REVIEW

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Comprehensive Review of Primary Posterior Fossa Tumors in Children

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Abstract

Approximately 50% of central nervous system tumors in children are primary posterior fossa tumors, ranking as the most common solid tumors in childhood. The most frequently encountered types are medulloblastoma, pilocytic astrocytoma, ependymoma, and brainstem gliomas. In addition, less common pathologies such as atypical teratoid/rhabdoid tumors, hemangioblastomas, schwannomas, cerebellar gangliocytomas, and epidermoid tumors are also present. This study comprehensively compiles the epidemiological, histopathological, radiological, and clinical characteristics of pediatric posterior fossa tumors considering current classifications, along with a detailed review of treatment approaches.

Keywords: Pediatric tumor, posterior fossa tumor, medulloblastoma, review

INTRODUCTION

The posterior fossa is a critical area in the human brain, housing vital structures such as the medulla, pons, mesencephalon, and cerebellum (1). Physicians across various specialties encounter posterior fossa lesions. Understanding the clinical presentation, differential diagnosis, investigations, and treatment of these lesions is crucial for all clinicians involved in the care of patients with such medical conditions. Referral of patients suspected or diagnosed with posterior fossa lesions to appropriate specialties is mandatory.

The posterior fossa is bounded anteriorly by the dorsum sella, the posterior part of the sphenoid body, and the clivus; posteriorly by the squamous part of the occipital bone and the petrous and mastoid parts of the temporal bone; and superiorly by a small part of the mastoid angle of the parietal bone. The cerebellum contains parts of the brainstem, including the pons and medulla, and the fourth ventricle (2). Lesions in the posterior fossa can be categorized on the basis of their etiology and classified as vascular, infectious, traumatic, neoplastic, or according to their anatomical location within the posterior fossa. These tumors are differentiated into intra-axial and extra-axial tumors based on their relationship with the pia mater. Intra-axial tumors originate from the brain stem, cerebellum, or fourth ventricle. Tumors that arise from the tissues of the posterior fossa are called primary tumors, whereas those spreading metastatically from another organ are termed secondary posterior fossa tumors. Posterior fossa tumors can occur in both adults and children, with approximately half of pediatric brain tumors developing in this region (3).

This study aims to review the most commonly observed primary pediatric posterior fossa tumors such as medulloblastoma, pilocytic astrocytoma, ependymoma, and brainstem gliomas, as well as less common types such as atypical teratoid/rhabdoid tumors, hemangioblastomas, schwannomas, cerebellar gangliocytomas, and epidermoid tumors, and to describe the treatment methods applied to these tumors.

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The Most Common Primary Posterior Fossa Tumors in Children

Medulloblastoma

Medulloblastoma is the most prevalent primary posterior fossa tumor in the pediatric age group, accounting for 30-40% of such cases. It is also the most common malignant brain tumor in childhood (4). Medulloblastoma occurs more frequently in males, with a bimodal peak incidence at ages 3 and 9. Before the 2016 World Health Organization (WHO) classification, these tumors were divided into histological variants: classic, large cell, anaplastic, desmoplastic/nodular, and extensive nodular types. In the new molecular era, various intracellular mechanisms have been discovered, including the deregulation of Sonic Hedgehog (SHH) and Wingless (WNT) signaling pathways. The recent classification includes groups based on genetic identification of medulloblastomas, namely WNT-activated, SHH-activated TP53 mutant, SHH-activated TP53 wild type, and non-Wnt/non-SHH (subgroups Group 3 and Group 4) (5). Thus, the 2016 WHO classification identifies medulloblastomas by both histological variants and genetic definitions (6). Each molecular subgroup displayed distinct methylation and gene transcription features, epidemiology, recurrence patterns, clinical findings, and prognosis. The 2021 WHO classification consolidates all histological subtypes under the single term "medulloblastoma, histologically defined" (7) (Table 1). This approach, which incorporates genetic changes, emphasizes the importance of molecular biology in determining the prognosis of medulloblastoma, suggesting that molecular changes, rather than histological variants, define tumor behavior (8).

