Pathological and haematological aspects of posterior fossa haemangioblastomata¹

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SYNOPSIS A retrospective study has been carried out on 67 patients harbouring 78 posterior fossa haemangioblastomata. The site, macroscopic nature, and histological features are described, and correlations sought with the degree of erythrocytosis in the peripheral blood. The problems of aetiology are discussed and a single hypothesis advanced.

Haemangioblastomata are histologically benign tumours of the neuraxis. There are two aspects which are remarkable—the association with the von Hippel-Lindau complex and the association with erythrocytosis of the peripheral blood. Although the latter is well documented no attempt has previously been made to relate the histological features to the haematological findings. In order to do so, and to attempt a single hypothesis regarding aetiology, a retrospective study of posterior fossa haemangioblastomata has been carried out. The details of clinical presentation, the von Hippel-Lindau complex and surgery have been reported previously (Jeffreys, 1975).

METHODS

Sixty-seven patients harbouring 78 posterior fossa haemangioblastomata were studied. Seventy-four tumours were histologically verified and the sections were re-examined. Three of the unverified tumours were deemed irremovable at operation though they were associated with other removable and histologically verified posterior fossa tumours. The last tumour occurred in a patient with erythrocytosis and in whom a cyst only was found at operation.

SITE AND MACROSCOPIC NATURE OF TUMOURS A cystic tumour was defined as one from which 5 ml or more of golden fluid could be aspirated at operation. Tumours with large cysts nearly always had small

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TABLE 1
SITE AND MACROSCOPIC NATURE OF
POSTERIOR FOSSA HAEMANGIOBLASTOMATA

Site	Cystic		Solid		Total	
	(No.)	(%)	(No.)	(%)	(No.)	(%)
Right cerebellar hemisphere	23	(30)	8	(10)	31	(40)
Left cerebellar hemisphere	26	(33)	4	(5)	30	(38)
Vermis	5	(6)	6	(8)	11	(14)
Floor of fourth ventricle	2	(2.5)	4	(5)	6	(8)
Total	56	(72)	22	(28)	78	(100)

Figures represent actual number of tumours. The figures in parentheses are these figures expressed as a percentage of the 78 tumours.

tumour nodules. The details of site and macroscopic nature of the tumours (Table 1) are in close agreement with the combined totals of the four major series in which the relevant details are given (Perlmutter *et al.*, 1950; Olivecrona, 1952; Krayenbühl and Yaşargil, 1958; Stein *et al.*, 1960).

An attempt was made to estimate the size of the cysts by needle aspiration at operation. As a general rule, this technique will tend to underestimate the size, since it is impossible to empty a cyst completely this way. The average volume of 37 cystic tumours in which the volume was estimated was 33 ml (range 6-90 ml). The average protein content of the cyst fluid measured in 12 tumours was 3.7 g/100 ml. Estimations of the size of solid tumours were thought too unreliable for accurate analysis.

MICROSCOPIC NATURE OF TUMOURS Although at first sight histological sections of a posterior fossa

FIG. 1 High power view of haemangioblastoma showing capillary in centre containing numerous red blood cells. The endothelial cells are well shown at the lower end of the capillary. H and E, G, $\times 810$.

FIG. 2 Reticulin stain in haemangioblastoma, showing the interstitial fibres as well as the basement membrane of the blood vessels. Gomori, $\times 75$.

haemangioblastoma, whether from a cystic or solid tumour, look much the same, there are subtle distinctions between tumours, a point first appreciated by Cushing and Bailey (1928). The salient feature is a fine meshwork of blood channels and capillaries. The endothelial cells appear normal, both on ordinary microscopy (Fig. 1) and on electron microscopy (Castaigne *et al.*, 1968). The intervascular stroma consists of sheets or regular columns of regular

FIG. 3 Juvenile (type A) haemangioblastoma, removed from 12 year old boy. H and E, $\times 115$.

spheroidal cells with no mitoses. The cells may be quite small or large and swollen with lipid material (labelled 'pseudoxanthomazellen' by Lindau in 1926).

Reticulin staining, first advocated for the diagnosis of these tumours by Cushing and Bailey (1928), reveals a remarkably regular pattern (Fig. 2). The stain demonstrates the basement membrane of the blood vessels and additional fibres can be seen to run between the stromal cells. Using this stain Cushing and Bailey (1928) divided the tumours into three types—capillary, cellular, and cavernous. In this present series 63 tumours were capillary, six cellular, and five cavernous. There was no correlation between this classification and the macroscopic nature of the tumour, nor between this classification and the degree of erythrocytosis in the peripheral blood.

Silver and Hennigar (1952) divided the tumours into three histological types:

Type A: Juvenile Contain sheets or columns of regularly small cells with few or no pseudoxanthomazellen (Fig. 3).

