Hereditary haemorrhagic telangiectasia : neuropathological observations¹

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While the literature pertaining to hereditary haemorrhagic telangiectasia (Osler-Weber-Rendu disease) has been quite extensive, very few reports have dealt with the neurological manifestations of the disease. Occasional anatomical studies have appeared, but reports of neuropathological findings have been rare. The purpose of the present paper is to provide neuropathological observations in a patient with many features of the disease, including involvement of the central nervous system.

CASE REPORT

CLINICAL HISTORY This 65-year-old Negro man was first seen at the Yale-New Haven Hospital at the age of 54 with anaemia secondary to gastrointestinal bleeding. Diagnostic studies included an upper gastrointestinal series, barium enema, and sigmoidoscopy, but no source of bleeding was found. At the age of 63 he again entered hospital with melaena and offered the history of occasional episodes of epistaxis. Multiple telangiectases were noted on the lips, palate, tongue, conjunctivae, and skin. Gastroscopy revealed numerous telangiectases on the anterior gastric wall. The diagnosis of Osler-Weber-Rendu disease was made. The patient's daughter, aged 37, also had a history of anaemia and telangiectasia and a grandchild suffered from epistaxis, telangiectases, and anaemia.

A year later the patient was hospitalized with persistent severe bifrontal headaches. Neurological examination disclosed hyperactive reflexes and bilateral positive Babinski signs which subsequently became normal during his hospital stay. Skull radiographs and cerebrospinal fluid examinations were normal. The clinical impression was temporal arteritis, prompting a biopsy of the right temporal artery which showed slight arteriosclerosis. The patient's symptoms spontaneously resolved and he was discharged from the hospital without a definitive diagnosis. He was seen six months later com-

plaining of numbness of the right face. There was decreased sensation to pin-prick in the same area. An active snout reflex was elicited. The reflexes were hyperactive. In addition, the patient was thought to be demented and the diagnosis of 'chronic brain syndrome secondary to arteriosclerosis' was made. Again his focal neurological signs spontaneously cleared and he was discharged.

On his final hospital admission the patient complained of recurring bifrontal headaches. His reflexes and muscle tone were increased. During the next few days the patient became unresponsive, with numerous episodes of myoclonus. Shortly before he died, he had several generalized convulsions. Neurological diagnostic studies which included lumbar puncture, brain scan, and radiographs of the skull were unrevealing.

POST-MORTEM EXAMINATION The oral and cutaneous telangiectases were not as prominent as in life. The heart weighed 370 g and was dilated. Moderate coronary arteriosclerosis and left ventricular hypertrophy were present. Bilateral pleural effusions were noted. There was panacinar emphysema of the lungs. Multiple telangiectases were found in the gastric mucosa. The kidneys were small and scarred by arteriosclerosis. There was benign overgrowth of the prostate gland.

No abnormalities of the skull or the scalp were present. The brain was fixed in 10% formalin for 10 days, after which multiple coronal sections at 5 mm intervals were made. The brain weight was 1,300 g. The meninges were slightly thickened over the convexity of the cerebrum. No telangiectases were seen in the leptomeninges. There was minimal arteriosclerosis of the vessels at the base of the brain. No gyral atrophy was present. The ventricles were only slightly dilated. Several telangiectatic lesions were found on the cut surface of the brain. The largest, in the right frontal lobe, involved both the grey and white matter and measured 4.0 cm in greatest dimension (Fig. 1). Similar telangiectases were seen in the pons and cerebellum. The former was located along the midline raphe and measured 3.5 cm in length (Fig. 2), while in the cerebellum the telangiectases centred around the right dentate nucleus, although they extended into the cortex (Fig. 3). All three lesions were composed of blood vessels ranging in size from 0.1 to 1.5 mm. No heterotopia or hamartomata were associated with the vascular lesions.

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FIG. 1. Frontal lobe. Numerous telangiectases, particularly in the white matter.

FIG. 2. Pons. Telangiectases clustered about midline raphe.

Two small cystic infarcts unrelated to the telangiectases were observed, one in the cortex of the left occipital lobe, the other in the left globus pallidus.

Sections from the frontal lobe, basal ganglia, Ammon's horn, occipital lobe, pons, medulla, and cerebellum were embedded in paraffin, cut at 6 micra, and stained by the haematoxylin and eosin, haematoxylin-van Gieson, elastic-van Gieson, thionin (Holzer), Weil modification of the Weigert (myelin), and the von Braunmühl methods. In addition to the small old

FIG. 3. Cerebellum. Telangiectases centred around dentate nucleus.

cystic infarcts noted above, there was a moderate loss of neurones in Sommer's sector of Ammon's horn with a corresponding increase in astrocytes which was interpreted as evidence of chronic anoxic change. Senile plaques and neurofibrillary changes were not found. The telangiectases in the frontal lobe, cerebellum (Fig. 4), and pons (Fig. 5) were composed of two elements, capillaries and veins. In this respect they resembled the lesion of Sturge-Weber disease, but they lacked the characteristic calcifications and gliosis and they were not found in the meninges. Both capillaries and veins were dilated and varicose. The capillaries were of smaller calibre, up to 0.5 mm in diameter, and were thin-walled, the walls being composed of endothelial and perithelial cells and a few thin strands of collagen. The walls of the venules were thicker, composed mainly of collagen, and free of elastic fibres.

