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Surgical Neurology International

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SNI: Pediatric Neurosurgery

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Review Article

Posterior fossa tumors in children: An update and new concepts

Juan Pablo Mengide[1], María Florencia Berros[2], Mariana Estefanía Turza[2], Juan Manuel Liñares[1]

[1]Division of Pediatric Neurosurgery, Hospital Provincial Neuquen Dr. Castro Rendon, [2]Department of Pediatrics, Grupo CMIC, Neuquen, Argentina.

E-mail: *Juan Pablo Mengide - juanpablomengide@gmail.com; María Florencia Berros - floop839@gmail.com; Mariana Estefanía Turza - marianaturza@gmail.com; Juan Manuel Liñares - juanmanuel.linares.86@gmail.com

***Corresponding author:**
Juan Pablo Mengide,
Division of Pediatric Neurosurgery, Hospital Provincial Neuquen Dr. Castro Rendon, Neuquen, Argentina.

juanpablomengide@gmail.com

Received : 14 January 2023
Accepted : 15 March 2023
Published : 31 March 2023

DOI
10.25259/SNI_43_2023

Quick Response Code:

ABSTRACT

Background: Posterior fossa tumors account for approximately half of the central nervous system tumors in children. Major technological advances, mainly in the fields of molecular biology and neuroimaging, have modified their classification, leading to a more detailed description of these entities. Into the classic taxonomy, used for many years, new concepts have been incorporated at times eliminating or modifying former ones.

Methods: A literature search was conducted in PubMed using the medical subject headings involving the five most common pediatric posterior fossa tumors: diffuse midline glioma, medulloblastoma, ependymoma, atypical teratoid/rhabdoid tumor, and pilocytic astrocytoma. Only English published articles in the past 11 years that provided technological, neuroimaging, and molecular biology insight into posterior fossa tumors in children were considered.

Results: Substantial changes have been introduced in the nomenclature of pediatric posterior fossa tumors. Diffuse midline gliomas are named based on alterations in histone H3. Molecular rearrangements of medulloblastomas are more important in defining the prognosis than histological variants; therefore, these tumors are currently named based on their molecular subgroups. Posterior fossa ependymomas and atypical teratoid rhabdoid tumor classification have incorporated new groups based on different genetic profiles. Pilocytic astrocytoma has been placed in a new category that distinguishes circumscribed from diffuse entities.

Conclusion: Advances in molecular biology and neuroimaging have substantially changed the way pediatric neoplasms are studied. The classical taxonomy has been modified leading to more accurate classifications that are based on the genetic alterations.

Keywords: Pediatrics, Posterior fossa, Tumor

INTRODUCTION

The posterior fossa is the area of the brain that extends from the tentorium to the foramen magnum and contains the most complex brain structures that regulate vital functions.[31] Tumors of this region account for approximately half of all central nervous system (CNS) tumors in children.[27]

In recent years, there have been great technological advances in molecular biology and neuroimaging, which have extended our knowledge of these entities, thereby improving associated morbidity and mortality rates.[22] The latest editions of the World Health Organization (WHO) classification of tumors of the CNS have introduced major changes in the taxonomy of

these neoplasms.[16] These modifications are complex and, in some cases, the classic nomenclature, used for many years, has been eliminated or greatly modified.[32]

In this review, we provide an update and describe new concepts of the five most common posterior fossa tumors in pediatrics: diffuse midline glioma, medulloblastoma, ependymoma, atypical rhabdoid teratoid tumor, and pilocytic astrocytoma.

