Review Article

Posterior fossa hemangioblastoma in children: a literature review

Aline Rabelo Rodrigues[1], Pedro Lucas Bessa dos Reis[2], Gabriel Bagarolo Petronilho[3], Caio Araujo de Souza[4], Pamela Lopes Carvalho[5], Ricardo Santos de Oliveira[6], Rodrigo Inácio Pongeluppi[6], Matheus Ballestero[7]

[1] Universidade Federal de Jataí, Jataí, Goiás, Brasil

[2]Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brasil

[3] Centro Universitário Fundação Assis Gurgacz , Toledo, Paraná, Brasil

[4] Universidade Federal Fluminense, Niterói, Rio de Janeiro, Brasil

[5] Universidade do Vale do Sapucaí - UNIVÁS, Pouso Alegre, Minas Gerais, Brasil

[6] Division of Neurosurgery, Department of Surgery and Anatomy, University Hospital, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil

[7] Department of Medicine, Federal University of São Carlos, São Carlos, Brazil

✉ Matheus Ballestero, MD, PhD

e-mail: ballestero@gmail.com

Available at:
http://www.archpedneurosurg.com.br/

Introduction: Posterior fossa hemangioblastomas (HBs) are uncommon benign neoplasms, comprising 1.5-2.5% of intracranial tumors and 7-8% of posterior cranial fossa tumors. They predominantly impact the central nervous system, often localizing within the cerebellar hemispheres of individuals aged 50-60 years, with higher prevalence among adults and limited occurrence in the pediatric population. This review sheds light on the distinctive clinical characteristics of pediatric HBs

Methods: Employing the PRISMA guidelines, databases like SciELO, Lilacs, and PubMed were meticulously searched, deploying keywords "hemangioblastoma" and "posterior fossa." Inclusion criteria spanned articles published from 2003-2023 in English or Portuguese, focusing on pediatric cases.

Results: The search yielded 16 relevant articles from PubMed and 72 from Lilacs, with SciELO yielding no relevant results. Rigorous assessment against the predetermined criteria identified 10 pertinent articles from Lilacs discussing pediatric posterior fossa HBs, encompassing topics like imaging, pathophysiology, immunohistochemistry, and therapeutic modalities. Diverse themes were explored, including pregnancy-related manifestations, tumor growth patterns, and treatment approaches such as surgical resection, radiotherapy, neuronavigation, and presurgical embolization. Advanced imaging techniques, like high-resolution 3D multifusion medical imaging, were also explored.

Conclusion: Early diagnosis and a comprehensive multidisciplinary strategy are essential in managing pediatric posterior fossa HBs. Genetic insights and advanced imaging techniques, coupled with precise surgical interventions, play a pivotal role in improving prognosis and elevating the quality of life for patients. The genetic context of VHL mutations, the centrality of MRI in early detection, and the prominence of complete surgical resection underscore the multifaceted comprehension indispensable for effective management.

Keywords: neoplasm, tumor, posterior fossa, hemangioblastoma

INTRODUCTION

Posterior fossa hemangioblastomas (HB) are infrequent benign neoplasms, comprising approximately 1.5 to 2.5% of intracranial tumors and constituting 7 to 8% of tumors located within the posterior cranial fossa. They primarily impact the central nervous system, often manifesting within the cerebellar hemispheres of individuals aged between 50 and 60 years. Notably, they stand as the predominant primary cerebellar tumors among adults, while their occurrence within the pediatric age cohort is notably scarce(1).Pediatric hemangioblastomas have clinical singularities and differences compared to adult cases. VHL disease should be suspected in pediatric hemangioblastomas(1).These tumors manifest as highly vascularized growths originating from stromal cells that serve as precursors to blood vessels. Frequently characterized by the presence of cystic lesions housing sporadic singular mural nodules, they can prompt symptomatic presentations upon attaining substantial dimensions, engendering compression upon neighboring neural structures. Nonetheless, instances of these tumors presenting in multiplicity exist, often linked to Von Hippel-Lindau disease, typically affecting younger populations(2).

This sistematic review endeavors to underscore the imperative nature of early posterior fossa hemangioblastoma diagnosis, alongside elucidating the treatment modalities applicable to this neoplasm.

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MATERIALS AND METHODS

This literature review adheres to the methodological guidelines stipulated by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The investigation draws upon the following databases: Scientific Electronic Library Online (SciELO), Latin American and Caribbean Literature (Lilacs), and PubMed. The search strategy employed encompassed the utilization of the search descriptors "hemangioblastoma" and "posterior fossa," linked by the Boolean operator AND, across all aforementioned databases (Figure 1).