Table 1. WHO 2021 Classification of tumors of the CNS, medulloblastoma classification

Medulloblastomas, molecularly defined
Medulloblastoma, WNT-activated
Medulloblastoma, SHH-activated, and wild-type TP53
Medulloblastoma, SHH-activated and TP53-mutant
Medulloblastoma, non-WNT/non-SHH Group 3 Group 4
Medulloblastomas, histologically defined

WHO: World Health Organization, CNS: Central nervous system

Like all posterior fossa tumors, medulloblastomas typically present with symptoms indicative of increased intracranial pressure. Tumors located in the fourth ventricle may cause obstructive hydrocephalus. Early symptoms commonly include headache and vomiting, whereas later stages may present with cerebellar signs such as ataxia, nystagmus, and dysmetria (9). On magnetic resonance imaging (MRI), medulloblastomas typically appear as round lobulated masses with iso-hypointense signals on T1-weighted sequences and heterogeneous iso-hypointense signals on T2-weighted sequences, showing irregular, patchy, or focal contrast enhancement (4).

The crucial part of medulloblastoma treatment is the determination of prognostic factors. Before treatment, these factors are considered to be select appropriate therapy modalities. The most common prognostic classification used is the Chang Staging System, as shown in Table 2 (10) (Table 2). Patients were categorized into standard-risk and high-risk groups before treatment. High risk is considered in patients over 3 years of age with metastases and postoperative residual tumor greater than 1.5 cm^3 (11). During childhood, male gender is a poor prognostic factor. Postoperative radiotherapy (RT) doses and chemotherapy (CT) agents are determined on the basis of these risk groups. Treatment involves maximal surgical resection, craniospinal RT, and CT in children over 3 years. In children under 3, RT is delayed until after the age of 3, and these children receive intensive CT.

Pilocytic Astrocytoma

Pilocytic astrocytoma is the most common low-grade tumor in children and ranks second among primary posterior fossa tumors in childhood, accounting for 25-35% of these tumors (12).

Table 2. Chang's staging system

T1: Tumor <3 cm	M0: No metastasis
T2: Tumor ≥3 cm in diameter	M1: Tumor in the CSF
T3a: Tumor >3 cm in diameter with extension producing hydrocephalus	M2: Intracranial tumor beyond the primary site
T3b: Tumor >3 cm in diameter with unequivocal excision into the brainstem	M3: Gross nodular seeding in the spinal subarachnoid space
T4: Tumor >3 cm in diameter with extension up past the aquaduct and/or down past the foraman magnum	M4: Metastasis outside the cerebrospinal axis

CSF: Cerebrospinal fluid

The average age at diagnosis was between 6 and 8 years, and there was no significant gender predominance. The prognosis of pilocytic astrocytomas is generally favorable because of the tumor's low grade and slow growth rate, with an average 10-year survival rate exceeding 90% (13). However, the rate of tumor recurrence postoperatively is close to 50% (12). In the 2021 WHO classification, pilocytic astrocytomas are placed under the subheading of "circumscribed astrocytic gliomas", separate from diffuse astrocytomas (7). These tumors are often sporadic, arising from translocations or activation of mutations in the *BRAF* gene. BRAF-KIAA fusions are responsible for pilocytic astrocytomas occurring in cerebellar pathways (14).

Pilocytic astrocytomas classically present as a cerebellar mass composed of a large cyst and a solid nodule. On magnetic resonance imaging, the cystic fluid appears slightly hyperintense on T1-weighted sequences and hypointense on T2-weighted sequences. The solid component shows homogeneous contrast enhancement.

