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Headache in Hemangioblastomas: A Histopathology and Structural

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Abstract: *Background:* To determine the efficacy of treatment of central nervous system (CNS) hemangioblastomas in von Hippel-Lindau disease (VHL), long-term outcomes in patients with hemangioblastoma and VHL variant were accepted. Hemangioblastoma is rare, histological origin. Highly vascularized tumors that can be found throughout the neuraxis but are mainly located in the cerebellum and in the spinal cord. The most common primary tumor of the posterior fossa in adults. Hemangioblastomas may also occur within the spine. *Material and Methods:* This meta-analysis was performed to evaluate headaches in Hemangioblastoma (HBL) tumors structurally and separately based on randomized controlled trial studies. Electronic databases (PubMed, MEDLINE, Embase, and Cochrane Library) were searched for randomized and controlled trial studies that searched for the results of treatment of brain tumors (Hemangioblastoma type) and headache in Hemangioblastoma (HBL) tumors. *Result:* This meta-analysis was performed using Review Manager (Rev Man) software (version 5.2) provided by Cochrane Collaboration. The data used were hazard ratios with 95% confidence intervals calculated for time-to-event data extracted from survival curves and local tumor control rate curves. A consecutive series of patients with hemangioblastomas on between 2010 and 2020 by the senior author (A. AN) is Reviewed. *Conclusion:* Adequate knowledge of the treatment and correct use of microsurgical techniques allows complete resection of these tumors with minimal complications and maximum functional improvement. The result appears to be directly related to the preoperative condition.

Keywords: Hemangioblastoma, Vascularized Tumor, Primary Tumor, Von Hippel-Lindau, Neuraxis

1. Introduction

Hemangioblastoma (HBL) is a highly vascularized tumor of not well-defined histological origin that is frequently associated with cysts [1]. HBL arises preferentially in the cerebellum, medulla, and spinal cord and is histologically indistinguishable from vascular lesions in the retina. Cerebellar HBL is one of the most frequent manifestations of the autosomal dominantly inherited von Hippel-Lindau syndrome (VHLS) and may manifest as a sporadic tumor [2-7]. Although the tumor is histologically benign, its multiplicity and eloquent location still make it one of the patients' major causes of death [3]. Hemangioblastomas can be found throughout the neuraxis, but the most common sites of occurrence in the CNS are the cerebellum and the spinal cord [8-10].

The tumors occur either as a sporadic entity, or, in approximately 20 to 30% of cases, as a component tumor of

von Hippel-Lindau (VHL) disease, an autosomal dominantly inherited disorder with incomplete penetrance and expression [16]. Because of their vascular nature, these tumors harbor a risk of hemorrhage, which can occur spontaneously, intraoperatively, or postoperatively. Several case reports have been published regarding hemangioblastomas that resulted in spontaneous hemorrhage. Among these were cases of subarachnoid hemorrhage (SAH) [16-22], intracerebral hemorrhage [24, 25], and intramedullary hemorrhage [26].

The most common symptoms that most patients present with are severe headache, Nausea/ Vomiting, Ataxia, Dizziness, Pain, Sensory changes, Motor deficits, and others, but in general, the range of symptoms and age groups are different.

Before the introduction of magnetic resonance imaging (MRI), angiography was essential to establish the diagnosis of hemangioblastoma. With increasing MRI experience, the indication for angiography has become increasingly debatable; angiography is an invasive investigation, can result in severe complications, and its clinical utility is ambiguous. In most cases, the diagnosis is sufficiently established by MRI, as hemangioblastoma has a typical appearance of an extraordinarily bright-enhancing, well-circumscribed mass often associated with a cyst. Several authors have performed embolization of hemangioblastomas [21] with ambiguous results and in some cases, posterior fossa swelling requiring emergency craniotomy [26].

2. Epidemiology

Hemangioblastomas are uncommon in the general population, with an overall incidence of 0.141 per 100,000 person-years in the United States [36]. They account for less than 2% of all CNS neoplasms but comprise an estimated 11% of primary posterior fossa tumors [37, 38]. Approximately 70% of cases are believed to be sporadic with the remaining 30% representing VHL-associated familial cases [16, 39, 40]. An estimated 60%–80% of patients with VHL disease develop CNS hemangioblastoma during their lifetime [40-42]. The average patient age genetic subgroup VHL-associated tumors presenting on average two decades earlier than sporadic tumors [16] Table 1.