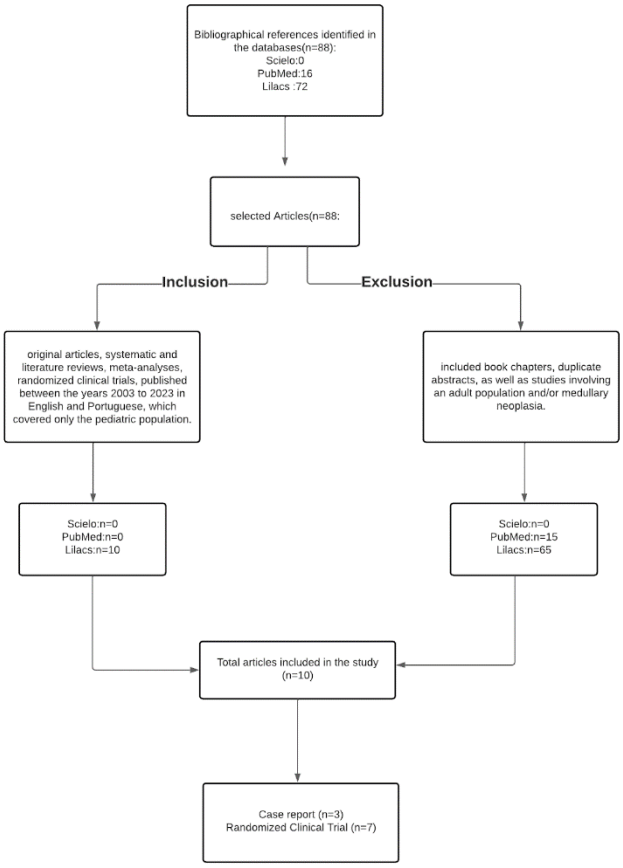

Figure 1 – PRISMA flowchart

The inclusion criteria encompassed original articles, systematic and literature reviews, meta-analyses, and randomized clinical trials, published between the years 2003 to 2023 in either English or Portuguese. These selected studies were constrained to the pediatric population and aligned with the research's defined objectives. Conversely, the exclusion criteria encompassed book chapters, redundant abstracts, as well as studies focused on adult populations and/or medullary neoplasms.

RESULTS

Following the implementation of the PRISMA framework, the outcomes revealed the following distribution across databases: SciELO yielded no articles meeting the criteria, PubMed produced 16 articles, and Lilacs generated 72 articles. Subsequent scrutiny of the retrieved articles against the stipulated inclusion and exclusion criteria specified in the methodology resulted in no qualifying articles from SciELO.zero, from PubMed, and zero article fulfilled the criteria Scielo , and from Lilacs 10 articles were identified that pertinently discussed imaging examinations in pediatric patients afflicted with posterior fossa hemangioblastomas.

DISCUSSION

he posterior fossa hemangioblastoma is a rare vascular neoplasm situated within the cranial cavity, predominantly localized in the posterior fossa compartment encompassing the cerebellum and brainstem. While its occurrence is more prevalent among adults, it can also manifest in the pediatric population. HB represent benign lesions characterized by pronounced vascularization, attributed to the functional impairment of the von Hippel-Lindau (VHL) gene. This genetic alteration results in a discernible local hypoxic microenvironment, subsequently triggering the activation of pathways associated with the hypoxia-inducible factor (HIF) as well as the vascular endothelial growth factor (VEGF), as elucidated by Laviv et al. in their work published in 2017 (3).

The work authored by Campero et al. (2) presents an examination of 16 cases of posterior fossa HB accompanied by a comprehensive review of the existing literature. Although the age range of the subjects incorporated into the study remains unspecified, the literature review encompasses fundamental aspects pertinent to posterior fossa hemangioblastomas, thereby potentially holding relevance for the pediatric population. The study underscores pivotal clinical attributes, diagnostic protocols, and available therapeutic avenues concerning these neoplasms, thereby furnishing a holistic portrayal of the subject matter.

For instance, the investigation conducted by Laviv and colleagues (3) delves into the manifestation of hemangioblastomas during pregnancy. This specific phase, characterized by pronounced physiological changes, is conducive to accelerated tumor hyperplasia, thus leading to the emergence of an acute presentation. The occurrence of this phenomenon tends to escalate post the 20th week of gestation; however, its underlying pathophysiological mechanisms remain yet to be fully elucidated.

Of note, the work by Laviv et al. (3) undertakes an exhaustive examination of a cohort exceeding 40 cases, consequently unearthing profound insights concerning pro-angiogenic factors. These discerned patterns cast a spotlight on the placental growth factor's role, which operates in

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tandem with an escalated expression of the vascular endothelial factor 1 receptor. It is noteworthy that these entities demonstrate an amplified presence specifically within the context of pregnancy(3).

