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Review Article

New CNS tumor classification: The importance in pediatric neurosurgical practice

Ramiro José del Río[1], Santiago Ezequiel Cicutti[1], Daniel C. Moreira[2], Javier Danilo Gonzalez Ramos[1]

[1]Department of Neurosurgery, Hospital de Pediatría Juan P. Garrahan, Ciudad Autónoma de Buenos Aires, Argentina, [2]Department of Oncology, St. Jude Children's Research Hospital, Memphis, United States.

E-mail: *Ramiro José del Río - rjdelrio@gmail.com; Santiago Ezequiel Cicutti - santiagocicutti@gmail.com; Daniel C. Moreira - daniel.Moreira@stjude.org; Javier Danilo Gonzalez Ramos - jdgonzalezramos@gmail.com

***Corresponding author:**
Ramiro José del Río,
Department of Neurosurgery,
Hospital de Pediatría Juan P.
Garrahan, Ciudad Autónoma
de Buenos Aires, Argentina.

rjdelrio@gmail.com

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ABSTRACT

Background: The management of the central nervous system (CNS) tumors in the pediatric population is crucial in neurosurgical practice. The World Health Organization (WHO) has evolved its classification of CNS tumors from the 19th century to the 5th edition, published in 2021, incorporating molecular advancements. This transition from morphology to molecular characterization is ongoing.

Methods: This manuscript analyzes the modifications introduced in the 5th edition of WHO's CNS tumor classification, particularly focusing on pediatric tumor families. The paper integrates clinical, morphological, and molecular information, aiming to guide pediatric neurosurgeons in their daily practice and interdisciplinary discussions.

Results: The 5th edition of the WHO classification introduces a hybrid taxonomy that incorporates both molecular and histological components. The terminology shifts from "entity" to "type" and "subtype," aiming to standardize terminology. Tumor grading experiences changes, integrating molecular biomarkers for prognosis. The concept of integrated layered diagnosis is emphasized, where molecular and histological information is combined systematically.

Conclusion: The 5th edition of the WHO CNS classification signifies a paradigm shift toward molecular characterization. The incorporation of molecular advances, the layered diagnostic approach, and the inclusion of clinical, morphological, and molecular information aim to provide comprehensive insights into pediatric CNS tumors. This classification offers valuable guidance for pediatric neurosurgeons, aiding in precise diagnosis and treatment planning for these complex neoplasms.

Keywords: Brain tumors, Central nervous system, Pediatric central nervous system tumors, Pediatric neuro-oncology, Pediatrics, World Health Organization classification

INTRODUCTION

The management of the central nervous system (CNS) tumors in children and adolescents is a rapidly evolving field. Pediatric CNS tumors represent approximately 20% of the burden of childhood malignancies. For pediatric neurosurgeons, this group of diseases is of high importance to neurosurgical practice due to the importance of a comprehensive interdisciplinary approach.

In 1979, the World Health Organization (WHO) published the first classification of CNS tumors, attempting to group different entities based on their common histopathologic features. Over

the years, as knowledge about this type of neoplasm has advanced, several updates have been made, leading up to the 5th edition published in 2021. The purpose of this report is to highlight the most important points about the most common tumors in the pediatric population, considering the newest classification and providing key information of interest to pediatric neurosurgeons.

HISTORICAL CONTEXT

Virchow compiled the initial report on brain tumor classification in the mid-19th century.[42] In 1929, Bailey and Cushing introduced the majority of the terms that are still in use today.[1] However, in 1949, Kernohan *et al*. presented a distinctly different approach to classifying these entities.[12] Finally, in 1979, the first WHO classification was published, aimed at unifying the previously proposed concepts for diagnosis and grading.[46]

In 1988, Daumas-Duport *et al*. introduced an alternative CNS tumor grading system known as the St. Anne-Mayo grading scheme.[7] The popularity of this staging system shed light on a secondary classification introduced by the WHO in 1983,[13] followed by subsequent editions: a third edition in 2000,[14]and a fourth in 2007.[19]

The emergence of molecular biology, coupled with the reconsideration of the Zülch grading model, led to a revision of the fourth classification, published in 2016.[20] One of its advancements was the incorporation of layered diagnosis, as later described by David Louis.