Table 1. *Summary of epidemiologic data for sporadic and hereditary hemangioblastomas.*

	Sporadic	**Hereditary**
The proportion of total cases (%)	~70	~30
Mean age of onset (yr)	47	29
No. of tumors	Single	Multiple
Sex (M:F)	1–1.25:1	1–1.25:1
Molecular alterations	Cerebellum most common	The higher proportion of extra cerebellar sites (e.g. spine)
Localization	Somatic loss of VHL detected in a subset of cases	VHL loss of function with germline mutation and somatic alteration

3. Methods

3.1. Eligibility Criteria

Studies were included if [1] exclusively targeted Hemangioblastoma patients; [2] published to Jan 2014; [3] written in the English language; A systematic review was conducted that follows the preferential reporting guidelines for systematic review and meta-analysis (PRISMA) [4]. published in peer-reviewed journals indexed in PubMed, MEDLINE, Embase, and Cochrane Library, Library Genesis was used to searching for Headaches with an emphasis on Hemangioblastoma; [5] they used any type of Hemangioblastoma as a part of or the whole intervention; and [6] utilized a quantitative design for evaluation. Studies published in the past three years were included because a previous systematic review covered studies published before 2020. Studies that did not meet any of the criteria were excluded. The studies were extracted independently by two authors. Duplicates were excluded by reference manager software (Endnote). we descriptively summarized the included articles with six tables. Additionally, studies were excluded if [1] they were incomplete or ongoing; [2] used qualitative methodology; [3] they were abstracts of conference proceedings, duplicates, letters to the editor, editorials, and commentaries. Moreover, the references of all the identified eligible articles were manually searched for additional relevant citations.

3.2. Inclusion Criteria

Studies published in English.

Only randomized controlled trials (RCTs) were eligible for inclusion in the review and meta-analysis.

RCTs that compared any of the following interventions were eligible for inclusion: WBRT versus WBRT plus SRS, SRS versus WBRT versus WBRT plus SRS, and SRS alone versus SRS plus WBRT.

Patients who had been diagnosed with one or more brain metastases less than 4 cm in diameter.

Participants were eligible regardless of the primary tumor histology and status if they had not received prior cranial irradiation.

3.3. Study Quality Assessment

Two reviewers independently assessed the studies' validity and evaluated each study's bias using the Cochrane tools [1]. The assessment item included sequence generation, allocation of sequence concealment, blinding of participants and personnel, blinding of outcomes and assessments, incomplete outcome data, selective outcome reporting, and other biases.

Disagreements were resolved through discussion.

3.4. Data Extraction

Two reviewers extracted the data from all eligible. Median survival and local tumor control rates were extracted either directly or from survival curves, and hazard ratios with 95% confidence intervals (CIs) were calculated for time-to-event data. 8 Data on other outcomes of interest were also extracted. All available data were extracted from relevant texts, tables, and figures. All analyses were performed on an intention-to-treat basis. Any disagreements in study selection were resolved through discussion.

3.5. Statistical Analysis

This meta-analysis was performed using the Review Manager (Rev Man) software v 5.2, provided by Cochrane Collaboration. Pooled HRs with 95% CIs were calculated for time-to-event data using a fixed-effects model. Weighted mean differences with 95% CIs were calculated for continuous data, while pooled Odds ratio with 95% CIs were calculated for dichotomous data. Statistical heterogeneity was assessed using chi-square statistics.