As with all low-grade tumors, gross total resection is the primary treatment method, depending on the location of the lesion. If tumor recurrence develops despite total resection, if the tumor has been subtotally removed and residual tumor causes neurological deficits, or if the subtotally resected tumor progresses radiologically, adjuvant therapies such as RT or CT can be considered. Common CT agents used in clinical practice include temozolomide, vemurafenib, and vinblastine (15).

Ependymoma

Ependymomas are the third most common primary posterior fossa tumors in children, accounting for 10-15% of such cases (16). They most often originate from the base of the fourth ventricle. Previously classified on the basis of histological variants, the 2021 WHO classification now divides them into two groups, A and B, on the basis of DNA methylation patterns, as shown in Table 3. Group A ependymoma exhibit significantly increased methylation of CpG islands in promoter regions compared with Group B ependymomas and are associated with worse prognosis (7). Group A ependymomas are characterized by chromosomal balance and are more common in infants and young boys, with an average survival of approximately 65%. Group B ependymomas show chromosomal instability and are more common in girls over 5 years old, with an average survival of 80-90%. Group A typically presents in paramedian and lateral locations, whereas Group B is usually found in the midline (17).

Table 3. Classification of posterior fossa ependymomas

Group A	Group B
Choromosomal balance	Choromosomal instability
Predominantly infants and children	Predominantly >5-year- old children
Male > female	Female > male
A more lateralized location	A more centralized location
Worse prognosis	Better prognosis

In pediatric ependymomas, gene amplifications in chromosomes 1q, 7, and 9 are most frequently reported (18). In addition, approximately three-quarters of cases show deletions in chromosome 22 (19). Other chromosomal deletions include 1p, 3, 6, 6q, 9p, 13q, and 17 (18). Childhood ependymomas may also have translocations involving chromosomes 1, 11, and 22 (19).

Optimal MRI for ependymomas should include spinal MRI to evaluate metastases. These tumors show heterogeneous contrast enhancement and may rarely present with intratumoral hemorrhage. On MRI, the masses can be solid or may have cyst and mural nodule formation. Differential diagnosis should consider tumors such as pilocytic astrocytoma, ganglioglioma, and pleomorphic xanthoastrocytoma. Ependymomas typically appear as iso-hypointense lesions on T1-weighted sequences and as iso-hyperintense lesions on T2-weighted and FLAIR sequences (20).

Surgical intervention followed by RT is the primary treatment for most pediatric posterior fossa ependymomas. The overall survival rate for patients with near-total resection ranges from 67 to 93%. In patients where only subtotal resection is possible, the average survival may drop to 22-52% despite RT (21). Recurrence occurs locally in approximately 80% of cases, with isolated distant recurrence occurring in 3-9% of cases. This usually occurs in higher-grade tumors and is associated with a poor prognosis (22,23).

RT is typically indicated after excision in children over 12 months old, in cases without tumor spread, for WHO grade III tumors, and in non-completely resectable WHO grade II ependymomas. Better local control is achieved when high-dose radiation includes a 1-cm margin around the tumor (22). Delaying RT until the age of 3 years has been reported to increase the rate of recurrence (16). However, in completely resected posterior fossa group B ependymomas, the chance of recurrence is low, and RT may not be necessary. CT may be considered in infants under 1 year of age to prevent or delay radiation toxicity or in high-risk patients before radiation or a second surgical intervention (24). Recurrences are typically treated with re-surgery and CT. Some subgroups that respond to chemotherapeutic agents such as cyclophosphamide, vincristine, cisplatin, and etoposide may not require RT. In particular, in children under 3 years of age

and in cases with metastatic ependymomas, high-dose use of chemotherapeutic agents such as methotrexate, vincristine, cisplatin, cyclophosphamide, and vinblastine is recommended (20).

Brainstem Glioma

Before the 2016 WHO Classification of Central Nervous System Tumors, the most commonly encountered brainstem tumor was known as diffuse infiltrative brainstem glioma. These gliomas usually originate from the pons part of the brainstem and can extend rostrally and caudally, making total resection impossible. Although the average age at diagnosis is 7, they are most commonly observed in children aged 5-10 years, and the average survival time is typically less than one year (25).