MATERIALS AND METHODS

A literature search was conducted in PubMed using the medical subject headings (MESH): adolescent, brain neoplasms/diagnostic imaging, brain neoplasms/epidemiology, brain neoplasms/pathology, cerebellar neoplasms/epidemiology, cerebellar neoplasms/pathology, ependymoma/pathology, glioma/epidemiology, glioma/pathology, infant, magnetic resonance imaging (MRI)/methods, medulloblastoma/pathology, newborn, rhabdoid tumor/epidemiology, and rhabdoid tumor (RT)/pathology. Articles published in the past 11 years that provided technological, neuroimaging, and molecular biology insight into posterior fossa tumors in children were considered. Only English published articles describing diffuse midline glioma, medulloblastoma, ependimoma, atypical teratoid rhabdoid tumor (AT/RT), and pilocytic astrocytoma were reviewed. Other posterior fossa tumors (hemangioblastoma, familial cancer syndromes, arachnoid cysts, epidermoid/dermoid cysts, etc.) were excluded from the study.

RESULTS

General concepts

The clinical presentation of posterior fossa neoplasms is variable. Onset may be acute, subacute, or chronic with cognitive or behavioral disturbances as well as neurological or gastrointestinal manifestations.[1,23] Intracranial hypertension syndrome may be caused directly by the growth of an expansive lesion in the posterior fossa or indirectly secondary to obstructive hydrocephalus often caused by these lesions.[9]

Whole brain and spine MRI are currently a mandatory study for the presurgical planning and staging of these patients and multiple techniques of broad clinical utility may be used [Figure 1].[30] There have been several advances in this diagnostic method of which the following are the most clinically relevant to characterize these tumors:

- T1-weighted MRI sequences are the classic technique to evaluate the anatomy of the CNS and contrast administration provides information on the blood-brain barrier permeability. Disruption or integrity of the latter provides insight into the possible tumor type.
- T2 and fluid-attenuated inversion recovery techniques can show tumor vascularization, edema, and white matter lesions.[26]
- Diffusion-weighted imaging (DWI) uses movement of water molecules to assess tumor cellularity and tissue swelling, showing restrictive diffusion in the above-described conditions. When combined with the previous mentioned techniques, DWI is useful to differentiate higher grade tumors including medulloblastoma and ependymoma from lower grade tumors such as pilocytic astrocytoma.[10]
- MRI spectroscopy is useful to investigate the metabolic profile of the tumor, that is, it provides information on the concentration of certain metabolites (choline, taurine, lactate, etc.) in the tumor, providing information on tumor grade and possibly type as well as the presence of necrosis.[30]
- Susceptibility-weighted imaging is used to evaluate the presence of blood and calcium. The technique assesses vascularity as well as presence of hemoglobin molecules and intratumoral calcifications, and has, in certain contexts, replaced the computed tomography (CT) scan for the identification of calcium in the tumor. Noteworthy, there are some surgical scenarios where the presence of calcium during the presurgical planning is better assessed using CT scan.
- Perfusion techniques compare tumor blood volume and blood flow to that of normal brain parenchyma and are used to evaluate the possible tumor grade, recurrence, or tumor type. They may be used with or without contrast-enhancement.[7]
- Finally, tractography is used to evaluate the location of the tumor regarding the white matter tracts providing the surgeon with important information to avoid white matter-related postoperative impairments.
- Functional MRI is used to localize eloquent areas of the brain mainly in the setting of supratentorial tumors; however, these are beyond the focus of this study.

The techniques described above, when interpreted by an expert neuroradiologist, allow for the preoperative prediction of the histology and the altered molecular pathway of the tumor. These new MRI techniques may reveal particular radiological patterns that suggest specific biological behavior of the tumor and can be useful to determine certain genetic alterations, a concept that is currently called "radiogenomics."[2]

The main treatment of posterior fossa tumors consists of surgery, chemotherapy, and radiotherapy. At present, molecularly targeted approaches have been described.[22,28] A detailed description of the treatment of posterior fossa tumors is beyond the scope of this article.

Below we provide an update of the five most common posterior fossa tumors in pediatrics according to the fifth edition of the WHO classification of tumors of the CNS.

