Background: Posterior cranial fossa (PCF) hemangioblastomas are benign, highly vascularized, and well-differentiated tumors with well-described histopathologic features. Although relatively rare, this tumor is the most prevalent primary tumor of the cerebellum in adults.

Objective: Because the demographics of patients with such a tumor (as well as the clinical, morphologic, pathologic, surgical features, and outcomes) are not fully understood, we systematized characteristic patient and tumor features.

Methods: We undertook a systematic review of the English-language literature in PubMed for PCF hemangioblastomas in adults published in the past 31 years. We analyzed geographic distribution and year of publication of articles; demographic data of patients; presenting symptoms and clinical signs; tumor location and morphology; histopathologic features, extent of tumor resection, perioperative blood loss, and postoperative complications; length of hospital stay; and outcomes.

Results: We reviewed 207 articles describing 1759 infratentorial hemangioblastomas in a cohort of 1515 adult patients. We found female predominance in patients with Von Hippel-Lindau disease (VHLD) compared with male predominance in the general patient group. Symptoms of intracranial hypertension were more common in the VHLD group compared with the general group of patients. The cerebellar location was more common in the VHLD group and solid (parenchymatous) tumor was the most common type. Most patients underwent total resection but rate of resection did not differ between the general and VHLD groups. Most patients had a favorable outcome.

Conclusions: The literature of adult PCF hemangioblastomas is limited and general surgical experience with such tumors is scarce because of their rarity. Rates of postoperative complications and mortality remain higher than expected. However, prognosis and surgical outcomes are generally favorable. Nevertheless, surgery of adult PCF hemangioblastomas is a demanding and challenging task.

Introduction: Hemangioblastomas are relatively rare tumors of the central nervous system representing 1.5%–2.5% of all intracranial tumors and 7%–8% of all posterior cranial fossa (PCF) tumors. They mainly arise in the cerebellar hemispheres (76%), making them the most common primary neoplasm of the cerebellum in adults. These tumors are believed to appear more often in males than in females and are most common in the fifth and sixth decades of life. Single tumors may appear sporadically in the general population, but multiple tumors almost always occur earlier in life and in patients with Von Hippel-Lindau disease (VHLD) (35%). Many of the details of these tumors are not well known. These details include precise demographics, sex and geographic distribution of patients, rate of different morphologic types, and ratio of sporadic versus VHLD cases. Also not well known are the rates of...
resection, intraoperative blood loss for different tumor types, rate of different tumor locations within the PCF, proteins used for diagnostic staining, postoperative complications and their rates, mortality, and clinical outcomes. Whether a difference in these parameters exists between sporadic and VHLD cases is also unknown.

We reviewed all reports of PCF hemangioblastomas published in the past 31 years to investigate all these parameters. We also examined possible demographic disparity among patients of different origin and gender, as well as between those having sporadic tumors and VHLD tumors, comparing differences in tumor location and surgical outcomes. A systematic review of case reports and patient series was undertaken to summarize, synthesize, and better understand the literature results.

METHODS

Because no review protocol for the management of PCF adult hemangioblastoma exists, we performed a systematic review of all available literature over a span of 31 years (January 1, 1985—December 31, 2015). We used a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) structured checklist for our study.

Eligibility Criteria

We searched the PubMed/Medline database to identify all English-language articles that focused on the PCF hemangioblastomas.

Information Sources

We included case reports and series in the review, and excluded articles describing hemangioblastomas outside the PCF, as well as articles that included pediatric cases (<18 years old).

Search Strategy, Selection of Studies, Data Collection Process, and Data Items

Case reports and series were analyzed according to the year, country, and continent of publication. The articles included were analyzed for 9 parameters of interest: geographic distribution and year of publication of articles; demographic data, including age and gender of patients; presenting symptoms and clinical signs; tumor location and morphology; histopathologic diagnosis; the extent of surgical resection and perioperative blood loss; postoperative complications; length of hospital stay; and outcomes.