Recent molecular biological studies have identified histone H3 alterations in 85% of these gliomas (26). The 2016 WHO classification introduced the term "diffuse midline glioma, H3 K27M-mutant" in reference to the presence of an amino acid mutation in histones 3.3 and 3.1 (27). In the 2021 WHO classification, these tumors have been renamed diffuse midline gliomas, H3 K27-altere, to account for other possible molecular changes (7).

Because of the tumor's infiltrative nature and the delicate structures of the brainstem, diagnostic surgery is not recommended, and diagnosis is made through MRI (28). On T1-weighted MR images, the lesions appear hypointense, whereas on T2-weighted images, they have a heterogeneous hyperintense appearance, with patchy contrast enhancement observed on contrast-enhanced series. Pediatric diffuse infiltrative brainstem gliomas still have an extremely poor prognosis. Focal conventional RT (total dose of 60Gy, 1.5-2 Gy/day, approximately 6 weeks) is administered as the standard treatment (29). Various CT applications and agents, such as adjuvant CT, pre-RT CT, high-dose CT, and concurrent CT-RT, have been attempted without significant improvement in survival duration (30). However, research on monoclonal antibodies, immunotherapy, and various CT protocols ongoing.

Less Common Primary Posterior Fossa Tumors in Children

Atypical Teratoid Rhabdoid Tumor

Atypical teratoid rhabdoid tumor (ATRT) is a rare embryonal tumor, highly vascularized, and aggressive, constituting 1-2% of childhood brain tumors (31). It predominantly affects children under the age of 2 years and is more common in males. The usual location is the posterior fossa. Radiological findings are non-specific; they can mimic the morphological features of choroid plexus papillomas and medulloblastomas. Although some reports indicate better outcomes, the average survival time is less than one year.

In the WHO 2021 classification, ATRTs are categorized under the heading of "Other Embryonal Tumors of the Central Nervous System" (7). ATRTs are currently divided into three subgroups based on gene overexpression: AT/RT-MYC, AT/RT-SHH, and AT/RT-TYR. AT/RT-SHH and AT/RT-TYR commonly occur in the posterior fossa. While AT/RT-TYR is typically seen in infants under 2 years of age, AT/RT-SHH is more prevalent in older children (32).

Radiological findings are non-specific. ATRTs can appear as heterogeneously thick-walled cystic masses with extensive necrosis, hemorrhage, or calcification areas. Immunohistochemistry is valuable for differential diagnosis. Rhabdoid cells, EMA, SMA, and vimentin are positive biomarkers. The absence of INI1 staining is also significant (33). Molecular studies have shown mutations in the rhabdoid tumor suppressor gene (INI1/hSNF5), a member of the SWI/SNF chromatin remodeling complex, on the long arm of chromosome 22q11 in ATRTs. The most definitive diagnosis of ATRTs currently is made through immunohistochemical or fluorescence in situ hybridization demonstration of inactivation or deletion of SMARCB1/INI1, along with loss of expression in tumor cell nuclei, and focal positivity for EMA and smooth muscle actin (34).

Optimal treatment for atypical teratoid rhabdoid tumors remains uncertain. Despite treatment regimens consisting of maximal surgical resection, focal and craniospinal RT, and multiple chemotherapeutic agents, the course of the disease is poor. Most cases show rapid recurrence and progression, leading to a high mortality rate.

Hemangioblastoma

Although hemangioblastomas constitute 1-3% of intracranial masses in all age groups, they are less common in children. Up to 25-40% of cases are associated with Von Hippel-Lindau (VHL) syndrome, in which multiple masses can be present. Cases related to VHL syndrome generally occur in younger patients. Approximately 48% of VHL-associated hemangioblastomas are located in the cerebellum and 12% in the brainstem (35).