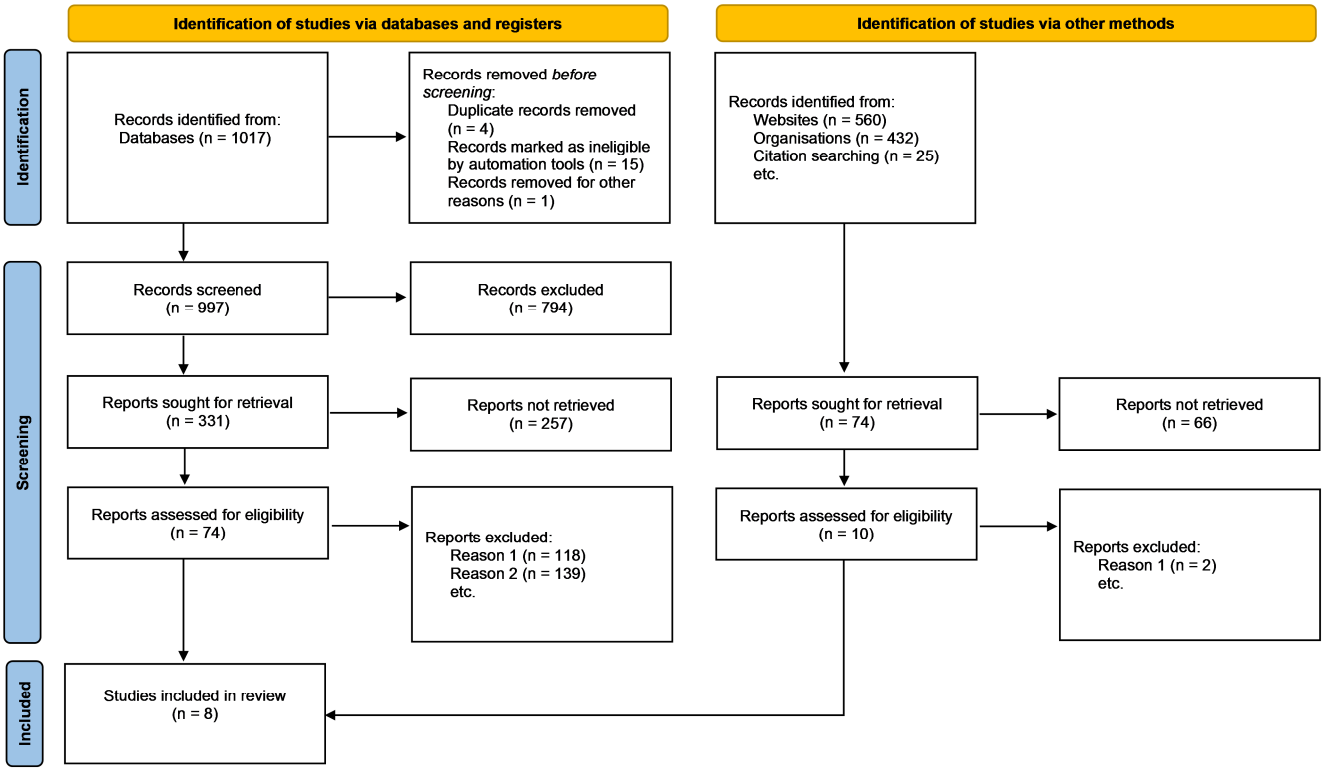

Figure 1. *The flow chart shows the study selection procedure, eight studies were included in this meta-analysis [34].*

4. Results

From 2010 to 2020, 8 Patients with Hemangioblastoma (HBL) were identified, fit eligibility criteria, and were included in the analyses. The characteristics of the tabulated patients are summarized in Table 1. The mean age at diagnosis for the whole group was 45 years (21 to 79 years). All results used at the time were marked, sorted, and used according to the subject. The average duration of treatment for patients was about 3 months according to research. The most common symptom was headache (49%). Other symptoms included cervical headache, Nausea/ Vomiting, Ataxia, Dizziness, Pain, Sensory changes, Motor deficit, and others. According to the tumors, there were all kinds of them (there were solid tumors and five cystic tumors). Several patients had more than one lesion. Von Hippel Lindo syndrome was diagnosed in these individuals. The diagnosis was based on radiological findings. Patients underwent diagnostic angiography before surgery due to the large size of the lesion. Patients underwent embolization.

The items in the table included information on the following characteristics:

General Information: author's name, country of research, year of publication

Study characteristics study design, randomization type, study sample, number of arms in the study, and participants per arm/group.