Type B: Transitional Contain more or less equal

FIG. 4 Transitional (type B) haemangioblastoma, removed from 23 year old man. H and E, $\times 115$.

FIG. 5 Clear cell (type C) haemangioblastoma, removed from 41 year old woman. H and E, $\times 115$.

proportions of small cells and pseudoxanthomazellen (Fig. 4).

Type C: Clear cell Comprise nearly all pseudoxanthomazellen (Fig. 5).

These authors felt that there was a tendency for type A tumours to occur in younger patients and type C in more elderly patients, with type B in the intermediate age group.

Using this classification in this present series the results were as follows: six (8%) tumours were type A; 36 (48%) tumours were type B; 32 (44%) tumours were type C.

There was no correlation between the histological type and macroscopic nature of the tumour. There was a correlation between histological type and the age of the patient (Fig. 6). With one exception, type A tumours occurred only in the 10 to 30 year age group. Types B and C occurred maximally in the 30 to 40 and 50 to 60 year age groups respectively.

HAEMATOLOGY Haemoglobin estimations were performed on all patients. When the haemoglobin level

was in excess of 16.0 g/100 ml other indices of the formed elements of the blood were also recorded. The haemoglobin level was estimated either by the carboxy-haemoglobin or cyan-met haemoglobin methods. No significant difference in the results were obtained by the two methods. Patients were thought to be hydrated normally if the serum sodium was less than 143 mEq/l, a level exceeded in only one patient. Analysis of the blood indices in those patients with raised haemoglobin and red blood cell levels indicated that a genuine erythrocytosis was present rather than a polycythaemia, which might have been the case if dehydration had been significant.

In Table 2 the results of the haemoglobin levels are presented and compared with the levels given for normal patients (Whitby and Britton, 1969). An analysis was performed of the haemoglobin levels on admission of 51 patients suffering from acoustic schwannomata and cerebellar astrocytomata. These were matched for age and sex so that the average age was 40.7 years and the sex ratio was 2:1 in favour of males (the comparative figures for patients with haemangioblastomata were 38.4 and 2:1). The average haemoglobin level for the control group was

FIG. 6 Relationship of age of patient to histological type of haemangioblastoma.

TABLE 2

AVERAGE HAEMOGLOBIN VALUES FOR NORMAL ADULTS AND PATIENTS WITH HAEMANGIOBLASTOMA*

	This series: haemangioblastomata (Hb g/dl)	Normals* (Hb g/dl)
Males	15.9	15.6
Females	15.4	13.7
All	15.6	14.8

* Whitby and Britton (1969).

14.0 g/dl compared with 15.6 g/dl for patients with haemangioblastomata (Fig. 7).

There was a wide range of haemoglobin levels and it seemed that further analysis would be more fruitful if they were divided into three groups:

Group 1: haemoglobin less than 15.9 g/dl.

Group 2: haemoglobin between 16.0 and 17.9 g/dl.

Group 3: haemoglobin greater than 18.0 g/dl.

There were 16 patients in the second group and 12 in the third. In other words the haemoglobin level exceeded 18.0 g/dl in 12 (18%) patients and 16.0 g/dl in 28 (42%).

Check haemoglobin estimations were performed one month postoperatively on 23 of 28 patients in whom the level was greater than 16.0 g/dl pre-operatively. In all but two cases the haemoglobin had fallen to normal levels. In one of these two exceptions a mural nodule was not removed, having been

FIG. 7 Distribution of haemoglobin levels in patients with haemangioblastomata and other posterior fossa tumours.

undetected at operation, and in the other a second tumour appeared one year after removal of the first tumour. This second tumour had almost certainly been present at the time of the first operation.

Three patients were found to have erythrocytosis before any evidence of a posterior fossa tumour had appeared. In one of these close observation detected signs of a tumour within a few months. In the second the erythrocytosis was attributed to coexisting chronic bronchitis and emphysema. The third patient was actually diagnosed as suffering from polycythaemia rubra vera and treated by phlebotomy and the injection of phosphorus³², before she developed neurological signs which led to the detection of a haemangioblastoma.

RELATIONSHIP OF MACROSCOPICAL NATURE OF TUMOUR TO ERYTHROCYTOSIS In 12 (18%) patients with a haemoglobin level greater than 18.0 g/dl there were 14 tumours of which nine were cystic and five solid. In other words 16% of cystic tumours and 23% of solid tumours occurred in patients with high haemoglobin levels. In 16 (24%) patients with haemoglobin levels in the range 16.0–17.9 g/dl there were 21 tumours of which 13 were cystic and eight solid, thus showing that 24% of cystic and 37% of solid tumours were associated with unequivocally raised levels of haemoglobin.