Kim et al. (4) documented a case study involving a 57-day-old neonate who presented with primary motor seizures affecting the right arm and accompanying irritability. The pregnancy and delivery phases had transpired without any apparent complications. Upon neurological assessment, the neonate exhibited signs of right hemiparesis, alongside a conspicuously tense and protruding fontanelle, as well as lethargy.

The preoperative brain computed tomography (CT) scan revealed intracranial hemorrhagic lesions marked by cystic formations featuring fluid-fluid levels. These pathological changes were located within the left frontoparietal lobe and the left cerebellar hemisphere and vermis. The presence of perilesional edema further complicated the picture. Intracranial hemorrhage in the neonatal period remains an infrequent occurrence; however, when it does arise, it carries the potential for grave neurological repercussions. Crucially, the drainage of hematoma subsequent to bleeding plays a pivotal role in averting mass effect and neuronal tissue irritation. Such complications can arise when tumoral bleeding takes place in hemangioblasts following the rupture of delicate vascular structures, often in close proximity to seizure events.

It is worth noting that spontaneous intracranial hemorrhage in neonates bears a less favorable prognosis compared to adult counterparts. Rapid surgical intervention immediately following the initial lesion has been demonstrated to yield positive outcomes(4). As such, the timely identification and diagnosis of these instances emerge as paramount factors in ensuring a more favorable clinical trajectory for afflicted patients.

The utilization of Diffusion Weighted Imaging constitutes a pivotal aspect of the imaging diagnostic process. Onishi et al. (5) conducted a comprehensive analysis involving a cohort of 12 patient images, employing 3-T diffusion magnetic resonance imaging, to investigate posterior HBs in individuals devoid of von Hippel-Lindau disease. The same study encompassed the evaluation of 16 patients with brain metastases, aimed at establishing a clear demarcation between these two distinct types of tumors. It was observed that diffusion MRI coupled with a high b-value exhibited superior accuracy in discerning diffusion patterns compared to conventional b-value approaches.

Significantly, the apparent diffusion coefficient (ADC) values associated with hemangioblastomas were statistically found to be notably higher than those corresponding to metastatic tumors, particularly at b-values of 1000 and 4000 ($P < 0.0001$). Furthermore, this study underscored the indispensable role of this imaging modality in facilitating the exclusion of differential diagnoses (5).

To enhance diagnostic insights, a comparative analysis of diffusion images and ADC values comes highly recommended. Such an approach is particularly valuable due to the capacity of these mismatch patterns and cellularity assessments within central nervous system structures, which serve as potent predictors in effectively distinguishing tumors from other non-tumoral lesions.

In the context of immunohistochemistry, the cells constituting hemangioblastomas exhibit an origin rooted in the glial or neuroepithelial lineage. A noteworthy conjecture posits that stromal cells might express microtubule-associated protein 2 (MAP 2), an antigen found in both neoplastic cells and neural glial entities. An intriguing retrospective study, juxtaposing the quantification of inhibin against MAP 2, revealed the expression of MAP 2 by stromal cells in 32 out of 48 (67%) hemangioblastoma samples through immunohistochemistry. However, this investigation highlighted that MAP 2 manifests reduced specificity in distinguishing between clear cell tumors of the central nervous system (CNS) and glial cells (6).

In a distinct publication, malafronte et al.(6) elucidate the pivotal antigenic signaling pathways, encompassing VEGF/VEGFR2 and EphB4/EphrinB2 pathways. These pathways wield significant roles in vascularization growth and the signaling mechanisms guiding tumor proliferation. This insight was gleaned from the examination of surgical specimens retrieved from two patients afflicted with hemangioblastomas.

Following surgical resection, the therapeutic continuum extends to radiotherapy. Abboud et al. (2020) narrate the case of a 16-year-old patient beset by recurrent headaches. Imaging showed a cerebellar tumor measuring a diameter of 70 mm. The surgical intervention resulted in partial resection due to the intricate placement of the tumor and the attendant risk of intraoperative hemorrhage. Despite the procedure, there was no discernible amelioration in the patient's clinical presentation.In this scenario, a prescribed radiation dose proved to be a viable recourse, culminating in tumor regression within a three-month timeframe,without additional cerebellar damage. Notably, only grade 1 alopecia materialized alongside improvements in the patient's clinical symptoms(7).