Simultaneously, the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW), an entity distinct from the WHO, issued specific recommendations that were considered during the compilation of the new edition.[22]

In this manner, in 2021, building on the 2016 review and incorporating the latest advancements in clinical, morphological, and molecular domains, the 5th edition of the WHO CNS classification was released.

GENERAL CONSIDERATIONS AND MODIFICATIONS

The new classification takes into account both molecular and histological components, leading to a hybrid taxonomy that indicates an ongoing process of modification. The term "entity" has been replaced by "type," and the term "subtype" is now used instead of "variant," with the aim of standardizing nomenclature across diseases. Neoplasm nomenclature aims for simplicity by defining localization, age of presentation, and/or relevant genetic modifiers. For example, "diffuse midline glioma K27-altered" is used. Modifier terms such as "anaplastic" or "multiform" have been eliminated. Tumor grading has also changed, attempting to resemble more closely the grading of neoplasms outside the CNS while still preserving some classical features. As an illustration, Roman numerals have been substituted with Arabic numerals.[23]

Molecular biomarkers can serve as important prognostic indicators, which is why they have also been included in the determination of certain tumor grades. The Not Otherwise Specified (NOS) suffix, which groups tumors for which it is not possible to assign a specific category, is currently divided into two parts. On the one hand, the term "NOS" is still used for those entities that cannot be classified according to the WHO criteria due to a lack of specific tests, whether due to material shortages, sample impairment, or the absence of required molecular testing methods. On the other hand, the term "Not Elsewhere Classified" (NEC) is being added for those neoplasms where the necessary exams have been conducted, but the information is uncertain at the time of

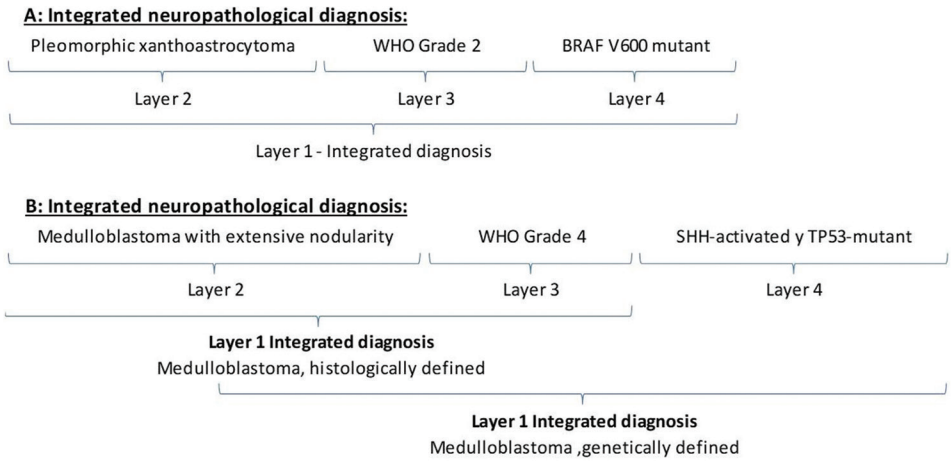

Figure 1: Two examples of diagnostic layers based on Harlem consensus in tumors often found in the pediatric population. SHH: Sonic Hedgehog

categorizing the sample into a specific type established by the WHO.[21]

INTEGRATED LAYER DIAGNOSTIC

Since the 2016 review, on the basis of a successful application for hematopoietic malignancies,[40] the new classification proposes to integrate molecular and histological information in layers. This innovative concept has gained acceptance among experts and received approval through the Haarlem consensus.[18,21]

This systematic approach serves as a guideline for pathologists when composing their reports. The concept involves a series of sequential evaluation levels. The first layer indicates the integrated diagnosis, the second identifies the histological type, and the third and fourth layers encompass the molecular features. From this model emerges the premise of "molecular biology defeats histology indicating a paradigm shift in tumor classification where molecular characteristics are increasingly prioritized over traditional histological features in determining diagnosis and prognosis."[2] For example, a midline glioma showing a disorder in histone K27 will be grade 4 regardless of the morphologic features associated with classic WHO grading. In summary, it can be inferred that lower levels yield higher levels, ultimately leading to the first level, where the integrated diagnosis is comprehensively elucidated [Figure 1].

2021 CLASSIFICATION OF PEDIATRIC TUMORS

As stated below, we will describe the most important changes that concern CNS tumor groups in childhood.