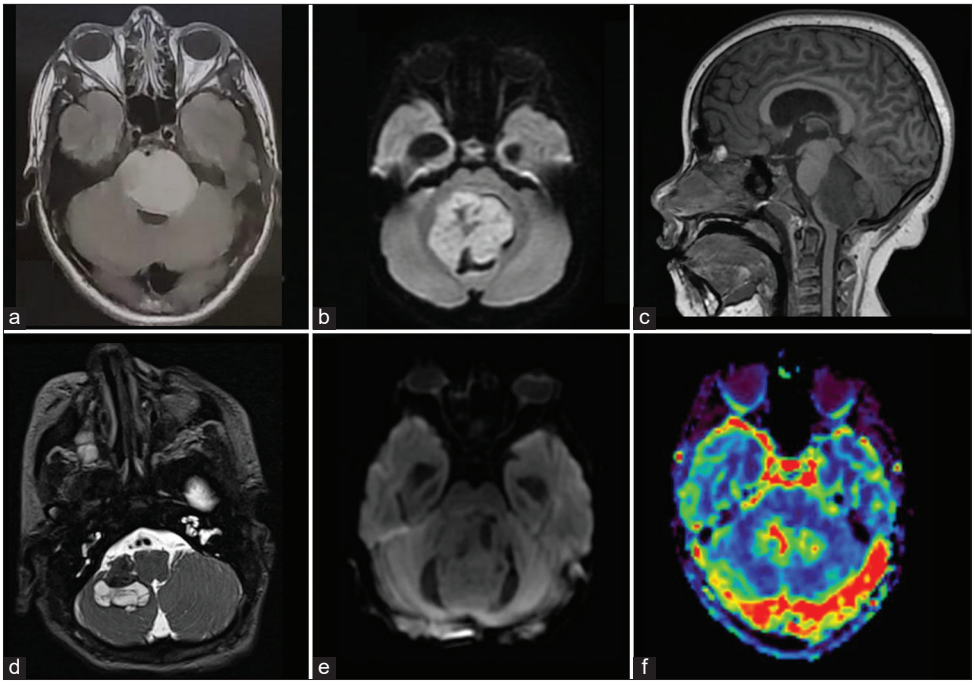

Figure 1: Magnetic resonance imaging showing some of the hallmark characteristics of posterior fossa tumors. (a) Axial fluid-attenuated inversion recovery sequence image showing the distorted anatomy of a diffuse midline glioma H3 K27-altered enlarging the pons, collapsing the fourth ventricle, and displacing the basilar artery, (b) Axial diffusion-weighted image of a medulloblastoma showing high signal intensity that is characteristic of this World Health Organization grade 4 hypercellular tumors, (c) Sagittal T1-weighted image showing a midline lesion involving the floor of the fourth ventricle due to a group B posterior fossa ependymoma, (d) Axial T2-weighted image of an atypical teratoid rhabdoid tumor showing hemorrhagic areas with low signal intensity and cystic regions of variable signal intensity, (e) Axial diffusion-weighted image of a pilocytic astrocytoma. Note the lower signal intensity in this tumor compared to image b; (f) Perfusion-weighted image of a highly vascularized medulloblastoma showing an area of increased cerebral blood volume.

Diffuse midline glioma

Before the 2016 WHO classification of tumors of the CNS, the most common pediatric brainstem tumor was termed diffuse intrinsic pontine glioma or DIPG as it is usually called on the hospital ward. DIPG arises in the pons of the brainstem infiltrating it locally and is not amenable to surgical resection [Figure 1a]. It mainly affects patients between 5 and 10 years of age, with a median age at diagnosis of 7 years and a median overall survival of less than one year.[4] In recent years, the molecular biology of this type of lesion has been described in depth mainly based on alterations in histone H3, which are found in approximately 85% of DIPGs.[6] Therefore, in the 2016 WHO classification, it was decided to name these tumors diffuse midline glioma, H3 K27M-*mutant*, referring to the presence of an amino acid mutation mainly in histone 3.3 and to a lesser extent in histone 3.1.[18] Nevertheless, in the 2021 WHO classification, the term has been modified to H3 K27-*altered* since it has been found that, in addition to the H3 K27M mutation, the molecular changes may be diverse including, for example, overexpression of the EZH inhibitory protein (EZHIP) [Table 1].[5,16] It is worth mentioning that this latter tumor is also included in a new category of gliomas called "pediatric-type diffuse high-grade gliomas."