The age and gender of patients were analyzed and the medians, ranges, means, and standard deviations were calculated, as well as the presenting symptoms and clinical signs.

Tumor location within the PCF was identified as follows: cerebllum; brainstem; cerebellopontine angle; the fourth ventricle; cranioceval junction; and unspecified. Tumor morphology was analyzed and the immunohistochemical markers used for staining were noted.

The surgical parameters analyzed were the following: the extent of tumor resection; intraoperative blood loss; postoperative complications; and length of hospital stay. The extent of resection was listed as total, subtotal/near total, partial, or not operated on. Postoperative complications were categorized into intracranial; infections; those involving cranial nerves; gastrointestinal; cardiopulmonary; and other unspecified complications.

Outcomes were categorized as the following: favorable (no postoperative neurologic deficits and no postoperative complications); fair (mild postoperative neurologic deficit or postoperative complications); poor (debilitating postoperative complications or grave neurologic deficits); and death. The mortality was calculated from the articles that provided such information. All parameters were analyzed and compared between the patients with sporadic hemangioblastomas and those with VHLD.

Risk of Bias

The risk of any bias in interpretation of individual studies reviewed was avoided by using 2 authors who independently analyzed the data at the study results and outcomes levels. The same strategy was used to avoid the risk of bias that may affect the cumulative data across the studies reviewed and possible reporting of overlapping patients’ results.

Synthesis of Results

A methodical synthesis of the results collected was performed to summarize evidence and reach the conclusions.

RESULTS

General Information on Study Characteristics

A total of 207 articles were identified, screened, assessed for eligibility, and included in qualitative synthesis. Of these 207 articles, 54 (26%) were series and 153 (73.9%) were case reports. The median number of patients in each series was 14 (interquartile range, 7.75–33.25). The number of articles reporting adult PFC hemangioblastomas per year of publication is shown in Figure 1.

Any overlapping of patients’ results as well as major differences in surgical strategy and outcomes occurring over the years were not observed.

Geographic Distribution

Most of the articles (20.7%) were published in the United States, followed by Japan (18.8%), China (10.1%), and the United Kingdom, with (8.2%).

Demographics

The total number of patients in articles included in the review was 1515. Of these patients, 805 (53.1%) were male and 682 (45.0%) were female. Four articles did not provide information about patients’ gender. Individual age information was available in 187 articles (90.3%), which accounted for 542 patients (35.8%). The median age of those patients was 40 years (range, 15–95 years; interquartile range, 31–54 years). The mean age was 42.7 years, with a standard deviation of 15.62 years.
Of the 1515 patients, information about VHLD was available for 882 (58.2%) in 112 (54.1%) of the reviewed articles. A total of 379 patients were affected by the disease (43.0%), whereas 503 (57.0%) were unaffected. Of 379 patients with VHLD, individual age and gender were available for 140 and 305 patients, respectively. A total of 138 patients (45.2%) with VHLD were male and 167 (54.8%) were female. Age and gender for patients with sporadic hemangioblastomas were available for 173 and 203 patients, respectively. A total of 112 (55.2%) were male and 91 (44.8%) were female.

**Presenting Symptoms and Clinical Signs**

Presenting symptoms and clinical signs were available for 1010 patients (66.6%). The most common presenting symptoms and clinical signs were related to increased intracranial pressure (ICP) (50.4%), followed by
cerebellar signs (33.4%). All other presenting signs and symptoms accounted for the remaining 16.2%.

Of 882 patients with VHLD information, presenting clinical signs and symptoms were noted in 398 (45.1%). The distribution of symptoms between patients with VHLD and those with sporadic hemangioblastomas is shown in Figure 4. Polycythemia was reported in only 41 articles, which accounted for 75 patients with polycythemia and 165 patients without it. No further analysis of this finding was available.