Gliomas

The first edition of the WHO classification has adopted a new approach to categorising glial, glioneuronal, and neural tumors. These tumors are now divided into six distinct families: (1) adult-type diffuse gliomas, (2) pediatric-type diffuse low-grade gliomas, (3) pediatric-type diffuse high-grade gliomas, (4) circumscribed astrocytic gliomas, (5) neuronal and glioneuronal tumors, and (6) ependymomas. Choroid plexus tumors are considered separately from these categories.[22]

Within this classification, a significant distinction between pediatric and adult gliomas becomes evident. While they may exhibit similar histology, there are well-known biological differences between them. An example of this distinction is that pediatric gliomas rarely transform higher histologic grades.

Pediatric diffuse low-grade gliomas comprise four distinct types: Diffuse astrocytoma MYB or MYBL1 altered, angiocentric glioma, polymorphous low-grade neuroepithelial tumor of the young, and diffuse low-grade glioma MAPK pathway altered [Table 1]. Among these, only angiocentric glioma exhibits a typical morphological feature, while the others are characterized by recurring molecular alterations (MYB, MYBL1, BRAF, and FGFR). Unlike circumscribed gliomas, these tumors can be challenging to remove completely, especially when they are deeply located. Disorders in the MAPK pathway warrant special attention, particularly those involving BRAF mutations or fusions.[11,38] These hold therapeutic implications, as BRAF and MEK inhibitors are currently under investigation as potential treatment options.

There are also four types of diffuse high-grade gliomas: H3 K27-altered diffuse midline glioma, H3 G34 midline diffuse

Table 1: Pediatric glial, neuronal, and glioneuronal tumors. WHO Classification, 5th edition.

Pediatric glial, neuronal, and glioneuronal tumors of the CNS from the World Health Organization Classification, 5th edition.
Pediatric-type diffuse low-grade gliomas:
Diffuse astrocytoma, MYB or MYLB 1-altered
Angiocentric glioma
PLNTY
Diffuse low-grade glioma, MAPK pathway-altered
Pediatric-type diffuse high-grade glioma:
Diffuse midline glioma H3 K27-altered.
Diffuse hemispheric glioma H3 G34-mutant
Diffuse pediatric-type high-grade glioma, H3-wildtype, and IDH-wildtype.
Infantile-type hemispheric glioma
Circumscribed astrocytic gliomas:
Pilocytic astrocytoma
High-grade astrocytoma with piloid features
Pleomorphic xanthoastrocytoma
SEGA
Choroid glioma
Astroblastoma, MN1-altered
Glioneuronal and neuronal tumors:
Ganglioglioma
Desmoplastic infantile ganglioglioma/desmoplastic infantile astrocytoma
Dysembryoplastic neuroepithelial tumor
Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters.
Papillary glioneuronal tumor
Rosette forming glioneuronal tumor
Myxoid glioneuronal tumor
Diffuse leptomeningeal glioneuronal tumor
Gangliocytoma
Multinodular and vacuolating neuronal tumor
Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)
Central neurocytoma
Extraventricular neurocytoma
Cerebellar liponeurocytoma

WHO: World Health Organization, PLNTY: Polymorphous low-grade neuroepithelial tumor of the young, SEGA: Subependymal giant cell astrocytoma, IDH: Isocitrate dehydrogenase, CNS: Central nervous system

hemispheric glioma, pediatric-type diffuse high-grade glioma with H3 wild type and isocitrate dehydrogenase wild type, and infant-type hemispheric glioma. These types represent 10% of brain tumors in children and are associated with a very poor prognosis.[4] The nomenclature for H3 K27 alterations has changed in midline diffuse gliomas from "mutated" to "altered" due to the presence of other changes that may also define this type of tumor, which includes diffuse intrinsic pontine glioma [Figure 2]. The other three types are new entities that require molecular biology techniques aimed at characterizing them; the infant-type hemispheric glioma occurs in newborns and infants with a typical molecular profile (ALK, ROS1, NTRK1/2/3, or MET).[5,9]

In addition, it is important to note the disappearance of two types in pediatrics, oligodendroglioma and glioblastoma, tumors that pertain to the adult population.

Circumscribed astrocytic gliomas differ from the previous ones by being well-defined solid lesions.[22] This family includes pilocytic astrocytoma, the CNS tumors most frequent in children (20% of CNS neoplasm in younger than 20 years old)[3,39,43] with the most frequent localization in the cerebellum and suprasellar region. The most frequent molecular marker is the KIAA1549-BRAF fusion (MAPK pathway).