Medulloblastoma

Medulloblastoma is the most common malignant brain tumor in children, affecting mostly males with a bimodal peak of incidence at 3 years and at 9 years of age [Figure 1b and f].[17] Before the 2016 WHO classification, this tumor was divided according to its histological variants into classic, giant cell, anaplastic, desmoplastic/nodular, and extensive nodular with their respective epidemiology and survival rates. In the new molecular era, several altered intracellular mechanisms have been discovered, including deregulation of the Sonic Hedgehog (SHH) and the wingless (Wnt) signaling pathways. These changes were incorporated into the 2016 WHO classification where molecular groups were added to the classic histological variants described above. The new taxonomy is based on the genetic definitions of medulloblastomas and includes the following: *WNT-*

activated, SHH-activated and TP53 mutant, SHH-activated and TP53 wildtype, and non-WNT/non-SHH (subdivided into Group 3 and Group 4 when possible) [Table 1].[15] Therefore, in the 2016 classification, medulloblastoma is both histologically and genetically defined. Table 2 lists the main characteristics of both categories. Each molecular subgroup shows a different methylation and gene transcription profile, epidemiology, clinical presentation, recurrence pattern, and prognosis.[5,25] A detailed description of the molecular alteration corresponding to each group is beyond the scope of this article. The 2021 WHO classification has included all histological subtypes in a single section termed *histologically defined medulloblastoma* (without the division into histological type it made in 2016) and has also added four subgroups for SHH and eight for non-WNT/non-SHH.[16]

This new approach prioritizes genetic changes and emphasizes the importance of the molecular biology of medulloblastoma in defining the prognosis. In other words, it is considered that not the histological variant, but the molecular alteration of medulloblastoma mainly defines the behavior of the tumor.[22] This can be observed in Table 2, showing that a medulloblastoma with a classic histological variant may be classified into any of the four genetic groups, and the prognosis of this histological variant will depend on the molecular subgroup it belongs to.[24]

Table 1: Changes in the tumor nomenclature.

Classical nomenclature	New taxonomy
DIPG	Diffuse midline glioma *H3K27-altered**
Medulloblastoma variants	*Molecularly defined medulloblastoma*
Desmoplastic/nodular	WNT-activated
Anaplastic	SHH-activated and TP53 mutant
Large-cell	SHH-activated and TP53 wild type
MB with extensive nodularity	Non-WNT/non-SHH
	Histologically defined medulloblastoma
Ependymoma and its variants. Anaplastic ependymoma	Posterior fossa ependymoma PFA/PFB
AT/RT	AT/RT-MYC, AT/RT-SHH, AT/RT-TYR

AT/RT: Atypical teratoid rhabdoid tumor, DIPG: Diffuse intrinsic pontine glioma, PFA/PFB: posterior fossa ependymoma group A or B SHH: Sonic hedgehog, WNT: wingless.*Note that this mutation is present in 85% of the formerly called DIPG

Ependymoma

Ependymoma is the third most common tumor of the posterior fossa and mainly arises from the floor of the fourth ventricle.[29] Previously, it was classified according to its different histologic variants. The 2021 WHO classification has incorporated *posterior fossa ependymoma group A* (*PFA*) *and group B* (*PFB)* into posterior fossa ependymomas. This classification is based on several criteria, including the methylation profile of H3K27.[14] Median age at onset of PFA is 3 years, with a male preponderance, and a median overall survival rate of 65%, while PFB is of later presentation, at a median age of 25 years with a similar sex distribution and a median overall survival rate of between 80% and 90%.[19] PFA is more commonly found in a paramedian/lateral location extending through the foramen of Luschka whereas PFB is typically localized in the midline [Figure 1c and Table 1].