FIG. 8 *Haemangioblastoma removed from 25 year old man. Small cysts containing translucent material are seen, with only a small number of tumour cells lying between them. Dark-staining capillaries are also seen. H and E, $\times 115$.*

Overall one can state that 40% of the cystic and 59% of the solid tumours were associated with haemoglobin levels in excess of 16.0 g/dl. There was slight overlap, in that some patients harboured both cystic and solid tumours.

RELATIONSHIP OF HISTOLOGICAL TYPE OF TUMOUR TO ERYTHROCYTOSIS The haemoglobin levels were related to the histological typing of Silver and Hennigar (1952) described above. There were nine type B and four type C tumours which were associated with haemoglobin levels greater than 18.0 g/100 ml; that is, 25% of type B and 13% type C tumours occurred in patients with unequivocally raised levels of haemoglobin. The corresponding figures for haemoglobin levels between 16.0 and 17.9 g/100 ml were 14 (39%) type B and 16 (50%) type C tumours.

It would seem that type A tumours were not associated with raised levels of haemoglobin. It has already been shown that this type of tumour occurs in younger patients. However, one cannot argue that these patients were too young or that the tumours were too recent in their development to cause erythrocytosis, since haemoglobin levels greater than 16.0 g/100 ml occurred in six of 24 patients less than 30 years old.

DISCUSSION

NATURE OF TUMOUR CELLS The nature and origin of the stromal cells has been the centre of

much interest. Cushing and Bailey (1928) discounted earlier theories of neuroepithelial and of microglial origin. They felt that the cells were of endothelial origin and supported the hypothesis of Lindau (1926) that they arose from the primitive blood vessels of the developing choroid plexus. After studies with electron microscopy Castaigne *et al.* (1968) and Cancilla and Zimmerman (1965) agreed on the structure of the pseudoxanthomazellen. The former authors excluded these cells from the glial, arachnoid, endothelial, and pericytic series and suggested that they belonged to the reticular system, a view advanced much earlier by Roussy and Oberling (1930) on the basis that extramedullary erythropoiesis could be found within the tumours. With the exception of one case (Ishwar *et al.*, 1971) this last finding has been unsubstantiated by any other author. In the present series even after a careful search, not one example of extramedullary erythropoiesis was found. Russell and Rubinstein (1971) sum up the view of most authors that the nature of these cells is still unresolved.

There has been further argument as to whether or not the stromal cells develop or degenerate into pseudoxanthomazellen. Bailey and Ford (1942) claimed that cutaneous haemangiomas undergo sclerosis with degeneration of the cells, resulting in an increase of collagen and the numbers of lipid-containing cells. They suggested that haemangioblastomata behave in a similar fashion. Silver and Hennigar (1952) concurred with this view. In this series a number of tumours contained areas of infarction and degeneration. However, there were many more tumours without these areas and yet containing large numbers of pseudoxanthomazellen. In addition these cells do not stain with silver carbonate (Rubinstein, 1972) as might be expected if they belonged to the macrophage series. It would seem more likely that pseudoxanthomazellen arise from the small round cells.

CYST FORMATION Lindau (1926) favoured the view that large cysts in association with haemangioblastomata were exudative in origin. The cyst wall is composed only of compressed neuroglia (Russell and Rubinstein, 1971). There certainly can be no question of cerebrospinal

fluid (CSF) leaking into the cyst, since in this present series the average protein content of the cyst fluid was 3.7 g/dl, whereas it was only 73 mg/dl in the CSF.

Although it has been suggested that cysts arise as a result of degeneration, it is difficult to imagine a tumour doing so to form a 90 ml cyst and 10 ml mural nodule. Cumings (1950) found the contents of haemangioblastomata to be similar to blood with respect to amino-acid nitrogen, mucoprotein and alkaline phosphatase, and he felt that the cyst fluid arose by diffusion from the blood by way of the mural nodule.

It is possible that small cysts may be formed initially and that later these coalesce to form larger cysts. In the present series it was found that 14 out of 24 macroscopically solid tumours contained small cysts, visible only on microscopy (Fig. 8). Pluvinage (1954) described a similar finding. These small cystic areas did not occur in association with infarcted areas and it would seem that they had been formed by some process of extracellular exudation.

HAEMATOLOGY The association of posterior fossa haemangioblastomata with increased levels of haemoglobin and red blood cells in the peripheral blood was first described by Carpenter *et al.* (1943), and many other reports now exist, such that Waldmann (1965) found over 50 cases reported in the literature. It is all the more surprising that there have been little data given, in other series of haemangioblastomata, with respect to haematological findings. Waldmann (1965) reviewing the literature estimated that 9–20% of cases experienced erythrocytosis, and this should be compared with 18% in this present series.