Another common tumor within this family in children is the pleomorphic xanthoastrocytoma (PXA), which can be either grade 2 or 3 and stands as one of the few examples of tumoral progression [Figure 3]. BRAF V600 mutations are frequently observed in PXA.[22]

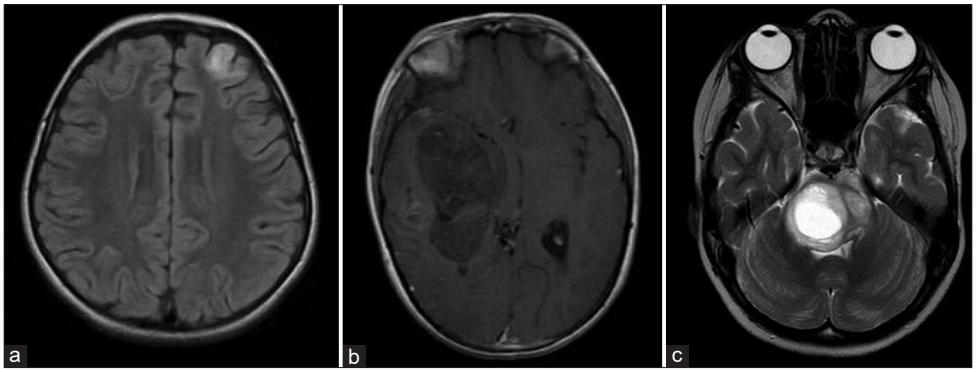

Figure 2: Pediatric-type diffuse gliomas: (a) MRI FLAIR, axial section of a 7-year-old patient with an angiocentric glioma (pediatric-type diffuse low-grade glioma), grade 1. (b) MRI T1 with gadolinium, axial section of a 12-year-old patient with a diffuse hemispheric glioma H3 G34-mutant, grade 4 (formerly glioblastoma). (c) MRI T2 axial section of a 7-year-old patient with diffuse midline glioma H3 K27-altered, grade 4 (former diffuse intrinsic pontine glioma). MRI: Magnetic resonance imaging, FLAIR: Fluid attenuated inversion recovery.

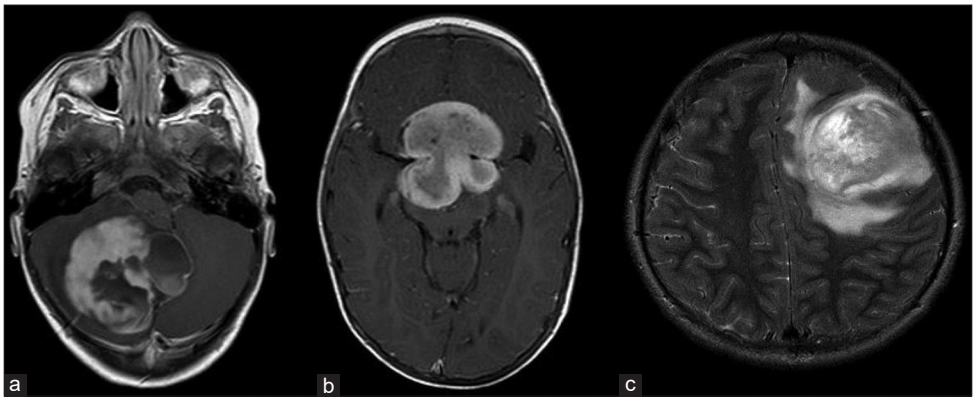

Figure 3: Circumscribed astrocytic gliomas: (a) MRI T1 with gadolinium, axial section of a 2-year-old patient suffering from a posterior fossa pilocytic astrocytoma, WHO grade 1. (b) MRI T1 with gadolinium, axial section of a 1-year-old patient with a suprasellar pilocytic astrocytoma, WHO grade 1. (c) MRI T2, axial section of a 13-year-old patient with pleomorphic xanthoastrocytoma, WHO grade 3 (former anaplastic pleomorphic xanthoastrocytoma). MRI: Magnetic resonance imaging, WHO: World Health Organization.