VHL disease results from mutations in the VHL gene on chromosome 3p25-26, leading to the loss of function of the pVHL tumor suppressor protein. The main function of this protein is the regulation of vascular endothelial growth factor, and its loss leads to neoplastic formations such as hemangioblastoma (36).

On MRI, the tumor cyst appears isointense to cerebrospinal fluid on T1-weighted sequences and isohyperintense on T2-

weighted sequences. Hemorrhagic findings are common. The tumor nodule stains intensely with the contrast material. Digital subtraction angiography may show tumor staining and varying degrees of arteriovenous shunts (37).

In cases of both sporadic and VHL-associated cerebellar hemangioblastomas, the goal is the total removal of the tumor to prevent residue and recurrence, following general principles. In sporadic cases with a single lesion, surgical treatment is preferred, and most cases do not recur following complete resection (35). Hemangioblastomas are highly vascularized by nature; hence, preoperative embolization may be considered in some cases to facilitate surgery.

For patients with VHL-associated hemangioblastomas who undergo multiple surgeries throughout their lives, craniospinal and infratentorial RT is considered an important potential treatment option. It is believed to reduce the tumor growth rate compared with its natural course, decrease the number of surgical interventions, and improve overall management (38).

Schwannoma

Schwannomas comprise 6-8% of intracranial primary tumors. Approximately 80-90% of all cerebellopontine angle tumors originate from the 8th cranial nerve and are known as acoustic schwannomas, whereas approximately 8% originate from the 5th cranial nerve and are called trigeminal schwannomas (39). In the pediatric age group, schwannomas constitute approximately 2% of posterior fossa tumors and are much less common compared with the adult population. In children, they can occur sporadically but are often associated with neurofibromatosis type 2 (NF2).

Diagnosis is made earlier in patients with NF2 than in sporadic cases because of characteristic symptoms of NF2 or the mass effect of bilateral vestibular schwannomas (39). The most significant indicators of disease severity are the age of symptom onset and the age at diagnosis. The majority of NF2 patients have vestibular schwannomas (40). NF2 diagnosis criteria include 1) bilateral vestibular schwannomas or a family history of NF2 and 2) the presence of unilateral vestibular schwannomas at a young age or any two of meningiomas, gliomas, schwannomas, juvenile posterior subcapsular lenticular opacities/juvenile cataracts (39,41). Developments in molecular biology have shown that defects on chromosome 22q12 are involved in the development of both sporadic and NF2-associated vestibular schwannomas.

On MRI, schwannomas appear as well-circumscribed, isointense or hypointense on T1-weighted images and hyperintense on T2. They show homogeneous contrast enhancement. Large tumors may show heterogeneous enhancement in the presence of intratumoral hemorrhage or cystic components (42). Histopathological examination is essential for a definitive diagnosis.

Asymptomatic vestibular schwannoma cases in NF2 patients or those with normal hearing on the lesion side can be managed conservatively regardless of mass size, as schwanomas are very slow-growing tumors. However, if there is hearing deterioration or other neurological symptoms, other treatment options should be considered. These include surgery and stereotactic radiosurgery (SRS). Surgery is preferred if the tumor size exceeds 1.5 cm, shows rapid progression even if smaller than 1.5 cm, or causes brainstem compression or hydrocephalus (43). The goal of surgery is total tumor resection although subtotal resection may be necessary to preserve the facial and vestibular nerves. Patients who benefit most from surgery are those with a small tumor diameter, better hearing function, younger age, and no family history or symptoms of NF2 (43).

The effectiveness of SRS in treating vestibular schwannomas is indisputable, and research in this area is increasing, especially as the main principles in NF2 treatment are function preservation, symptom relief, and quality of life improvement. Studies suggest that outcomes are better when diagnosed early (44). However, debates continue regarding SRS treatment in children because of the unexplored risks of radiation therapy at a young age.

