Headache in Hemangioblastomas : A Histopathology and Structural

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Systematic Review

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Abstract

Hemangioblastoma (HBL) are rare, benign, s highly vascularized tumor of not well-defined 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. Single tumors may be sporadic, but multiple tumors are almost always associated with von Hippel-Lindau (VHL) disease. 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 meta-analysis was performed to evaluate headache 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. This meta-analysis was performed using Review Manager (RevMan) 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 1985 and 2010 by the senior author (A.AN) is Reviewed. The functional scale proposed by McCormick was used to evaluate the patients' neurological status before and after surgery. Adequate knowledge for 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.

Introduction

Hemangioblastoma (HBL) is highly vascularized tumor of not well-defined histological origin that is frequently associated with cysts[1]. HBL arises preferentially in 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 also may manifest as a sporadic tumor[2]. Although the tumor is histological benign, its multiplicity and eloquent location still make it one of the major causes of death of the patients[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 [8,9,10].

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)[17,18,19,20,21,22,16], 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 deficit and other, 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].

Methods

Research method

The following electronic databases (PubMed, MEDLINE, Embase, and Cochrane Library) were searched up to Jan 2014 using various combinations of MeSH headings and keywords such as “Hemangioblastoma,” “brain metastatic,” “Headache in Hemangioblastomas,” without restricting languages. Moreover, the references of all the identified eligible articles were manually searched for additional relevant citations.

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 intervene - tions 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 as long as they had not received prior cranial irradiation.

Outcomes assessed

The meta-analysis evaluated WBRT alone versus WBRT plus SRS and SRS alone versus SRS plus WBRT. The primary outcomes were overall survival following treatment, quality of life (QOL) measured using a validated health- related QOL scale, and neurocognitive function. The secondary outcomes were local

tumor control rate, neurological death, and adverse effects defined as acute/early (within 90 days of treatment) or late/delayed (after 90 days of treatment) morbidity.

Study quality assessment

Two reviewers independently assessed validity of the studies and evaluated the bias of each study 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.

Data extraction

Two reviewers extracted the data from all eligible RCTs. Median survival and local tumor control rates were extracted either directly or from survival curves, and hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for time-to-event data. 20 Data on other out comes 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.

Statistical analysis

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

Results

patient and tumor characteristics

From 1985 to 2010, 148 Patient 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 and sorted and used according to subject. The average duration of treatment for patients was about 3 months according to research. The most common symptom was headache (89%). Other symptoms included cervical headache, Nausea/ Vomiting, Ataxia, Dizziness, Pain, Sensory changes, Motor deficit and other. 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 Hipple-Lindo syndrome was diagnosed in these individuals. 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 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, metastatic effect of pituitary gland on participants' breast cancer, which varied from study to study.

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 [8,9,10].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 the intramedullary tumors are hemangioblastomas. 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 cancer syndrome known as von Hippel–Lindau (VHL) syndrome[9,10,11]. 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.

Table 1

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	(52.4%)	(28.1%)	(52.6%)	(71.3%)	0.221
Male	(46.5%)	(61.9%)	(45.5%)	(38.7%)	
Female					
Hydrocephalus or syringomyelia	(23%)	(44.6%)	(22.0%)	(6.45%)	0.001
VHL					
Location	(51.3%)	NA	(51.1%)	NA	0.019
Cerebellum	(21.5%)		(27.0%)		
Brainstem	(24.6%)		(25.2%)		
Spinal cord	(0.2%)		(0.5%)		
others					
Symptoms	(49.2%)	(42.9%)	(52.6%)	NA	NA
Headache	(24.6%)	(42.9%)	(25.2%)		
Nausea/Vomiting	(12.3%)	(23.8%)	(28.1%)		
Ataxia	(24.6%)	(4.8%)	(30.4%)		
Dizziness	(14.4%)		(8.1%)		
Pain	(30.5%)				
Sensory changes	(15.5%)				
Motor changes	(7.5%)				
others					
Tumor characteristics	(40.34%)	NA	(45.6%)	NA	0.330
Cystic	(58.00%)		(55.1%)		
Solid					
NA = not applicable.					

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 cyst (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.

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 tumor (see 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.

STAGES OF EVOLUTION IN HEMANGIOBLASTOMA

Patients with sporadic tumors often present when the lesion has grown large enough to cause marked mass effect, resulting in symptoms referable to the area of the lesion. In the case of type 2 hemangioblastomas (cyst 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 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.

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 tumor to cyst with mural nodule requiring seurgery 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 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 stages types 3 and 4) because of the smaller space of the spinal column; they often require earlier intervention due to mass effect.

Conclusion

This is the first study with an almost large sample size that focuses on age-related differences in patients with HB. After several analyzes and a review of other studies, our study showed that patients in the pediatric / adolescent age group had more spinal tumors, and 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 headache is very severe and is followed by nausea and vomiting.

Declarations

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Competing interests

There is no other competing interest declared by authors.

Availability of data and materials

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

Consent to publish

Not applicable.

Ethics approval and consent to participate

Not applicable.

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Figures

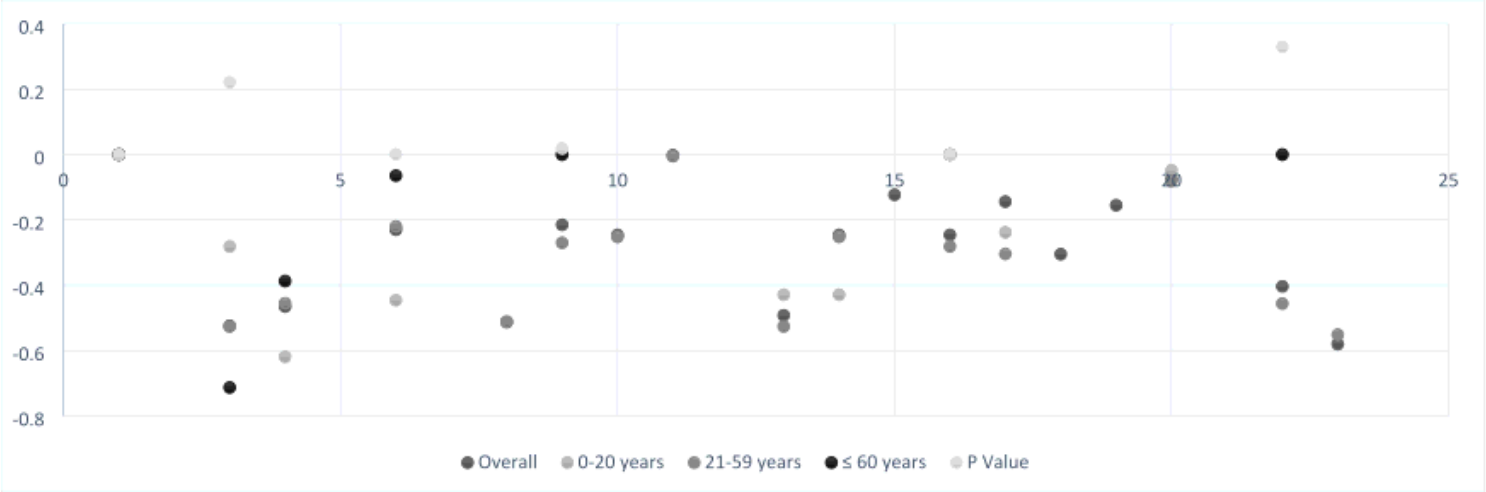

Figure 1

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.