Neural and neuronal-glial tumors

Tumors with a neural component are grouped into the new classification. To the previously known, three new types were added (even though the first one is still provisional): DGONC, myxoid glioneuronal tumor, and multinodular and vacuolating neuronal tumor [Table 1].[22]

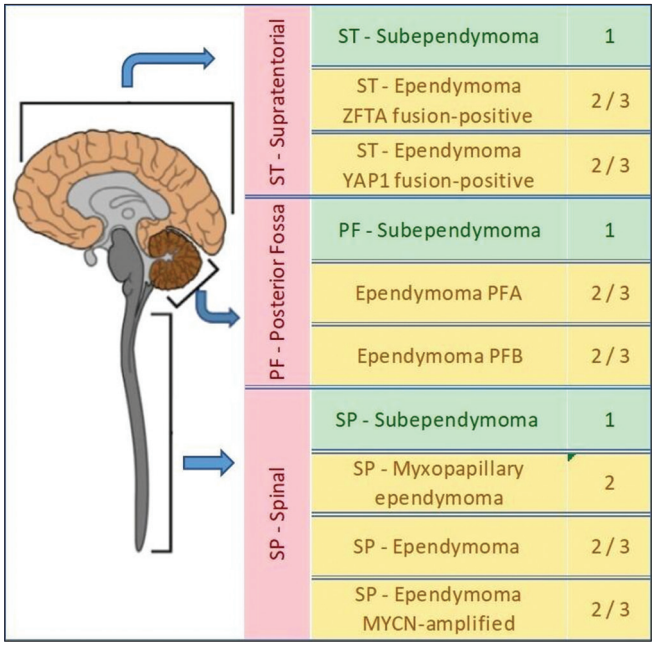

Figure 4: Classification of ependymomas according to the WHO classification 2021: This tumor type is categorized based on both its histological location and molecular characteristics. WHO: World Health Organization. ZFTA: Zinc finger translocation associated (previously known as C11orf95), YAP: Yes-associated protein, PF: Posterior Fossa, MYCN: Myelocytomatosis viral oncogene neuroblastoma derived homolog.

Ependymomas

Ependymomas are third in terms of frequency among children, after gliomas and medulloblastomas (comprising 5–10% of cases). Around 90% of ependymomas are intracranial, with the majority arising in the posterior fossa (PF).[25,34] To group them, a combination of histopathological, molecular features, and anatomic sites are considered [Figures 4 and 5]. This type of neoplasm can be classified as grade 1, 2, or 3. Among them, subependymoma (an infrequent occurrence) is the only grade 1, as myxopapillary ependymoma is now classified as grade 2 due to its potential for relapse, similar to other ependymal tumors. Notably, the term "anaplastic" has been removed from the current classification.[6]

Supratentorial ependymomas are classified based on two molecular fusions. On one hand, the C11orf95-RELA fusion is present in 70% of cases. At present, it is referred to as ZFTA (C11orf95 gene designation), given that it might fuse with more ligands than RELA.[22] On the other hand, YAP1 gene fusions characterize the other group. There exists a subset that cannot be classified under these disorders, which is designated as NEC.[22] The prognostic implications of these fusions remain unclear.[8,27]

In relation to PF ependymomas, the division has ultimately been incorporated based on the methylation profile into two more common subtypes (A and B). Subtype A (PFA) is characterized by a relative loss of the epigenetic marker trimethylation H3K27 and is associated with a worse outcome. Subtype B (PFB) is more prevalent in older children, and although it is associated with better survival,