AT/RT

AT/RT is a highly vascularized and aggressive neoplasm that mostly affects children under 2 years of age [Figure 1d]. Tumor location may be in the supra- and infratentorial areas with a greater predilection for the latter and median survival is less than 12 months although some reports have shown better outcomes.[5,13] In the new 2021 WHO classification, embryonal tumors have been divided into two types: Medulloblastomas (described above) and a new section called "*other embryonal tumors of the central nervous system.*" AT/RT is placed in this latter category. At present, the tumor is divided into three subgroups according to gene overexpression: *AT/RT-MYC*, *AT/RT-SHH*, and *AT/RT-TYR* [Table 1].[20]AT/RT-SHH and AT/RT-TYR most frequently occur in the posterior fossa; while ATRT-TYR is mainly found in infants less than 2 years of age, ATRT-SHH is more common in older children.

Table 2: Molecular subgroups of medulloblastoma.

Characteristics	WNT	SHH*	Non-WNT/non-SHH
Histological subtype	Classic, GC	D/N, E/N, classic, GC	Classic, GC
Gender/Frequency	M=F/10%	M=F/30%	M>F/60%
Age in years	3–17	0–17/>17	0–17
Prognosis†	Good	Children: Good, Others: Intermediate	Poor/intermediate

D/N: Desmoplastic/nodular, E/N: With extensive nodularity; F: Female, GC: Giant cell, M: Male, SHH: Sonic hedgehog. *Corresponds to both subtypes: SHH-activated and TP53 mutant and SHH-activated and TP53 wild type †This is a simplified table; prognosis will depend in each case on the corresponding molecular alteration

Pilocytic astrocytoma

Pilocytic astrocytoma is the most common low-grade tumor in children [Figure 1e]. The mean age at diagnosis is between 6 and 8 years with no clear sex predominance.[3] The 25-year survival rate for this tumor is higher than 90%. Historically, the WHO classified these tumors into the category of "other astrocytic tumors." In the 2021 edition, pilocytic astrocytoma was placed in the category of "*circumscribed astrocytic gliomas,*" a newly created category to distinguish well-circumscribed from diffuse entities (which are now found in other categories under the term "diffuse").[21] In recent years, it has been shown that the KIAA-BRAAF fusion oncogene is found in approximately 80% of infratentorial pilocytic astrocytomas.[8,13]

Other observations

Certain modifications in the general nomenclature introduced by the 2021 WHO classification of tumors of the CNS have an impact on how we approach the posterior fossa tumors described in this study. In addition, there are many others, such as the extensive modifications in the taxonomy of supratentorial tumors, that do not directly affect them. The following is a summary of the most relevant changes that are directly or indirectly associated with the lesions discussed here.

First, advances in the field of molecular biology and its role in the outcome of these diseases made it necessary to incorporate these data into the classification and pathology reports. The new approach to the description of tumors of the CNS is through the concept of an integrated diagnosis composed of different layers.[11] In the pathology report of a tumor, not only the histological information is described, but also the molecular alterations of the tumor in a four-layered format, in which the first layer consists of the integrated diagnosis with all the information pertaining to the tissue, the second layer corresponds to the histological classification, the third to the WHO grade of the lesion (from 1 to 4), and the fourth layer describes the molecular pattern [Table 3].