Study participants mean age and standard deviation (sd) of the study participants, mean age and sd of participants per group.

Outcome measurements of the criteria recorded from participants included efficacy, Hemangioblastoma on participants' Headaches, which varied from study to study.

5. Discussion

Hemangioblastomas can be found throughout the neuraxis,

but the most common sites of occurrence in the CNS are the cerebellum and the spinal cord [8-10]. They are rare, benign, highly vascularized tumors classified as Grade I according to the World Health Organization classification system [8, 9]. About 3% of all intramedullary tumors are hemangioblastomas [12-15]. Hemangioblastomas occur as sporadic lesions in about 70%–80% of cases, whereas in 20% – 30% of cases they can be secondary to a dominantly inherited genetic familial unpredictable growth cancer syndrome known as von Hippel–Lindau (VHL) syndrome [9-11]. Sporadic tumors appear in the fifth and sixth decades of life, whereas VHL-associated tumors are detected earlier, in the third and fourth decades. One-third of patients with cerebellar hemangioblastoma have VHL disease. Two-thirds of VHL patients develop hemangioblastomas; thus, screening and surveillance programs are required for this population. This pressure can cause neurological symptoms, such as headaches, weakness, sensory loss, balance and coordination problems, and hydrocephalus (buildup of spinal fluid in the brain). The cause of hemangioblastomas is a mystery, although some people may develop them as part of a genetic syndrome called Von Hippel-Lindau disease (VHL). VHL is characterized by the growth of a variety of benign and malignant tumors.

Table 2. *Summary of years of research on hemangioblastoma.*

	Overall	**0-20 years**	**21-59 years**	**≥60 years**	**P Value**
Age (y), M ±SD	38.10 ± 19.30	14.58 ± 4.50	30.19 ± 11.39	61.11 ± 5.22	NA
Gender					
Male	(52.4%)	(28.1%)	(52.6%)	(71.3%)	0.221
Female	(46.5%)	(61.9%)	(45.5%)	(38.7%)	
Hydrocephalus or syringomyelia					
VHL	(23%)	(44.6%)	(22.0%)	(6.45%)	0.001
Location					
Cerebellum	(51.3%)		(51.1%)		
Brainstem	(21.5%)	NA	(27.0%)	NA	0.019
Spinal cord	(24.6%)		(25.2%)		
others	(0.2%)		(0.5%)		
Symptoms					
Headache	(49.2%)	(42.9%)	(52.6%)		
Nausea/Vomiting	(24.6%)	(42.9%)	(25.2%)		
Ataxia	(12.3%)				
Dizziness	(24.6%)		(28.1%)	NA	NA
Pain	(14.4%)	(23.8%)	(30.4%)		
Sensory changes	(30.5%)				
Motor changes	(15.5%)				
others	(7.5%)	(4.8%)	(8.1%)		
Tumor characteristics					
Cystic	(40.34%)	NA	(45.6%)	NA	0.330
Solid	(58.00%)		(55.1%)		

NA = not applicable.

5.1. Clinical Hemangioblastoma

Cephalgia or pain is sensed in various parts of the head, not confined to any nerve distribution area. In general, in hemangioblastoma patients, the supply of CSF fluid is interrupted, and this change in level causes headaches. Diagnosis of hemangioblastoma relies most heavily on histologic and immunophenotypic features with pieces of clinical, radiologic, and molecular information lending additional support.

Clinical signs and symptoms of hemangioblastoma are mainly attributed to the tumor's mass effect on adjacent regions, generalized increase in intracranial pressure, or obstruction of cerebrospinal fluid flow. General symptoms may include manifestations of increased intracranial pressure such as headaches, nausea, and emesis [40, 42]. Clinical presentation may vary widely based on the anatomic localization of the tumor. Cerebellar tumors often present with dysmetria and ataxia [42]. In contrast, patients with spinal hemangioblastomas often present with symptoms associated with radiculopathy and myelopathy, including hypesthesia, weakness, hyperreflexia, pain, and incontinence [44, 45]. Peritumoral cysts frequently underlie the clinical findings associated with hemangioblastomas, with at least 72% of symptomatic tumors but only 13% of asymptomatic tumors containing cysts [45]. In rare cases, hemangioblastomas may present with intraparenchymal, subarachnoid, or ventricular hemorrhage [47-49]. Hemangioblastomas most frequently arise in the posterior fossa [40, 45].