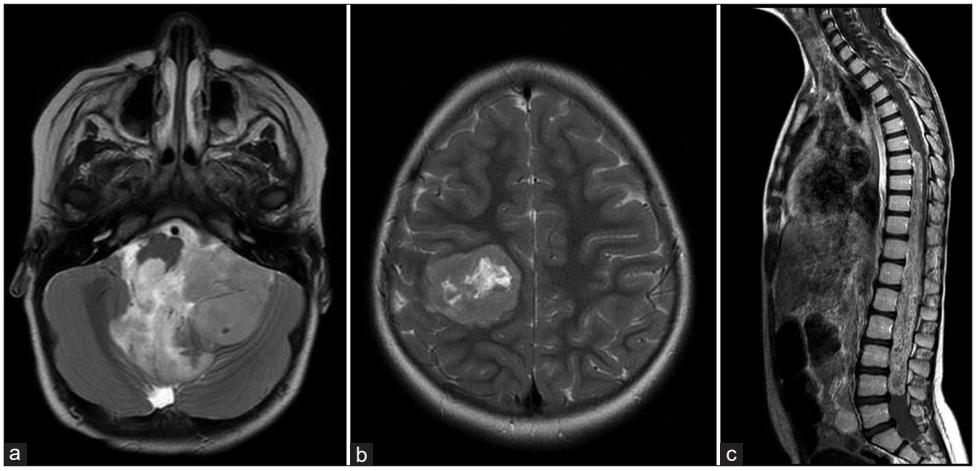

Figure 5: Ependymomas: (a) MRI T2, Axial section. 2-year-old patient with ependymoma PFA, WHO grade 3. (b) MRI T2, Axial section of a 2-year-old patient with a supratentorial ependymoma ZFTA fusion-positive, WHO grade 3. (c) MRI T1 with gadolinium, Sagittal section. 12-year-old patient with a spinal myxopapillary ependymoma, WHO grade 2. MRI: Magnetic resonance imaging, WHO: World Health Organization, PFA: Posterior fossa type A. ZFTA: Zinc finger translocation associated (previously known as C11orf95).

its prognostic value is not significant in patients who have received conformal radiotherapy.[8,27,33,45]

Choroid plexus tumors

The main modification observed is the grouping of these types of neoplasms into one family. They have been separated from neuroepithelial primary tumors. The remaining classification of choroid plexus neoplastic tumors has not undergone significant changes.[22]

Embryonal tumors

Embryonal tumors constitute a heterogeneous type of malignant neoplasm of the CNS.[6] They constitute 20% of pediatric CNS neoplasms.[26] Typically, they are defined by small, round, and blue cells. Historically, they were named primitive neuroepithelial tumors (PNET).[16,36] Those presented in the PF corresponded to medulloblastomas, pineal region to pineoblastomas (names still conserved), and those from the anterior or mid fossa to supratentorial PNET.[29,36]

In 2016, these types of entities were reclassified according to molecular profiles combined with histological features. In this way, the term PNET disappeared, grouping them in a unique family of CNS embryonal tumors. Based on an integrated taxonomy and putting special emphasis on molecular profile, the WHO 5th edition associates two groups: medulloblastomas and other embryonal tumors [Table 2].[6]

Medulloblastoma

Medulloblastomas constitute the most frequent solid malignant tumor in pediatrics.[32] Seventy per cent of the cases occur in children under the age of 10, and one-third of them present under the age of three. Medulloblastomas are exclusively located in the PF and represent more than 60% of childhood embryonal neoplasms.[28,31,37,41]

Factors related to poor outcomes included dissemination at the time of presentation, young age (<3 or five years), and residual tumor after surgery (>1.5 cm).[32,42] Originally, there were four morphological variants described: classical, non-small cell anaplastic, nodular desmoplastic, and with nodularity extended.[15] Then, with the advent of molecular biology, four groups arose: wingless-related integration site-activated (WNT-activated), sonic hedgehog (SHH) activated, group 3, and group 4.[41] Then, the SHH subtype may be subdivided into two categories based on the TP53 state (mutant vs. wild type), each exhibiting distinct clinical and pathological features [Figure 6].[22]

Even though there is a correlation between morphological and molecular variants, the new classification may inform them according to the analyzed features: medulloblastoma histologically defined or medulloblastoma genetically defined.[22]

Table 2: Embryonal tumors according to the WHO classification 2021 (5th edition).

Embryonal tumor of the central nervous system. The World Health Organization Classification, 5th edition.
Medulloblastoma
Medulloblastoma molecularly defined.
Medulloblastoma, WNT-activated
Medulloblastoma, SHH-activated and TP53-wildtype
Medulloblastoma, SHH-activated and TP53-mutant
Medulloblastoma, non-WNT, non-SHH
Medulloblastoma, histologically defined.
Other CNS embryonal tumors
Atypical teratoid/rhabdoid tumor
Cribriform neuroepithelial tumor
ETMR
CNS neuroblastoma, FOXR2-activated
CNS tumor with BCOR internal tandem duplications
CNS embryonal tumor

WNT: Wingless-related integration site, SHH: Sonic hedgehog, ETMR: Embryonal tumor with multilayered rosettes, CNS: Central nervous system, BCOR: BCL6 corepressor

