Hemangioblastomas at the University Hospital of the West Indies: a retrospective survey and review of the literature

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Citation

J Jaggon, G Char. *Hemangioblastomas at the University Hospital of the West Indies: a retrospective survey and review of the literature*. The Internet Journal of Third World Medicine. 2008 Volume 8 Number 1.

Abstract

We present our experience with hemangioblastomas at the University Hospital of the West Indies, Jamaica, over a 23 year period, between January 1985 to December 2007.There were a total of five tumors from five patients with an age range of 19 to 49 years and an average age of 32.8 years. The male to female ratio was 1:4. All the tumors were within the posterior cranial fossa and no patient had more than one lesion. None of the patients were diagnosed with polycythemia vera. All patients were found to have hydrocephalus at the time of presentation. All had definitive surgery and the mortality rate was zero. To date, there have been no recurrences. None of the patients were screened for von Hippel Lindau disease.

INTRODUCTION

The name hemangioblastoma (HMB) was first introduced by Cushing and Bailey in 1928 (1).These are richly vascular, benign neoplasms with stromal cells of uncertain histogenesis. HMBs have been classified as Grade I tumors of uncertain origin in the World Health Organization (WHO) classification of tumors of the central nervous system (CNS) (2).

They are relatively rare tumors accounting for 1-2.5% of all intracranial neoplasms (3, 4, 5). Most are located within the posterior fossa accounting for 8 -12% of all neoplasms within that compartment. They present mainly between the third to fifth decade and tend to be more common in men (6).

Most HMBs arise sporadically; however approximately one quarter of them are associated with von Hippel Lindau Disease(VHL) (6), an autosomal dominant hereditary syndrome that includes retinal angiomatosis, CNS hemangioblastomas and various tumors involving the kidneys, pancreas, adrenal medulla and inner ear. VHL disease-associated cases of hemangioblastomas tend to occur in younger patients and are often multiple (6).

To date there is no known data published about hemangioblastomas in the Caribbean. We present our experience with hemangioblastomas over a twenty three year period at the University Hospital of the West Indies in Kingston, Jamaica. A comparative review of these results with international data is presented along with a brief review of the epidemiology and biology of this tumor.

MATERIALS AND METHODS

All hemangioblastomas entered into the files of the Pathology Department of the University Hospital of the West Indies between the years 1985 and 2007, a period of 23 years, were reviewed. All were surgically resected specimens and include resections from peripheral hospitals within Kingston, namely the Kingston Public Hospital. Patient details were then acquired from the dockets.

RESULTS

During the study period, 5 cases of hemangioblastomas were identified from 5 patients: 1 male and 4 females (M: F ratio of 1:4). The ages ranged from 19 to 49 years with an average age of 32.8 years. All the HMBs were within the posterior cranial fossa with 3 occurring in the right cerebellar hemisphere and 2 in the cerebellar vermis (Table 1).

The most common symptoms were headache, cerebellar ataxia and recurrent vomiting which occurred in all patients, while anorexia and weight loss occurred in 60%. All patients were found to have hydrocephalus with associated papilloedema at the time of presentation. Hemoglobin levels ranged from 13.1g/dl to 17.4g/dl (Table 1).

Figure 1

Table 1. Details of patients diagnosed with hemangioblastoma at the UHWI

Case #	Age	Gender	Location of tumor	Hb level (g/dl)
1	19	Female	Right hemisphere	14.6
2	20	Male	Vermis	17.4
3	29	Female	Right hemisphere	14.7
4	47	Female	Right hemisphere	13.1
5	49	Female	Vermis	13.9

Three patients were correctly diagnosed on imaging while metastatic disease was the diagnosis in the remaining two. Imaging revealed that in 60% of the cases the lesion demonstrated a partly solid/partly cystic configuration while the remainder was completely solid.

All patients had their tumors resected. The mortality rate was zero and there have been no known recurrences (maximum documented follow up period being eight years).

DISCUSSION

HMBs are considered benign neoplasms. They are highly vascular tumors that are usually attached to the dura and get their blood supply from the pia. They have two principal components: capillaries and stromal cells. The origin of the stromal cells is still not known. They are quoted in the international literature to represent 1 – 2.5% of all primary CNS neoplasms (4, 5) with a previous study done by Char et al (3) at this institution realizing an incidence of 1.2% of all intracranial tumors. In this 15 year study in which 5 HMBs were diagnosed over the time period 1970 to 1984, it was noted that 4 were located within the posterior cranial fossa and 1 was within the supratentorial compartment. This can be compared to the present study in which a similar amount of HMBs were diagnosed and in which all tumors were located within the posterior cranial fossa.

HMBs usually occur more often in adults aged 30-50 years. In this study, the average age of occurrence was 32.8 years with an age range of 19 to 49 years. Patients with VHL usually present at a younger age than patients with sporadic cases, with an age range quoted in the literature of 25 -40 years (6) and with a mean age of 29 years (7). These patients also usually develop multiple lesions. Three of our patients were age 29 years or younger at the time of diagnosis; none of them were documented as having multiple tumors or tumors occurring at other sites, even though, in reviewing the dockets of all the patients in our series, only two (cases 1 & 4) had had abdominal ultrasound. None of the patients had been sent for ophthalmic evaluation. It follows, therefore, that none were diagnosed with VHL disease.