Data about the tumor location were available in 204 articles (98.5%). Of the 1759 tumors, most (n = 1230) were located in the cerebellum, accounting for 70% (Figure 5). The second most common location was the brainstem (24.3%), followed by the fourth ventricle (1.8%), the cerebellopontine angle (1.8%), and the craniocephalic junction (1.6%). In 9 cases (0.5%), the exact tumor location within the posterior fossa was not specified. Both the patients’ VHLD status and tumor location data were available for 760 cases (43.2%). Distribution of tumor location within the PCF between patients diagnosed with VHLD and those with sporadic tumors showed no major differences between groups (Figure 6).

Tumor morphology data were available in 153 articles (73.9%), which accounted for 1014 tumors. Morphologically, 4 types of hemangioblastomas were described: solid hemangioblastomas were the most common (47.7%), followed by cystic (26.3%) and cystic with a mural nodule (21.3%), whereas tumors described as being both solid and cystic were the least common (4.7%) (Figure 7). Of 1014 tumors with described morphologic types, only 289 cases (28.5%) had information about both the tumor morphology and the patients’ VHLD status (Figure 8).

There were only 2 cases describing multiple lesions in patients without VHLD. One article reported the case of a 52-year-old man who had presented with 6 lesions. The second article reported the case of a 40-year-old woman who had multiple lesions. All other articles that provided information on the patients’ VHLD status reported cases of multiple lesions exclusively in patients who were VHLD positive.
Histopathology and Immunohistochemistry

A total of 142 articles (68.6%) offered information about the histopathologic diagnosis of hemangioblastoma.1,2,4,5,10,13,17-20,22,23,27,29,30,31,37,38,40,43,45,49,50,53,56,58,59,61-63,65-67,70-72,74,77-82,84-89,94-100,102,103,107-114,117,119-121,123-128,130,131,134,137,138,140-147,149-152,154-156,159,161,163-172,174-181,183,184,187,189-193,195-206,208,209

In addition to histopathology, information about immunohistochemical staining was available in 40 articles (19.3%).2,17,22,37,45,53,59,61,65,66,70-72,76,77,78,80,82,88,97,102,107,110,123,134,136,142,149,156,159,164,165,170,177,184,189,199,202,204,205

The 8 most common proteins...
stained are listed in Table 1. The Ki-67 protein was mentioned in 9 articles (4.4%).

### Extent of Tumor Resection and Blood Loss

A total of 164 articles (79.2%) provided information about the extent of tumor resection, accounting for a total of 1167 hemangioblastomas. Most hemangioblastomas were totally resected (88.5%), with subtotal/near total resection (2.3%) and partial resection (3.6%) a rarity. Tumors were not operated on in 5.6% of cases (Figure 9).

With regard to the extent of resection, information about patients’ VHLD status was available for 27.3% of patients among the 164 articles.
1,167 hemangioblastomas. Data for intraoperative blood loss were available in only 7.3% of articles. The mean blood loss reported was 675.85 ± 470.29 mL.

**Postoperative Complications**

Postoperative complications were reported in 54.1% of the 207 reviewed articles, which accounted for 610 patients (40.3%). The most common intracranial complications were postoperative hemorrhage, hydrocephalus, and pseudomeningocele, whereas meningitis and pneumonia were the most common infections. The types and rates of reported complications were steady yearly during all 3 decades (1985–1995, 1996–2005, and 2006–2015). For example, the reported intracranial complications were 40% and 39%, respectively, for the first and third decades.

Because there was only a small sample of patients with information about both their VHLD status and postoperative complications, we did not analyze the differences in types of complications between sporadic and VHLD cases.

**Outcome and Mortality**

Outcomes were described in 154 articles (74.4%), which accounted for 1,106 patients (73.0%). A favorable outcome was the most common result (73.9%), followed by fair outcome (11.1%), and poor outcome (4.7%). Postoperative mortality was reported in 80.7% articles. The overall mortality was 10.3% (Figure 11). There were no major differences in outcome between sporadic and VHLD cases.

