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COMMUNICATIONS

VON HIPPEL-LINDAU DISEASE*

Clinical and Pathological
Report of a Case

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It is not often that an opportunity presents itself for the histological study of a case of von Hippel's disease; and it is even more unusual to combine this with microscopic examination of one of the tumours in the central nervous system, described by Lindau. The case here reported offers both opportunities, and may help to throw some light on the pathogenesis of the v. Hippel-Lindau complex.

The patient, a man aged 24 years, was seen for the first time at the Glasgow Eye Infirmary on March 22, 1948, complaining of defective vision in the right eye, and repeated attacks of epistaxis for a number of years. For one month

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there had been severe intermittent left occipital headache, especially severe in the mornings, and once or twice associated with projectile vomiting. Seven weeks before admission he had an attack of giddiness leading to collapse.

In the right eye (Fig. 1) the ophthalmoscope showed a large grey globular detachment of the retina in the lower nasal quadrant, and several smaller detachments above. The principal retinal vessels were much dilated and tortuous. There was diffuse white opacity of much of the detached retina. Transillumination

FIG. 1.

v. Hippel—Lindau disease. Ophthalmoscopic examination of right eye before excision. Extensive retinal detachment. Distension and tortuosity of vessels. New-built vessels. Gliosis.

gave an indefinite shadow in the lower area. The tension of the eye was normal. The fundus of the left eye was normal.

General examination revealed no abnormality of blood pressure, or of the circulatory, respiratory, gastro-intestinal or nervous systems. W.R. was negative. There were no cutaneous angiomas, and no X-ray evidence of intracranial disease.

The right eye was excised on April 16, and on April 21 he was transferred to the neuro-surgical unit at Killearn Hospital.

Operation (Dr. Schorstein) disclosed a cerebellar tumour, the removal of which was followed by deep X-ray therapy. The patient made an excellent recovery. The tumour was diagnosed as a haemangioblastoma.

PATHOLOGY

Serial sections of the retina of the right eye were cut in paraffin in the 12 to 6 o'clock meridian, and stained with haematoxylin and eosin, Mallory, van Gieson and Weigert's elastic tissue stain.

In a general survey the retina exhibits great distortion, variations in thickness, and degeneration of the retinal layers. At no part of the fundus is there a completely normal retina. In the least affected parts, about 5 mm. above and below the macula, there is destruction of the rods and cones and confusion of the nuclear and internuclear layers. In the more central area there is extensive destruction of the nuclear and ganglion cell layers, the retina for the most part consisting of coarse bands of neuroglia passing obliquely or anteroposteriorly through its whole thickness.

There are many cysts (Fig. 2) large and small, round and irregular in shape, empty or otherwise. The contents of the cysts consist of large cells with scanty pigment granules, apparently derivatives of the hexagonal pigment cells. There are so many gradations between the round, clearly defined cavities and the ragged fissures that it is difficult to say which are true cysts and which are the result of the tendency to cleavage of the retina along the lines of the glial framework.

FIG. 2.

Degenerate retina. A fibro-cellular septum which projects into a large cyst contains endothelial cells.

FIG. 3.

A large nodule, composed mainly of glial and endothelial cells. Small vessels are forming. The nodule occupies the whole thickness of the retina. In the upper part of the photograph a neighbouring nodule has undergone hyalinisation of the matrix.

FIG. 4.

v. Hippel—Lindau Disease. Diffuse gliosis and multiplication of small vessels. Hyaline change in the matrix of the tumour tissue.

FIG. 5.

Two large vessels in the degenerate retina. The coats of the vessel walls are not distinguishable, and the wall of one vessel (vein?) contains several intra-mural vessels.

Dark clumps of *pigment cells* are deposited in irregular fashion, especially in the posterior part of the retina, but also as far forward as the nerve fibre layer. They often form dark deposits in the walls of vessels or cysts.

Pseudo-membranes of varying thickness are found attached to both anterior and posterior surfaces of the retina. At some points these are in continuity with

substantial homogeneous masses (hyaline?) in the retina, some of which contain blood vessels.

A striking feature of this part of the retina is the presence of fibro-cellular nodules, of varying size and situated in any or all of the layers (Fig. 3). There are also more diffuse patches of somewhat similar fibro-cellular structure (Fig. 4).

In sections just temporal to the disc the principal vessels are recognised as an upper and lower pair, corresponding with the normal superior and inferior temporal vessels. Both artery and vein are expanded and have thickened walls. In some parts there is lymphocytic infiltration of the wall. Here and there additional large vessels appear, probably produced by expansion of subsidiary branches. Large vessels have not only encroached on the deep and superficial layers, but at several points are seen to have perforated the anterior and the posterior limiting membranes.