We must remember that the most effective treatment for these patients involves the complete removal of the hemangioblastoma. To achieve this goal, the use of neuronavigation is imperative. Neuronavigation helps guide the surgical process, ensuring that vital areas with essential functions remain unaffected. This approach is crucial to prevent unintended damage. In support of this notion, the study conducted by Chen et al. in 2012 strongly underscores the significance of neuronavigation. Their research

demonstrated that patients with posterior fossa hemangioblastomas who underwent resection with the aid of a neuronavigation system experienced numerous benefits. These advantages encompassed the absence of complications, reduced bleeding time, enhanced visibility of the tumor field, which facilitated its complete removal, minimized unintentional harm to neighboring normal structures, shorter surgery times, fewer complications, and a decrease in mortality rates(8).

Furthermore, the preoperative embolization technique proves beneficial for cases involving deeply situated feeding arteries that are challenging to coagulate during surgery. Sakamoto et al. (2012) conducted a retrospective study focusing on this aspect. In their investigation, they evaluated 15 cases, analyzing clinical outcomes and complications. Among these cases, 8 involved surgical excision without presurgical embolization, while 7 cases underwent excision after presurgical embolization. The embolization was accomplished using Guglielmi detachable coils with or without polyvinyl alcohol (GDC ± PVA) in 4 cases, and solely n-butyl 2-cyanoacrylate (NBCA) in 3 cases. Notably, the utilization of NBCA for presurgical embolization proved to be a secure method that led to reduced blood loss in cases involving posterior fossa hemangioblastomas (9).

For the effective resection of hemangioblastomas, a precise and detailed understanding of their location is imperative. This entails a comprehensive preoperative assessment that accurately pinpoints the positions of both the supplying arteries and the draining veins. As a result, both the choice of imaging studies and the selected techniques play a pivotal role in this process.

In their 2017 article, Yoshino et al. elucidate the utilization of high-resolution 3D multifusion medical imaging (hr-3DMMI) as a crucial component of preoperative planning for HB. This imaging modality seamlessly combines magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), thin-slice computed tomography (CT), and rotated 3D angiography. These techniques culminate in the creation of a comprehensive 3D image. Yoshino et al. employed this sophisticated approach to assess 5 patients during the preoperative phase, subsequently comparing these images to intraoperative findings. Impressively, the images faithfully replicated the surgical observations, illuminating the intricate network of arteries and veins associated with tumor drainage.

Furthermore, Yoshino et al. (2017) conducted a comparative analysis involving hr-3DMMI and other 3D imaging methodologies, such as 3D computed tomography (CTA) and 3D magnetic resonance imaging (MRI). They found that these alternative methods failed to yield spatial images that accurately reflected intraoperative conditions. Notably, the authors highlighted that the spatial resolution provided by 3D rotational angiography (3DRA) surpassed that of both 3D CTA and 3D MRA, enabling superior visualization of all nourishing arteries.

In summary, the achievement of successful hemangioblastoma resection necessitates a comprehensive and meticulous understanding of the tumor's precise location, a task that hinges upon the strategic utilization of advanced imaging techniques like hr-3DMMI. This approach, as demonstrated by Yoshino et al., offers unparalleled insight into the complex vascular structures associated with these tumors, ultimately contributing to more informed and effective surgical interventions.

CONCLUSION

In conclusion, this literature review on posterior fossa hemangioblastoma in children has underscored the significance of early diagnosis, genetic investigation, and appropriate treatment to achieve improved outcomes. With advancements in MRI, genetic research, and therapeutic techniques, the multidisciplinary approach is expected to continually enhance the prognosis and quality of life for these children.

In the genetic context, mutations in the VHL gene (Von Hippel-Lindau) are associated with a higher risk of developing hemangioblastomas. MRI continues to stand out as the primary imaging test for the early diagnosis of tumors, and complete surgical resection of the tumor remains the primary treatment method, yielding favorable results in the majority of cases.

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DISCLOSURES

Ethical approval

This study was executed in adherence to the principles outlined in the Declaration of Helsinki. Notably, no formal approval was necessitated, given the nature of the study as a literature review article

Conflict of interest

The authors declare no conflicts of interest with respect to the content, authorship, and/or publication of this article.

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CONTRIBUTIONS

-Aline Rabelo Rodrigues: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft
-Pedro Lucas Bessa dos Reis: Data curation, Formal Analysis, Investigation, Writing – original draft
-Gabriel Bagarolo Petronilho: Data curation, Formal Analysis, Writing – original draft
-Caio Araujo de Souza: Data curation, Formal Analysis, Writing – original draft
-Pamela Lopes Carvalho: Data curation, Formal Analysis, Writing – original draft
-Ricardo Santos de Oliveira: Conceptualization, Investigation, Methodology, Visualization, Writing – review & editing
-Rodrigo Inácio Pongeluppi: Investigation, Methodology, Visualization, Writing – review & editing
-Matheus Ballestero: Conceptualization, Investigation, Methodology, Visualization, Supervision , Writing – original draft, Writing – review & editing

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