A 45-year-old automobile mechanic was admitted to the Central Suffolk Hospital on March 1, 1970, in status epilepticus. Four months previously he had been hospitalized for cerebral concussion, having been briefly unconscious after striking a telephone pole while driving. Members of his family had noted several episodes of mild confusion since that time. The patient and several members of his family were known to be affected with Rendu-Osler-Weber syndrome (fig. 1). He experienced frequent nosebleeds which kept him in a state of borderline anemia and required the chronic administration of ferrous sulfate.

The patient's seizures were generalized and were brought under control with phenobarbital, dilantin, and paraldehyde. Following recovery from postictal depression, no neurological abnormalities could be demonstrated. General physical examination revealed numerous punctate telangiectases over the face, tongue, lips, and nasal mucous membranes. In the nasolabial region they were distributed in a bilaterally symmetrical manner. On the forehead, lesions were limited to the left side and were spidery rather than punctate in appearance, somewhat resembling the Sturge-Weber syndrome at a distance, but lacking the uniform staining on closer inspection. Occasional lesions were also present on his fingers and toes.

Spinal fluid examination was unremarkable except for a protein level of 60 mg %. Skull x-rays revealed no abnormalities. Brain scan using 5 mc of technetium revealed a focal area of increased uptake in the left frontal parasagittal region. It was felt that the seizure disorder was most likely due to a mass lesion and bilateral carotid angiography was performed. The left carotid angiogram showed branches of the anterior cerebral artery gently curving about a lesion corresponding to the area of increased uptake on the scan (fig. 2). There was no shift of midline structures.

A left frontal craniotomy was performed by one of the authors (WHB) two weeks after admission. The dura was not felt to be under increased pressure. A dural flap hinged on the superior sagittal sinus was reflected medially, exposing an island of abnormal tissue approximately 3 cm in diameter protruding slightly above the surrounding cortex. Punctate vascular dilatations resembling those on the patient's lips and tongue were distributed over the surface of the mass. A cone-shaped, somewhat friable, irregularly discolored mass of tissue was readily separated from the surrounding cortex and white matter and was removed. Little bleeding was encountered.

Right upper limb weakness was noted following surgery but resolved completely by the sixth postoperative day. Except for frequent nosebleeds, his course was uncomplicated and he was discharged on the thirteenth postoperative day, continuing on dilantin, 100 mg t.i.d., phenobarbital, 15 mg t.i.d., and ferrous sulfate.

After a period of convalescence he resumed his usual activities and, according to his wife, took his medication regularly. On September 25th, six months after discharge from the hospital, seizures recurred and the patient was brought to the Brookhaven Memorial Hospital by ambulance. Seizure activity was continuous in the right face and upper extremity with repeated generalized seizures supervening. Lumbar puncture revealed clear fluid containing six red blood cells per cubic milliliter. Parenteral anticonvulsant medication failed to bring the seizures under control and respiratory arrest ensued. Tracheostomy was performed and the patient was placed on a Bird respirator. Intermittent seizure activity continued and spontaneous respiratory activity failed to return. After 36 hours cardiac arrest occurred and the patient was pronounced dead.

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Pathological Examination

SURGICAL SPECIMEN
Microscopic examination of the tissue removed at surgery revealed cerebral cortex and subcortical white matter showing marked neuronal loss, ischemic necrosis of the remaining neurons, and a proliferation of macrophages, capillaries and plump astrocytes. There were scattered fresh petechial hemorrhages. Occasional large-caliber (up to 1 mm) blood vessels with thin, irregular fibrous walls were encountered. The changes were interpreted as showing cerebral infarction in the subacute stage of evolution and anomalous vessels suggesting the presence of a vascular malformation.

POSTMORTEM EXAMINATION
A report of the general autopsy findings and the intact brain were kindly supplied to this laboratory by James S. Magidson, M.D., Pathologist, Brookhaven Memorial Hospital. Relevant findings outside the central nervous system were limited to capillary telangiectasias of the tongue.

After fixation in formalin the brain weighed 1,380 gm. External examination revealed that the leptomeningeal vessels were prominent and congested, especially over the left hemisphere, but no abnormal vascular formations were present. The left cerebral hemisphere was swollen, and examination of the base of the brain showed evidence of herniation of the left hippocampal gyrus. The surgical defect, measuring 30 x 16 mm, was noted in the midportion of the left middle frontal gyrus.