Some vessels are seen which show little change from the normal histology, but in most there is not only thickening but also a varying degree of hyaline change.

One or two of the larger vessels show an incomplete differentiation of their coats; the walls contain some scattered endothelial cells, and here and there are intramural vessels, or *vasa vasorum*, similar to those described by Loewenstein (1947) (Fig. 5).

The gross changes so far described are largely degenerative, and do not in themselves offer any guide to the pathogenesis of the condition. For this we have to turn to the nodular lesions already mentioned. It seems to be here that we find a clue to the earliest stage in this tumour formation. The nodules vary greatly in size, the largest occupying the whole depth of the thickened retina

FIG. 6.

A cluster of endothelial cells, deep in the retina, resembles a giant-cell.

FIG. 7.

Another cluster of endothelial cells, in the anterior part of the retina, shows the formation of endothelium-lined vessels.

(Fig. 3). At a number of points we find clusters of endothelial cells, as small as 30μ in diameter, with a strong resemblance to giant-cells (Fig. 6). In some of these clusters clear vacuoles appear, lined with endothelium (now definitely blood-vessels) (Fig. 7). These increase in number and size, while the matrix in which they are embedded increases in amount and is seen to be composed of neuroglia together with endothelial cells.

These changes apparently represent a series of phases in the growth of the nodule; and a further change, which would appear to be the next stage in the process, is the gradual hyalinisation of the matrix. This begins in the central

part (Fig. 8) and extends gradually through the rest of the nodule, until the matrix loses its fibro-cellular character, and the vessels are seen to be embedded in a homogeneous waxy-looking mass (Fig. 9) which stains faintly red with eosin, blue with Mallory, and crimson with van Gieson. With Mallory a certain fibrillary structure is indicated.

A similar series of changes takes place more diffusely in this part of the retina. We have noted that much of the degenerative retina is composed of coarse bands of glial tissue. These are associated here and there with endothelial cells which do not group themselves in nodular form. This "gliosis" gives place to a hyaline material, sometimes with, and sometimes without enclosed capillary vessels.

In all these parts, both in the nodules and in the intervening tissue, the proportion of vessels to matrix varies a good deal. Sometimes large vessels join up to form a cavernous plexus, elsewhere the vessels may be few and of capillary structure, buried in a mass of "hyaline" tissue. Here and there we find a very small nodule of the endotheliomatous tissue in the wall of a large cyst, or in a

FIG. 8.

A large nodule, about 250μ in diameter, in the posterior part of the retina. It is full of small vessels. The matrix is becoming hyaline.

FIG. 9.

A large angiomatic nodule in which the vessel walls and the supporting matrix are almost completely hyaline.

septum of connective tissue projecting into the cyst (Fig. 2). This may have some relation to the haemangiomatic cysts in other organs discovered in Lindau's cases.

The aforementioned hyaline changes, which are a pronounced feature of most of the sections, are of interest, but their significance is not clear. The hyaline material appears:—(1) as a result of the progressive change in the fibro-cellular matrix of the nodules, as well as in the intervening tissues (Fig. 8); (2) as a result of a pathological change in the thickened walls of the retinal vessels, both small and large (Fig. 9); and (3) as hyaline masses at all depths in the retina and on its anterior surface, some of which contain a few small vessels while others are completely avascular (Fig. 4). It may be taken as a degenerative change in the overgrown neuroglial tissue of the retina, probably the latest phase in the growth of the retinal tumour.

THE CEREBELLAR TUMOUR

The histological character of the portion of the cerebellar tumour available to us differs from that of the retinal growth, (1) in the absence of nodular formations; (2) in the absence of the degenerative changes, such as cyst-formation,

gliosis and hyalinisation, as seen in the retinal tumour. Here and there we find clusters of unorganised endothelial cells resembling giant-cells, some of which contain one or two small vascular channels lined with endothelium, and the tumour tissue in general consists of a light matrix of endothelial and supporting cells containing many blood-channels of widely varying size, lined with flattened or almost cubical endothelial cells. In some parts a free inter-communication between neighbouring vessels gives the tumour a cavernous character.

Incidentally, sections from a case of cavernous angioma of the eyelid, for which we are indebted to Professor A. Loewenstein, show appearances almost identical with those in Fig. 8.

