Hereditary haemorrhagic telangiectasia: neuropathological observations

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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, conjunctive, 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 complaints 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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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 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, Boczko found that various vascular lesions including arteriovenous malformations (Boczko, 1964), angiomata (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 Boczko's paper for further details (Boczko, 1964). Three additional case reports have appeared since...
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. 4. Cerebellum. Low-power microscopic view showing many telangiectases in the white matter. (×70, Weil.)

FIG. 5. Pons. Low-power microscopic view of telangiectases interspersed among myelinated tracts. (×70, Weil.)
surgically removed after a subarachnoid haemor-
rhage, 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 obser-
vations. If, on the other hand, one wishes to con-
sider that the basic defect in this disease resides in
an as yet to be identified abnormality in the vascu-
lature, it may be that hereditary haemorrhagic
telangiectasia is a misnomer and, until the patho-
genesis 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 litera-
ture (Snyder and Doan, 1944; Brinkmann, 1950;
Vischer, 1951; Zeiman, 1962); however, in none
of these have the neuropathological findings been
adequately described or documented.

The neurological findings in this patient, par-
cularly 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 associ-
ated 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 con-
sidered to be highly distensible and could cause
sufficient swelling and pressure locally to produce
clinically detectable symptoms. The patient’s ap-
parent 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 com-
pletely 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 haemor-
rhage. Among these are seizures, hemiparesis,
reflex abnormalities, hemianesthesia, cranial nerve
palsies, headache, and signs of subarachnoid haemor-
rhage. However, in the cases described as having
telangiectases in the nervous system, the vascular
abnormalities generally were not considered respon-
sible 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 con-
vulsions and focal neurological signs. In their
review of previous cases of telangiectasia, neuro-
logical manifestations, often transient, were said
to be common.

SUMMARY

The neuropathological findings in a case of hereditary
haemorrhagic telangiectasia with clinical involve-
ment 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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