We observed causes of death within 3 groups: those directly related to surgery, those in the early postoperative period (<15 days postoperatively), and those in the later postoperative period (>15 days postoperatively). The most common cause of death directly related to surgery was postoperative hematoma. The most common causes of death in the early postoperative period, generally, were infections (most commonly pneumonias), followed by gastrointestinal bleeds and complications caused by altered states of consciousness. Death occurred most commonly in the later postoperative period (>15 days).

**DISCUSSION**

To the best of our knowledge, our study is the only one of such scope and magnitude that has systematically surveyed and summarized the literature concerned with PCF hemangioblastomas in adults. Therefore, we believe that it is an important critical analysis of this rare and challenging entity.

**General Information on Study Characteristics and Demographics**

Our research identified 207 articles describing 1,759 adult PCF hemangioblastomas in 1,515 patients over the last 31 years. Overall, the sporadic cases were more prevalent than those of VHLD (57% vs. 43%). Single tumors may be sporadic, but multiple tumors almost always occur in patients with VHLD.
Most of the articles included in this review were published during the past 10 years (Figure 1), most commonly in the United States, followed by Japan, China, and the United Kingdom (Figure 2). When the continental distribution reflected the number of patients, patients from Asia (49.1%), Europe (30.9%), and North America (16.8%) were strongly predominant. However, it would be highly speculative to hypothesize that the rate of hemangioblastomas is highest in Asians, followed by whites. This finding clearly needs further investigation by adequate demographic research.

Case reports accounted for 73.9% of all articles. Furthermore, the median number of patients per series was 14. These 2 facts emphasize that the general experience in treatment of patients with PCF hemangioblastomas is not abundant even in subspecialized centers. In additionally, we did not observe any overlapping of patients’ results after analyzing the data.

Although heterogeneity of study designs was found in the included publications and the availability of mostly small series and case reports, all analyzed parameters were available in most publications; for example, outcomes in 74%, extent of tumor resection in 79%, histopathology in 69%, presenting signs and symptoms in 67%, VHLD data in 58%, and complications in 54% of articles.

The mean age of patients was 42.7 years, with a slight male predominance (53.1%). Previous data support our findings and emphasize that hemangioblastomas appear more often in males than in females, most commonly in the fifth and sixth decades of life. Nonetheless, the notation of female predominance among patients with VHLD is an original and novel observation of this study previously unrecorded in the literature.

**Presenting Symptoms and Clinical Signs**

Presenting symptoms and clinical signs were mainly related to tumor size and/or cyst-associated mass effect, if a cystic component was present, most commonly, increased ICP (50.4%). Increased ICP was more common in patients with VHLD (55%) than in the sporadic group (42%) (Figure 4), as was the rate of purely cystic tumors (31%–15%) (Figure 8), as well as with multiple tumors. Thus, one may speculate that cystic tumors having a larger volume and producing a greater mass effect, together with multiple tumors effect, are probably responsible for the increased ICP, which occurred more frequently in patients with VHLD than in the sporadic group.

**Tumor Location and Morphology**

Most tumors were located in the cerebellum (Figure 9) and the cerebellar location was slightly more frequent in patients with VHLD than in the sporadic group (Figures 5 and 6). Nonetheless, almost one third of PCF hemangioblastomas were of extracerebellar location.

Solid hemangioblastomas were the most common, followed by the cystic type (Figure 7). Some investigators advocated a typical morphologic spectrum of 60% mostly cystic and 40% mostly solid tumors, but this view is clearly disputed by our review, which showed an opposite ratio between solid and cystic tumors. The solid tumor type was most frequently represented in both sporadic and VHLD groups. This is a novel observation not recorded previously in the literature.

**Histology and Immunohistochemistry**

In most of the articles reviewed (55.6%), the tumors were histopathologically confirmed. Information about the immunohistochemical analysis was available in only a few articles (19.3%). This finding clearly points out the importance of including the detailed histologic features and immunostaining information in future reports. The most frequent positive staining, in decreasing order of frequency, was for vimentin, vascular endothelial growth factor, neuron-specific enolase, reticulin, CD 56, S-100, and inhibin, which all stained at more than 80% (Table 1).