Cerebellar Gangliocytoma (Lhermitte-Duclos Disease)

Dysplastic cerebellar gangliocytoma, also known as Lhermitte-Duclos disease (LDD), is a disorder characterized by abnormal development and hamartomatous features of the cerebellum. Although histologically overlapping with gangliocytoma, it is more of a hamartomatous malformation with enlarged dysplastic cells than a true neoplasm (45). In the 2016 WHO classification, it is listed under "glioneuronal and neuronal tumors" as "Dysplastic Gangliocytoma of the Cerebellum, Lhermitte-Duclos disease" and is considered a benign (WHO Grade I) tumor (6).

This rare pathology, which can occur at any age but more frequently in late childhood and adolescence, has recently been associated with phacomatosis and Cowden syndrome (CS) (45). CS is a very rare, autosomal dominant condition closely associated with malignant tumors (46). Approximately 40% of LDD cases are proposed to be associated with CS. In addition, there are sporadic cases of LDD that occur in childhood.

Histopathologically, there is diffuse hypertrophy in the granular layer and mature ganglion cells with dysplastic features.

The presence of perivascular lymphocytic infiltration and the absence of glial neoplastic characteristics are important for diagnosis. Immunohistochemically, loss of PTEN protein production is frequently observed, with most mutations reported in the germline. Staining of neurofilaments, MAP2 protein, synaptophysin, chromogranin A, and S-100 proteins has also been demonstrated (47).

In LDD, the lesion is located in the cerebellar hemispheres and vermis. Bilateral LDD involving both cerebellar hemispheres has been reported. On MRI, T1-weighted sequences showed linear hypointense structures and T2-weighted sequences showed typical tiger-stripe-like hypertrophy of the cerebellar folia. Concomitant white matter atrophy is also present.

In LDD patients with CS, conservative treatment may be an option if there are no neurological signs or symptoms of cerebellar gangliocytoma and the tumor progresses slowly. However, the possibility of tumor progression should be considered during follow-up. There are two surgical options. If symptoms related to hydrocephalus develop, a shunt can be placed. The other option is surgical resection. There is no capsule formation at the margins of LDD, and it is a diffuse tumor, making it difficult to distinguish from normal cerebellar tissue. Therefore, surgical resection can be challenging and carries a risk of morbidity.

Epidermoid Tumors

Epidermoid tumors are rare benign tumors that arise from intracranial remnants due to incomplete separation of the neuroectoderm from the cutaneous ectoderm during neural tube closure. They contain cholesterol and desquamated keratin. These tumors constitute less than 1% of all intracranial tumors, with approximately half occurring in the cerebellopontine area (48).

Depending on their location, they are closely associated with cranial nerves and vascular structures and tend to grow slowly. On MRI, they appear hypointense on T1-weighted images and hypohyperintense on T2-weighted images, with signal intensities similar to those of cerebrospinal fluid. They typically show diffusion restriction on diffusion-weighted imaging, which helps distinguish them from arachnoid cysts (49).

Total resection is recommended to minimize the risk of postoperative aseptic meningitis, hydrocephalus, and tumor recurrence. However, aggressive resection can often lead to cranial nerve damage or ischemic deficits. Therefore, some sources report that total resection is only achievable in 50-80% of epidermoid tumor cases (50). There is limited information in the literature regarding the effectiveness of RT. A successful small case series treated with Gamma Knife Radiosurgery and external-beam RT as treatment options has been reported.

CONCLUSION

Recent studies aimed at understanding tumor biology and new imaging techniques are striving for a more accurate understanding of pediatric posterior fossa tumors. Thus, the application of accurate diagnosis and treatments can lead to a better quality of life and improved survival. All these approaches are possible with the multidisciplinary work of clinics such as neurosurgery, pediatrics, radiology, and medical and radiation oncology.

Ethics

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Authorship Contributions

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