Coronal sections through the cerebral hemispheres revealed the following abnormalities. The white matter of the left hemisphere was moderately and diffusely swollen. Much of
Reagan, Bloom

Figure 3
Coronal section of brain showing collections of large vessels in left superior and middle temporal gyri (arrows). White matter of superior temporal gyrus is discolored due to diffusion of blood pigment in edema fluid.

Figure 4
Coronal section through frontal lobes showing surgical defect in left middle frontal gyrus. A single large vein is present deep to defect (arrow).

The cortex of the left posterior frontal, superior temporal, and occipital areas was softened and showed dusky discoloration. The surgical defect in the left frontal lobe extended for a depth of 30 mm and there was a scattering of hemosiderin pigment in its walls. There were collections of three to eight prominent blood vessels, measuring up to 2 mm in luminal...
THE BRAIN IN HHT

FIGURE 5

A portion of vascular anomaly in left middle frontal gyrus showing vessels with irregular fibrous walls and normal intervening neural parenchyma. Azo-carmine stain, X50.

diameter (fig. 3), in the subcortical white matter of the left superior frontal, inferior frontal and superior and middle temporal gyri. A single large vessel was present in the white matter deep to the surgical defect (fig. 4). No similar lesions were noted in the right cerebral hemisphere. Coronal sections through the brain stem revealed midbrain and pontine tegmental hemorrhages characteristic of transtentorial herniation.

MICROSCOPIC EXAMINATION

The grossly softened and discolored cortex of the left cerebral hemisphere showed the changes of acute infarction. The prominent vascular collections consisted of vessels ranging from 0.1 to 2.0 mm in diameter. The vessel walls were irregular in outline and were composed of an endothelium surrounded by a collagenous investment of variable thickness (fig. 5). Muscle and elastic tissue could not be demonstrated. Mineral deposits were present in the walls of some vessels. Deposits of calcium salts were also present in the parenchyma neighboring these encrusted vessels (fig. 6). For the most part, the parenchyma between the vessels was normal, although there were scattered focal areas of rarefaction and gliosis.

Discussion

The frequency with which neurological disturbances occur as part of the syndrome of hereditary hemorrhagic telangiectasis (HHT) is difficult to assess and their cause, when they occur, often remains obscure. Most large kinships with HHT include a number of individuals who are reported to have suffered from premature strokes, cerebral hemorrhages, or other neurological syndromes, but documentation of the precise cause of these symptoms is generally lacking.
The suggestion that there is an increased frequency of certain unusual sites of involvement within particular kinships is supported to some extent by the presence of neurological symptoms in three of nine known affected members of our patient’s family (fig. 1). His father (fig. 1—II 3) died at age 36 with a clinical diagnosis of “cerebral hemorrhage.” His uncle (fig. 1—II 6), also affected with the disease, has had a seizure disorder of undetermined etiology since childhood.

Some authors have assumed that these events are related to telangiectasias of the central nervous system. Others have contended that CNS symptoms in HHT are rarely due to vascular anomalies, but are most often due to hypoxemia, polycythemia, embolism and brain abscess arising as complications of pulmonary arteriovenous fistulas which are common in individuals with this disease.

Surgical, radiological, or autopsy documentation of cerebral vascular anomalies in HHT is rare. The pertinent cases which we were able to find in the literature are summarized in table 1.

Three of the six documented cases were neurologically asymptomatic and simply represent autopsy documentation of the occurrence of vascular anomalies in the brains of individuals with HHT. Thus, there are only two previously reported cases of well-documented symptomatic vascular anomalies in the brain, and the patient presented here is the first with a complete examination of the brain at autopsy. The pertinent neuropathological finding in this patient was the presence of multiple collections of irregular vessels of venous structure in the white matter of the left cerebral hemisphere. Infarction of a gyrus related to one of these angiomas was apparently the event that initiated the seizures leading to his initial hospitalization.