VHL disease is inherited through an autosomal dominant trait and is characterized by the development of HMBs of the CNS and retina as well as clear cell renal cell carcinoma, adrenal or extra-adrenal phaeochromocytomas, pancreatic cysts or tumors, epididymal cystadenomas, endolymphatic sac tumors and broad ligament cystadenomas. The VHL gene is located on chromosome 3 and acts as a tumor suppressor gene (8). In patients with a positive family history, a single cerebellar HMB is sufficient to make the diagnosis. If no known family history exists, at least two cerebellar HMBs or one HMB plus one visceral tumor are necessary to justify the diagnosis of VHL. If available, performing VHL germline mutation analysis is confirmatory. Morbidity and mortality rates are higher in patients with VHL, in whom cerebellar hemangioblastoma is the most important cause of mortality, affecting 47.7% of patients with VHL (9), followed by renal cell carcinoma (9, 10).

HMBs are more common in men than women with a male to female ratio quoted in the literature as 1.3-2.6:1 (11) in sporadic cases, while patients with HMBs related to VHL show no sex differences in frequency. In the study done previously by Char et al at this institution (3), the ratio was 1.5:1. In our study the male to female ratio was now reversed at 1:4. There have also been reports in the literature of HMBs rapidly enlarging during pregnancy and the debate exists as to whether this is due to angiogenic factors or hormonal factors. It has been shown that many HMBs are positive for progesterone receptors (12) but there is controversy as to whether they respond positively to this hormone. The question to be asked, therefore, is whether or not this could possibly explain why we are seeing a reversal of the male:female ratio in our series. Progesterone receptors, unfortunately, were not done on the specimens from this study. To date, there is no other report in the literature showing this ratio reversal.

Polycythemia occurs in up to 20% of cerebellar HMBs and tends to be more common with solid tumors (9). Polycythemia is caused by the production of erythropoietin by the tumor cells, which has been demonstrated within the

encysted fluid (13). Occasional intratumoral foci of erythropoiesis are yet another expression of local erythropoietin production. The average hemoglobin in our study ranged from 13.1 to 17.4 g/dl; none of our patients, however, were clinically diagnosed with polycythemia. None of our tumors demonstrated intratumoral erythropoiesis histologically.

All the patients in this study were found to have hydrocephalus at the time of presentation, which is significantly higher than the 20% mentioned in the literature (16). This could in part be due to the late referral/presentation of our patients.

Macroscopically and on imaging, HMBs can be placed into the following four groups (with the frequency of each type quoted in the literature shown in brackets):

Type 1: Simple cyst form with no obvious mural nodule (6%)

Type 2: Variably sized cyst with mural nodule (65%)

Type 3: Solid form (25%)

Type 4: Solid with many small cysts (4%)

In our study, the most common type radiologically was Type 2 (60%) followed by Type 3 (40%), which corresponds to the pattern seen in other studies (11). Neither Types 1 nor 4 were seen in our series. In a study coming at the National Institute of Health in Maryland, it was shown that by the time symptoms appeared in patients with HMBs, the majority of the mass- effect producing symptoms are actually derived from the cyst, rather than from the tumor causing the cyst (14). This group also showed that cysts can enlarge up to fifteen times faster than the HMB causing them, with no tumor or cyst ever spontaneously diminishing in size. The cystic fluid was shown to be xanthochromic, with a concentration of amino acids, alkaline phosphates and mucoproteins similar to blood, suggesting that it originates by diffusion from the vascular component of the solid tumor (15).

An important histologic differential includes renal cell carcinoma (RCC), especially in a patient known or suspected to have VHL. RCCs, however, will have foci of necrosis, a higher MIB-1 index as well as positivity for epithelial membrane antigen (EMA) immunostain, in contrast to HMBs. Negative radiologic studies of the kidneys are also reassuring in doubtful cases.

The mortality rates quoted in the literature varies from 4.3-6% (6, 16). The mortality in this series was zero. There have been no known recurrences to date (maximum documented follow up period being eight years). It has been suggested that factors predicting a poor outcome are multiple HMBs, association with retinal HMBs and/or onset of disease before 30 years of age (17). All of these features are also associated with patients with VHL. In our series, it would therefore be very important to screen our patients, especially those younger than 30 years of age, for possible VHL disease as this may improve outcome.

In conclusion, HMBs are relatively rare, benign (WHO Grade I), highly vascular tumors of controversial origin. However, they are clinically and pathologically important tumors as they may be associated with significant morbidity and mortality and may be the first sign of VHL. It has been recommended by some that all patients with HBMs of the CNS should be screened for VHL by MRI of the brain and spinal cord, ophthalmoscopy, abdominal CT scan and by obtaining the family history and performing VHL gene mutation analysis where available (18), as this syndrome is associated with many other tumors.

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