The only report in the literature relating the degree of erythrocytosis to the macroscopic nature of the tumour (Cramer and Kimsey, 1952) found that solid tumours were associated with higher average haemoglobin levels than cystic tumours. This is in agreement with the findings of this present series. No information exists in the literature on the relationship of erythrocytosis to the histological type of tumour. Haemangioblastomata appear well suited to the role of an endocrine gland, with their particular structure in which stromal cells are closely applied to large numbers of thin walled blood vessels. A hor-

mone, erythropoietin, has been found in the cyst fluid, within the tumour and in the plasma of the host patient (Waldmann *et al.*, 1961; Race *et al.*, 1964; Waldmann, 1964; Boivin *et al.*, 1965; Hennessy *et al.*, 1967). That the formation and release of erythropoietin in haemangioblastomata is not due to hypoxia is shown by the presence of normal arterial oxygen tensions (Waldmann, 1965). The erythropoietin found in haemangioblastomata is identical with that found in patients suffering from hypoxia, anaemias, or renal cysts (Krantz and Jacobson, 1970).

Erythropoietin is a protein with a molecular weight in the range 27 000 to 70 000 and has an electrophoretic mobility similar to the alpha-2-globulins (Krantz and Jacobson, 1970). At present its potency can be estimated only by bioassay (Gurney *et al.*, 1957; Jacobson *et al.*, 1960; Cotes and Bangham, 1961). It has been estimated that in normal conditions 90% of erythropoietin is formed in the kidney and 10% at some unidentified extrarenal site (Krantz and Jacobson, 1970). The amount of erythropoietin released appears to be related to the ratio of oxygen supply to oxygen demand (Yoffey, 1966). It is now generally accepted that the principal action of erythropoietin is to initiate differentiation of stem cells into the erythroblastic series of cells within the bone marrow (Alpen and Cranmore, 1959; Krantz and Jacobson, 1970). In addition high levels of erythropoietin may have a secondary effect leading to accelerated cell division and differentiation (Stohlman *et al.*, 1964; Jeffreys, 1966).

Erythrocytosis occurs in only a proportion of patients harbouring these tumours. It might be that all tumours produce erythropoietin, but in some patients a specific antibody neutralizes its effect. This would seem unlikely, since erythropoietin produced by haemangioblastomata is identical in every way with erythropoietin produced under normal conditions. If a homeostatic mechanism compensated for increased levels of erythropoietin, one would not expect to see any patient with erythrocytosis. Some tumours may not produce erythropoietin at all, or in such small amounts that there is no effect upon the bone marrow stem cells. In favour of this hypothesis is the fact that type A tumours are not associated with erythrocytosis and that there is a spectrum of erythrocytosis (Fig. 7). Since type A tumours

occur in younger patients one might postulate that types B and C tumours grow more slowly but differentiate more quickly, whereas type A tumours grow quickly but do not differentiate very well. However, there is no clear answer at present.

AETIOLOGY Cushing and Bailey (1928) likened the relationship of solitary haemangioblastoma with the multiple and familial forms to the relationship of solitary acoustic schwannoma to multiple neurofibromatosis. This begs the question as to whether or not the solitary tumour is a *forme fruste* in each of these two conditions. Certainly one is unable to separate the solitary haemangioblastoma from the multiple or familial tumour by histological criteria. The fact that 75% of haemangioblastomata are sporadic and solitary would tend to argue against the *forme fruste* hypothesis.

In the belief, now mistaken (Wylie *et al.*, 1973), that haemangioblastomata occurred only within the posterior fossa Lindau (1926) and Cushing and Bailey (1928) advocated the idea that in the twelfth week of intrauterine existence part of the primordial choroid plexus was incorporated within the developing cerebellum. A hamartoma was thus formed from which at a later date a haemangioblastomata developed. By inference, therefore, it was felt that haemangioblastomata arose from structures of mesodermal origin, in agreement with van der Hoeve (1932) but not with the neuroectodermal hypothesis of Chapman and Diaz-Perez (1962), Mulholland *et al.* (1969), and Sander *et al.* (1970) which arises from attempts to relate haemangioblastomata to phaeochromocytomata, of which there have been 15 reported cases in the literature (Jeffreys, 1974).

Recently evidence has come to light which suggests that one of the functions of the primordial choroid plexus is haematopoiesis (Kappers, 1958). It may well be that the original hypothesis advanced by Lindau (1926) and Cushing and Bailey (1928) is correct, though it takes no account of haemangioblastomata occurring elsewhere within the neuraxis. The vast majority of haemangioblastomata remain in contact with the pia mater (Russell, 1950) and one might suggest that these other tumours arise by pial invagination of primitive tissues similar to the primordial choroid plexus.

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