Hemangioblastoma is approximately 2% of the intracranial neoplasms and 2–10% of the primary spinal cord neoplasms [52, 53]. Highly vascularized tumors are mostly located in the cerebellum (45%–50%), followed by the spinal cord (40–45%) and brain stem (5–10%) [40, 55]. CNS hemangioblastoma usually presents unpredictable growth [23, 56, 57]. Although metastasize they can cause symptoms by tumor-related bleeding or compression of the adjacent structure. Both surgery and radiotherapy have a role in the management of CNS hemangioblastomas [58]. Most gross

total resection offers definitive therapy [58, 59]. Radiation therapy is also an option for residual, recurrent, or surgically inaccessible lesions [60, 61]. which collects cancer statistics that cover nearly 28% of the United States population, was used to identify a relatively large population-based cohort of patients with CNS hemangioblastomas.

This study analyzed what may be more generalizable than previously published literature with a relatively small case series [56, 59, 42-65]. Neoplasms whit an overall incidence of 0.141 per 100,000 person-years and the highest incidence among Caucasian males between ages 65–69.

Multivariate analyses, age at diagnosis, race, tumor location, number of tumors, and prior surgery are significantly associated with overall survival. However, gender, marital status, tumor size, the extent of tumor resection, and prior radiotherapy did not demonstrate significant associations with overall survival. Our study demonstrated decreased overall survival among patients with an age greater than 60 compared with younger patients, which was most likely caused by the shortened life expectancy in aged patients. Comorbid conditions that are associated with age may play a role in the mortality of aged patients. Furthermore, worse access to high-quality neuro-oncologic care in aged patients may also contribute to survival differences. a predominance of CNS hemangioblastomas in males, with a male-to-female ratio of 1.25:1 [60]. It was suggested that gender or race-specific oncological mutations and environmental and lifestyle factors may be associated with the differences in incidence [33, 34].

Nearly 34% of CNS hemangioblastomas appear in the context of VHL disease and the remainder appears sporadically [40]. 23.3% of the patients in this cohort have multiple hemangioblastomas, which were usually associated with VHL disease [63, 64].

5.2. Types of Hemangioblastoma

Hemangioblastomas are traditionally categorized as one of four types by either histology or imaging. Type 1 (5% of posterior fossa hemangioblastomas) is a simple cyst without a macroscopic nodule. Type 2 is a cyst with a mural nodule (60%). Type 3 is a solid tumor without cysts (26%), and type 4 is a solid tumor with small internal cysts (9%). Types 3 and 4 lesions predominate in the spinal cord. Of note, many authors have disputed the existence of type 1 (purely cystic tumors), questioning the quality of presurgical imaging (contrast not given or slice thickness limitations) or detail of histologic sectioning.