DISCUSSION

Eleven cases of hereditary haemorrhagic telangiectasia with central nervous system involvement verified by pathological examination have been recorded in the medical literature. In his review of the eight cases reported through 1964, Boczeko found that various vascular lesions including arteriovenous malformations (Boczeko, 1964), angiomas (Cohn and Rosenthal, 1948), venous malformations (Courville, 1957; Bird and Jaques, 1959), and capillary telangiectases (Snyder and Doan, 1944; Brinkmann, 1950; Vischer, 1951; Zelman, 1962) may occur in the brain and spinal cord in association with Osler-Weber-Rendu disease. The reader is referred to Boczeko's paper for further details (Boczeko, 1964). Three additional case reports have appeared since

FIG. 4. *Cerebellum. Low-power microscopic view showing many telangiectases in the white matter. ($\times 70$, Weil.)*

1964. Chandler (1965) described a patient with headache and seizures who had an arteriovenous malformation involving the right temporal lobe and an associated arteriovenous fistula of the lung. Czernobilsky and Bouzarth (1965) reported a patient with diplopia, right facial hyperaesthesia,

nuchal rigidity, and headache. At necropsy she had extensive subarachnoid haemorrhage secondary to a ruptured right middle cerebral artery aneurysm and an arteriovenous malformation in the midbrain. A case concerning a 17-year-old girl with an angioma involving the left caudate nucleus, which was

FIG. 5. *Pons. Low-power microscopic view of telangiectases interspersed among myelinated tracts. ($\times 70$, Weil.)*

surgically removed after a subarachnoid haemorrhage, was published by Quickel and Whaley (1967).

Since the basic lesion in this disease is presumed to be the capillary telangiectasis, one may consider the other vascular abnormalities found in the central nervous system to be merely coincidental observations. If, on the other hand, one wishes to consider that the basic defect in this disease resides in an as yet to be identified abnormality in the vasculature, it may be that hereditary haemorrhagic telangiectasia is a misnomer and, until the pathogenesis of the vascular lesion has been determined, the eponym, Osler-Weber-Rendu disease, seems more appropriate. The patient reported herein represents a typical case of Osler-Weber-Rendu disease with associated telangiectasia of the brain. Four similar cases have been reported in the literature (Snyder and Doan, 1944; Brinkmann, 1950; Vischer, 1951; Zelman, 1962); however, in none of these have the neuropathological findings been adequately described or documented.

The neurological findings in this patient, particularly their transient nature, are difficult to explain. Other than the telangiectases, no fixed lesions in the form of gliosis, demyelination, or neuronal damage were found. The anatomical loci of the telangiectases are appropriate for many of the patient's neurological signs. The telangiectases in the cerebellum and mesencephalon might explain the myoclonus, hyperactive reflexes, positive Babinski signs, and facial numbness. The snout reflex and the convulsions seen late in his course could be related to the capillary lesion in the frontal lobe. The difficulty arises in attempting to account for the transient nature of the clinical findings. Recurrent haemorrhage from these vessels could have provided cause for such symptoms; however, there was no evidence of recent or old bleeding. Temporary local circulatory disturbances with associated hypoxia may have been responsible for the clinical picture. There was evidence of non-specific anoxic effect in the loss of neurones in Ammon's horn. The telangiectases, which were dilated at the time of our examination, are considered to be highly distensible and could cause sufficient swelling and pressure locally to produce clinically detectable symptoms. The patient's apparent dementia is more puzzling. We have no histological indication of so-called senile dementia characterized by senile plaques and neurofibrillary changes. Dementia has been reported in association with telangiectasia of the brain-stem (Davison and Rosenheck, 1937). In that instance there was hydrocephalus, the result of compression of the cerebral aqueduct. The ventricles were not appreci-

ably dilated in the present case, but the possibility of a low-pressure hydrocephalus cannot be completely excluded.

In previously reported cases of Osler-Weber-Rendu disease with central nervous system lesions other than telangiectasia, neurological findings are common and usually secondary to haemorrhage. Among these are seizures, hemiparesis, reflex abnormalities, hemianaesthesia, cranial nerve palsies, headache, and signs of subarachnoid haemorrhage. However, in the cases described as having telangiectases in the nervous system, the vascular abnormalities generally were not considered responsible for any neurological findings. The neurological literature dealing with telangiectasia in general is contradictory. Cushing and Bailey (1928) report only one symptomatic case in their series of over 2,000 brain tumours. Davison and Rosenheck (1937) report a case of mesencephalic telangiectases and discuss the rarity of neurological signs in telangiectasia of the central nervous system. Michael and Levin (1936) on the other hand, report a family with hereditary telangiectasia which caused convulsions and focal neurological signs. In their review of previous cases of telangiectasia, neurological manifestations, often transient, were said to be common.

SUMMARY

The neuropathological findings in a case of hereditary haemorrhagic telangiectasia with clinical involvement of the brain are presented. The mechanism of clinical expression of the telangiectases in the central nervous system is discussed. The pertinent literature is briefly surveyed.

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