**Extent of Tumor Resection and Intraoperative Blood Loss**

It has been stated that the complete tumor resection remains the most effective treatment for hemangioblastomas with minimal morbidity and mortality. Our study clearly affirms the first part of this statement and clearly disputes the second. Most hemangioblastomas disclosed by our research were totally resected (88.5%), with subtotal/total resection (2.3%) and partial resection (3.6%) being a rarity (Figure 9). Although marked improvements in management and technique have occurred over the last 3 decades, we did not record any major differences in surgical strategy over the years. Although it is well known that hemangioblastomas are highly vascularized tumors, the available blood loss data were too restrictive to be analyzed.

**Postoperative Complications**

Postoperative complications were reported in more than half (54.1%) of the reviewed articles. The most common complications were intracranial (31.5%), consisting of postoperative hemorrhage and hydrocephalus and pseudomeningocele formation (Figure 10). We did not record any major changes in type, rates, and types of complications over the years. Rate and ration of complications were similar in the first and third decade of the 31 years review span. This important and novel finding indicates that many patients can be expected to have some complication postoperatively. Accordingly, the same proportion of patients seemed to be prone to repeated surgery to avoid permanent neurologic deficits. Because almost half of the articles (45.9%) did not report complications, that number may be even higher. Thus, the surgeon should discuss this possibility with prospective patients. It is reasonable to speculate that patients with solid tumors may be more likely to have complications because of the bleeding propensity of that type of hemangioblastoma.

**Outcomes and Mortality**

It has been stated that after complete tumor removal, the prognosis and surgical outcomes are generally good. A favorable outcome was the most commonly recorded (Figure 11), and there were no major differences in outcomes between patients with VHLD and those having sporadic tumors.

Some previous reports recorded a mortality of 2% after complete tumor resection. However, we calculated an overall postoperative mortality of 10.3%, which was a significantly greater number than previously recorded in the literature. This is an important finding. Consequently, surgical management of adult PCF seems to be demanding.
Summary of Evidence and Limitations

There are no evidence-based guidelines for surgical management of posterior fossa hemangioblastomas in adults.

The limitations of this review are the heterogeneity of study designs found in the included publications, and the availability of only small series and case reports. Accordingly, postoperative complications incidence was high but almost certainly underestimated. Furthermore, some characteristics, such as intraoperative blood loss and the length of hospital stay, had too few details and number of samples to be conclusive.

CONCLUSIONS

There is a female predominance of PCF hemangioblastomas among patients with VHLD as opposed to male predominance in the sporadic group. The solid type of tumor is the most common type generally. The increased ICP symptoms are more common in patients with VHLD compared with the sporadic group (possibly because of a higher rate of cystic and multiple tumors in this group) and the cerebellar location is more common in the VHLD group.

Most patients undergo total tumor resection; the rate of resection does not differ between sporadic and VHLD groups and radical tumor resection rate is high (88.5%). However, the rate of postoperative complications (at least 40%) as well as postoperative mortality (10.3%) still seem to be high.

The literature of adult PCF hemangioblastomas is limited and general surgical experience with such tumors is scarce because of their rarity.

Prognosis and surgical outcomes are generally favorable. Nevertheless, surgery of adult PCF hemangioblastomas is a demanding and challenging task.

ACKNOWLEDGEMENTS

The authors wish to thank Julie Yamamoto, M.A., for her assistance with the English language editing and manuscript preparation and to Andrew J. Gienapp, B.A., for copyediting, preparation of the manuscript and figures for publishing, and publication assistance.

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Conflict of interest statement: F.A.B. serves as a consultant for Medtronic. The other authors report no financial relationships or conflicts of interest.

Received 28 September 2017; accepted 30 November 2017