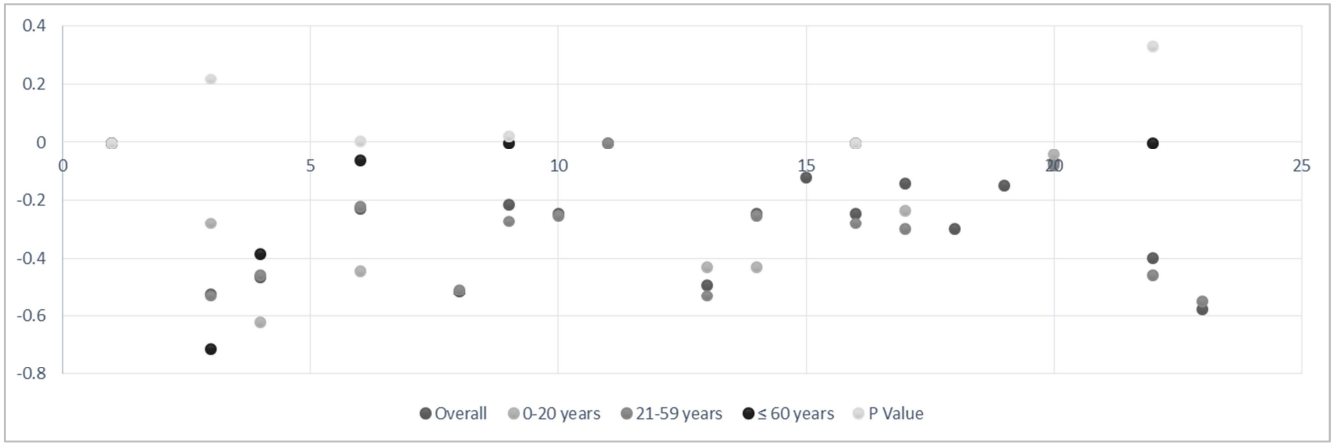

Figure 2. *General diagrams showing the age distribution of research by HB CNS, and differences in sex, tumor characteristics, and tumor location among three different age groups.*

5.3. Imaging Appearance

Hemangioblastomas are vascular tumors; thus, the solid tumor components demonstrate intense enhancement following contrast administration. It should be noted that when a cyst is associated with this tumor, it is a true "peritumoral cyst"; the wall does not enhance and the wall does not contain a tumor (see the section titled "Stages of Evolution," further on). Hemangioblastomas often have enlarged feeding vessels that may enhance or manifest as serpiginous hypointense flow voids on T2-weighted images.

Multiple lesions would suggest underlying VHL. A less common VHL-associated tumor that may be detected on CNS screening examinations is the endolymphatic sac tumor, which typically causes permeated destruction of the posterior surface of the temporal bone [27-32].

5.4. Stages of Evolution in Hemangioblastoma

Patients with sporadic tumors often present when the lesion has grown large enough to cause a marked mass effect, resulting in symptoms referable to the area of the lesion. In the case of type 2 hemangioblastomas (cysts with a mural nodule), the cystic component is typically the predominant feature and largely responsible for the degree of mass effect.

Screening of VHL patients will often detect small solid hemangioblastomas, which are asymptomatic. Surgical resection at this stage is associated with an unnecessary risk of neurologic injury. However, progression from solid tumor to cyst with mural nodule has been described in the VHL population, with surgery required for decompression of mass effect related to the

enlarging peritumoral cyst [35] 30% representing.

A study by Lonser et al. describes the development of peritumoral edema prior to the development of a peritumoral cyst. The mean time required for peritumoral edema to evolve into a cyst was 27 ± 19 months (range, 8 – 67 months) in the cerebellum and 47 ± 22 months (range, 9 – v72 months) in the spinal cord. Cases of sporadic (not VHL-associated) hemangioblastomas progressing from solid tumors to cysts with mural nodules requiring surgery have also been reported.

Peritumoral cysts develop as leakage of ultrafiltrate from the tumor into the surrounding normal brain parenchyma exceeds the parenchymal reabsorption rate. The resultant increase in interstitial pressure causes a cyst with a rim of gliosis to develop. This evolution is supported by reports of simple cyst drainage being insufficient for definitive management due to the prompt return of the cyst and associated mass effect.

The notion that hemangioblastomas follow a specific pattern of progression suggests that anticipation of this progression is important for the recommendation of follow-up imaging or timing of surgical resection. The importance of this evolution in the cerebellum has been the focus of this discussion. However, spinal lesions often present at earlier stages (solid tumor stage types 3 and 4) because of the smaller space of the spinal column; they often require earlier intervention due to mass effect.

6. Conclusion

This is the first study with an almost large sample size that focuses on headaches in patients with HB. After several analyses and a review of other studies, our study showed that patients in the pediatric/adolescent age group had more. In patients over 45 years of age, up to 79% of HBs occurred in the cerebellum and were solid in nature. The likelihood of HBs should be considered in elderly patients with cerebellar mass. And the most common apparent mechanism of disease onset in patients with headaches is very severe and is followed by nausea and vomiting. As the aggregate experience of neurosurgeons accrues and as surgical technology improves, the range of patients for whom surgery is a viable option to prevent devastating may expand.

Competing Interests

There is no other competing interest declared by the authors.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

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