No thromboses of the component vessels of this or any of the other angiomatos
TABLE 1

Pathologically Documented Cases of Cerebral Vascular Anomalies Associated With HHT

<table>
<thead>
<tr>
<th>Case</th>
<th>Author</th>
<th>Patient Age, sex</th>
<th>Documentation</th>
<th>Description of malformation</th>
<th>Location</th>
<th>Neurological symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ytrehus(^{12})</td>
<td>54 F</td>
<td>Autopsy</td>
<td>Dilated capillaries and veins</td>
<td>R. frontal</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>Bird and Jaques(^{8})</td>
<td>68 M</td>
<td>Autopsy</td>
<td>Thin-walled veins</td>
<td>Widespread in white matter</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>Zelman(^{11})</td>
<td>56 M</td>
<td>Autopsy</td>
<td>Telangiectasis with thin fibrous walls</td>
<td>Multiple</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>Chandler(^{5})</td>
<td>? F</td>
<td>Angiography, surgery</td>
<td>Arteriovenous malformation</td>
<td>R. parietal</td>
<td>Headaches, seizures</td>
</tr>
<tr>
<td>5</td>
<td>Quickel and Whaley(^{7})</td>
<td>17 M</td>
<td>Angiography, surgery</td>
<td>Capillary angioma</td>
<td>L. caudate</td>
<td>Subarachnoid hemorrhage</td>
</tr>
<tr>
<td>6</td>
<td>Present case</td>
<td>45 M</td>
<td>Surgery, autopsy</td>
<td>Venous angioma</td>
<td>Multiple L. cerebrum</td>
<td>Seizures</td>
</tr>
</tbody>
</table>

collections were found. Hemodynamic alterations that led to shunting of arterial blood away from the involved gyrus might, therefore, be postulated. Degenerative changes such as dystrophic calcification, and focal rarefaction and gliosis which may have resulted from poor tissue oxygenation, were found in relationship to several of the vascular malformations. Of considerable interest, in this regard, was acute infarction of large portions of the left cerebral hemisphere which occurred during his terminal episode of status epilepticus. No vascular occlusions could be found, and we are forced to postulate that the focal damage occurring during a period of uniform systemic hypoxia was due to focal hemodynamic alterations related to the venous malformations.

The fundamental defect in HHT appears to be a dysplasia of the walls of blood vessels primarily on the venous side of the circulation.\(^{8, 13}\) This congenital weakness of the wall leads to the progressive dilatation and tortuosity of the involved vessels and accounts for the progressive increase in the number and prominence of the mucocutaneous lesions with increasing age. It appears that a similar process may occur in almost any internal organ where, in addition to the capillary-venous ectasias, arterial ectasias and communications with the venous lesions may open up, leading to arteriovenous shunting. In keeping with this concept, most lesions described in the brain have consisted of ectatic vessels primarily of venous and capillary structure (table 1, cases 1-3, 6), with occasional development of arteriovenous communications (table 1, cases 4 and 5).

Small vascular malformations of the brain rarely cause clinical symptoms before a catastrophic hemorrhage occurs, and they have, therefore, been referred to as “cryptic.”\(^{14, 15}\) Purely venous anomalies are the rarest of these cryptic malformations, and Wolf et al.\(^{16}\) were able to find only nine autopsy-proved examples of bleeding from this sort of abnormality recorded in the literature. None of those cases were associated with HHT.

It appears that mechanisms other than bleeding can cause these venous anomalies to become symptomatic. Ischemic necrosis of tissues related to venous anomalies has only occasionally been mentioned in the literature. It is probably the mechanism whereby progressive spinal cord dysfunction occurs in at least some cases that have been designated the “Foix-Alajouanine syndrome.”\(^{16}\) and may well be the mechanism whereby progressive cerebral degeneration occurs in relationship to the predominantly leptomeningeal venous angiomas in the Sturge-Weber syndrome.\(^{17}\) The analogy of the Sturge-Weber syndrome is further amplified in our case by the fact that the abnormal venous collections were confined to the left hemisphere, corresponding to the lateralization of an unusually dense accumulation of telangiectasias on the left forehead.

In an individual case, the differential diagnosis between infarction, hemorrhage, abscess, or some mass lesion unrelated to HHT may be difficult. Cryptic venous angiomas are
rarely visualized as such on angiography and nonspecific displacement of vessels is a finding common to all the above conditions. Additional diagnostic methods may be required to resolve the problem including, in some cases, surgical exploration.

References