Two new suffixes have been added to describe different clinical scenarios. The suffix not otherwise specified (NOS) is used when histopathological or molecular data are not sufficient to make the diagnosis. If the corresponding molecular and histological analyses have been performed, but do not lead to a diagnosis based on the WHO classification, the suffix not elsewhere classified (NEC) is added.[32]

On the other hand, in the 2021 WHO classification, pediatric gliomas are separated from adult gliomas, resulting in four groups for gliomas: adult diffuse gliomas, pediatric-type diffuse low-grade gliomas, pediatric-type diffuse high-grade gliomas, and circumscribed gliomas (of which the latter includes pilocytic astrocytoma as described above).[12]

Table 3: Pathology report in a four-layered format.

Cerebellum*		
Layer 1	Integrated diagnosis	Medulloblastoma genetically defined SHH-activated and TP53 mutant
Layer 2	Histological classification	Desmoplastic/nodular
Layer 3	WHO grade of the lesion	WHO grade 4
Layer 4	Molecular pattern	SHH-activated and TP53 mutant

Example of a layered report. *Site of diagnosis, SHH: Sonic hedgehog, WHO: World Health Organization

Finally, for a better understanding and to avoid confusion, the Roman numerals to denote tumor grade have been replaced by Arabic numerals and a lesion previously named "Grade IV tumor" is now termed "Grade 4 tumor" [Table 3].[21]

CONCLUSION

Advances in molecular biology and neuroimaging have substantially changed the way pediatric neoplasms are studied, improving the understanding of posterior fossa tumors and leading to more accurate classifications. The classical taxonomy has been modified and the new terms based on the genetic alterations of tumors allow for a better understanding and study of tumors. Undoubtedly, this new taxonomy will lead to better diagnosis and treatment and improvement in the quality of life of children with brain tumors.

Acknowledgments

We thank Janneke Deurloo for providing language and insightful writing assistance.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Adachi K, Murai Y, Teramoto A. Infantile cerebellar pilocytic astrocytoma with autism spectrum disorder. J Nippon Med Sch 2012;79:228-31.
2. AlRayahi J, Zapotocky M, Ramaswamy V, Hanagandi P, Branson H, Mubarak W, *et al*. Pediatric brain tumor genetics:

What radiologists need to know. Radiographics 2018;38:2102-22.
3. Bonfield CM, Steinbok P. Pediatric cerebellar astrocytoma: A review. Childs Nerv Syst 2015;31:1677-85.
4. Chiarelli PA, Chu JK, Krieger MD. Brainstem tumors. In: Textbook of Pediatric Neurosurgery. 1st ed. Berlin: Springer International Publishing; 2019.
5. Cohen AR. Brain tumors in children. N Engl J Med 2022;386:1922-31.
6. Cohen KJ, Jabado N, Grill J. Diffuse intrinsic pontine gliomas-current management and new biologic insights. Is there a glimmer of hope? Neuro Oncol 2017;19:1025-34.
7. Dangouloff-Ros V, Varlet P, Levy R, Beccaria K, Puget S, Dufour C, *et al*. Imaging features of medulloblastoma: Conventional imaging, diffusion-weighted imaging, perfusion-weighted imaging, and spectroscopy: From general features to subtypes and characteristics. Neurochirurgie 2021;67:6-13.
8. Faulkner C, Ellis HP, Shaw A, Penman C, Palmer A, Wragg C, *et al*. BRAF fusion analysis in pilocytic astrocytomas: KIAA1549-BRAF 15-9 fusions are more frequent in the midline than within the cerebellum. J Neuropathol Exp Neurol 2015;74:867-72.
9. Fustinoni O. Semiología del Sistema Nervioso. 15th ed. Argentina: Editorial el Ateneo; 2014.
10. Jaremko JL, Jans LB, Coleman LT, Ditchfield MR. Value and limitations of diffusion-weighted imaging in grading and diagnosis of pediatric posterior fossa tumors. AJNR Am J Neuroradiol 2010;31:1613-6.
11. Komori T. The 2016 WHO classification of tumours of the central nervous system: The major points of revision. Neurol Med Chir (Tokyo) 2017;57:301-11.
12. Komori T. The 2021 WHO classification of tumors, 5th edition, central nervous system tumors: The 10 basic principles. Brain Tumor Pathol 2022;39:47-50.
13. Leland Albright A. Principles and Practice of Pediatric Neurosurgery. New York: Thieme; 2014.
14. Levine AB, Wong D, Fatehi M, Yip S. Ependymoma and chordoma. Neurosurgery 2020;87:860-70.
15. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, *et al*. The 2016 World Health Organization classification of tumors of the central nervous system: A summary. Acta Neuropathol 2016;131:803-20.
16. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, *et al*. The 2021 WHO Classification of tumors of the central nervous system: A summary. Neuro Oncol 2021;23:1231-51.
17. León MI. Review and update about medulloblastoma in children. Radiología 2011;53:134-45.
18. Mosaab A, El-Ayadi M, Khorshed EM, Amer N, Refaat A, El-Beltagy M, *et al*. Histone H3K27M mutation overrides histological grading in pediatric gliomas. Sci Rep 2020;10:8368.
19. Myseros JS. Ependymomas. In: Textbook of Pediatric Neurosurgery. Berlin: Springer International Publishing; 2018.
20. Nesvick CL, Lafay-Cousin L, Raghunathan A, Bouffet E, Huang AA, Daniels DJ. Atypical teratoid rhabdoid tumor: Molecular insights and translation to novel therapeutics. J Neurooncol 2020;150:47-56.
21. Osborn AG, Louis DN, Poussaint TY, Linscott LL, Salzman KL. The 2021 World Health Organization classification of tumors of the central nervous system: What neuroradiologists need to know. AJNR Am J Neuroradiol 2022;43:928-37.
22. Pollack IF, Agnihotri S, Broniscer A. Childhood brain tumors: Current management, biological insights, and future directions. Neurosurg Pediatr 2019;23:261-73.
23. Purves D. Neuroscience. 6th ed. United Kingdom: Oxford University Press, Incorporated.; 2017.
24. Ramaswamy V, Remke M, Adamski J, Bartels U, Tabori U, Wang X, *et al*. Medulloblastoma subgroup-specific outcomes in irradiated children: Who are the true high-risk patients? Neuro Oncol 2016;18:291-7.
25. Ramaswamy V, Remke M, Bouffet E, Faria CC, Perreault S, Cho YJ, *et al*. Recurrence patterns across medulloblastoma subgroups: An integrated clinical and molecular analysis. Lancet Oncol 2013;14:1200-7.
26. Raybaud A, Barkovich AJ. Hydrocephalus. In: Pediatric Neuroimaging. 5th ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2012. p. 808-57.
27. Reynolds R, Grant G. General approaches and considerations for pediatric brain tumors. In: Youmans Neurological Surgery. 8th ed. Philadelphia, PA: Elsevier Inc.; 2022.
28. Robinson GW, Gajjar A. Genomics paves the way for better infant medulloblastoma therapy. J Clin Oncol 2020;38:2010-3.
29. Thompson YY, Ramaswamy V, Diamandis P, Daniels C, Taylor MD. Posterior fossa ependymoma: Current insights. Childs Nerv Syst 2015;31:1699-706.
30. Villanueva-Meyer JE, Mabray MC, Cha S. Current clinical brain tumor imaging. Neurosurgery 2017;81:397-415.
31. Wen HT, Rhoton A, Mussi AC. Surgical anatomy of the brain. In: Winn HR, editor. Youmans Neurological Surgery. 7th ed. Philadelphia, PA: Elsevier Inc.; 2016.
32. WHO Classification of Tumours Editorial Board. Central Nervous System Tumours. 5th ed., Vol. 6. France: International Agency for Research on Cancer; 2022.

How to cite this article: Mengide JP, Berros MF, Turza ME, Liñares JM. Posterior fossa tumors in children: An update and new concepts. Surg Neurol Int 2023;14:114.