Comment

The problem of the isolation and identification of the initial lesion is one which is common to all retinal diseases of "massive exudative" type; for the eyes in these cases are seldom submitted to pathological examination until marked secondary changes have occurred. In this country the first important contribution to our knowledge of the disease was that of Collins (1894), who had the opportunity of studying the histology of an eye which had been clinically examined and described two years earlier by Wood (1892), and subsequently of examining both eyes of this patient's sister. In each of these eyes there was complete retinal detachment and advanced degenerative changes, but the central retinal tumour had the structure of a capillary naevus, the matrix of which contained many scattered cells apparently endothelial in character. Cystic spaces abounded in the tumour and in the retina generally, and Collins described the condition as a capillary naevus of the retina with cystic degeneration.

v. Hippel discussed the condition in 1895 from the clinical, and in 1911 from the pathological aspect, and earned for it the name of von Hippel's disease. Coats (1908) described the disease among the forms of retinal disease with massive exudate, and supported the view of Collins, v. Hippel and Czermak that it must be considered as a true vascular new-formation. Lindau (1926) established the close association of v. Hippel's disease with the haemangiomatous cysts of the cerebellum and other organs described by himself. In the subsequent literature on the pathology of v. Hippel's disease emphasis has been placed on the presence of endothelial cells throughout the retinal tumour.

Two views are expressed regarding the pathogenesis of the condition, namely; (1) that the growth is primarily a gliosis which undergoes a secondary vascularisation, and (2) that the vessel formation is primary and the gliosis a secondary reaction. Møller and Marburg (1928) and others who support the first view point out that the glial formation is out of all proportion to the vessels, which may be very scanty. They have also found a massive gliosis without any vascularisation or endothelial cells.

They emphasise that glial masses may be found in the deeper non-vascular layers of the retina: but we are bound to admit that there may be not only persistence and proliferation, but also displacement, of the embryonic cells of origin. One argument in favour of the primarily vascular nature of the growth is that the vessels in the tumour nodules appear to be independent of the local circulation, and have no resemblance to the vascular pattern of the retina. Again Lindau (1936), Paton (1929) and others have examined cases in which the tumour contained no glial tissue, and clinically the vascular aspect of the tumour may be evident for some time before gliosis appears.

The occurrence, in the present case, of clusters of endothelial cells without vessels is significant, and supports the view that the lesion is a haemangio-endothelioma or haemangio-blastoma. The ophthalmoscopic and microscopic features of the case bring it into line with the cases of Lindau (1927), Paton, Williamson-Noble and Greenfield (1929), Sladden (1930) and A. E. Macdonald (1948), which are among the few cases in which the complete v. Hippel-Lindau complex was present and both microscopic and ophthalmoscopic examinations were obtained. The feature common to all these cases is that the actual tumour is composed largely of endothelial cells, some of which proceed to form rudimentary blood vessels. The relative abundance of endothelial cells, blood vessels and glial tissue varies from case to case and even in different parts of the same retina.

From the findings in the present case, it would seem that the initial pathological unit is a cluster of endothelial cells destined to form a vascular endothelium, but persisting in a more or less embryonic state, proliferating and invading the avascular layers of the retina. The overgrowth of neuroglia, the formation of retinal cysts, the widespread hyaline change and the general disorganisation of the retina must be looked upon as secondary. It is evident that the vessels of the angioma are not formed by budding from mature retinal vessels but by the pursuit, by the endothelial cells, of their destined function of vessel-formation. The tumour shows no signs of malignancy, but the eye may be destroyed by the occurrence of haemorrhage, glaucoma or detachment of the retina.

Summary and conclusion

The case is described of a young man who suffered from angiomatosis retinae (v. Hippel) accompanied by cerebellar haemangioma (Lindau). The affected eye was excised and subsequently the cerebellar tumour was removed. Both were subjected to microscopic examination.

The cerebellar tumour consisted of a soft fibro-cellular mass, containing many clear endothelial-lined spaces, some cystic, others vascular. Unorganised endothelial cells were diffused through the matrix of the tumour.

In the retina, which was grossly disorganised, there were

(1) Clusters of endothelial cells, some of the latter grouping themselves to form capillary vessels. The endothelial cell cluster seems to be the pathological unit.

(2) Larger clusters or nodules, some of them filling the whole thickness of the retina, and consisting of a fibro-cellular (glial) matrix containing new vessels of varying size as well as unorganised endothelium.

(3) A hyaline change, first of all at the centre of the nodules, but later converting the whole nodule to a hyaline mass.

(4) Similar changes in a more diffuse form, predominantly a gliosis.

(5) Cystic, pigmentary and other forms of degeneration.

The findings support the view that the vessel-formation is primary and the gliosis of the retina secondary.

The tumour cells are not derived from the large mature retinal vessels. It is probable that they are derived from the capillary endothelium, or rather from the anlage of such endothelium. Such an anlage develops by budding from the vascular endothelium confined at an early embryonic stage to the optic nerve region, and does not develop from neural cells.

The tumour is a true haemangio-blastoma or haemangio-endothelioma.

We would express our thanks to Prof. A. J. Ballantyne for his close interest in this case and his help in working-out the histology.

Fig. 1 is from a coloured drawing of the fundus by Mr. Gabriel Donald.

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