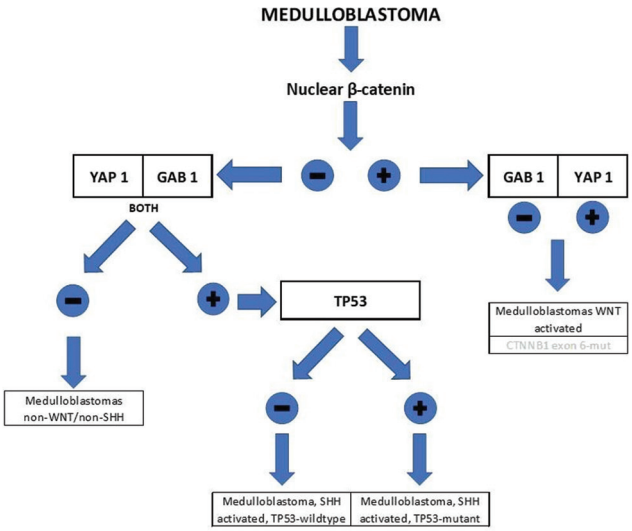

Figure 6: Medulloblastoma diagnosis algorithm used for classification into molecular groups according to WHO classification 2021. WHO: World Health Organization. YAP: Yes-associated protein, GAB: Grb2-associated binding protein.

Given the heterogeneity of these tumors and the need for classification based on molecular and histological combinations, it is necessary to present them in an integrated manner using the layered method described above. In addition, the terms NOS and NEC should be employed as needed.

Other embryonal tumors

The rest of the embryonal tumors include the following types: Atypical teratoid rhabdoid tumors, embryonal tumor with multilayered rosettes, CNS neuroblastoma, FOXR2-

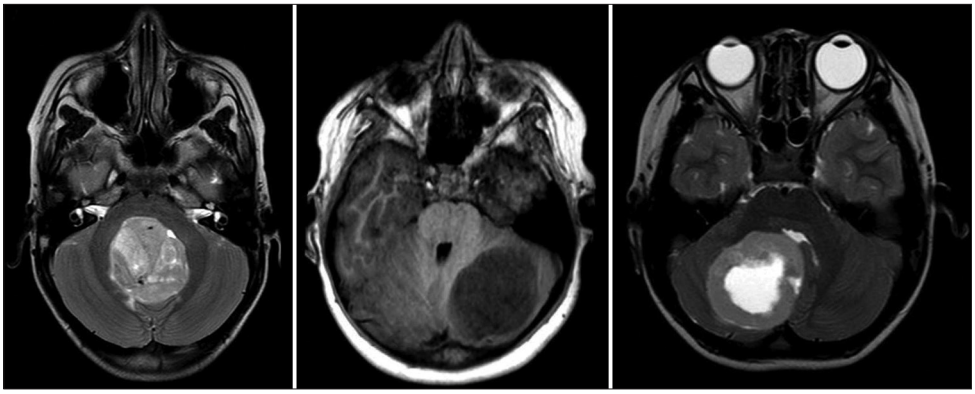

Figure 7: Embryonal tumors: (a) MRI T2, an axial section of an 11-year-old boy with a histologically defined medulloblastoma (desmoplastic), WHO grade 4. (b) MRI T1 with gadolinium, an axial section of an 8-year-old patient with a molecularly and histologically defined hemispheric medulloblastoma. Subtype: desmoplastic nodular. SHH TP53-mutant. WHO grade 4. (c) MRI T2, an axial section of a 2-year-old patient with a CNS tumor with BCOR internal tandem duplications. WHO grade 4. MRI: Magnetic resonance imaging, WHO: World Health Organization, SHH: Sonic hedgehog, CNS: Central nervous system. BCOR: BCL6 corepressor.

activated, and CNS tumor with BCOR internal tandem duplication. While the first two were present in prior classifications, the last three have been included in the latest classification. There has been an important discussion about the incorporation of BCOR-altered tumors, considering their potential neuroectodermal nature due to features resembling mesenchymal neoplasms [Figure 7].

Nevertheless, many times, it is not possible to count with all diagnostic methods to classify them, giving rise to being informed as NOS or NEC embryonal tumors if they do not have molecular features that could categorize them in some of the previously described.[24]

Pineal tumors

The types previously included are still present in this group: pineocytoma, pineal parenchymal tumor of intermediate differentiation, and pineoblastoma. The 2021 classification introduced the addition of the desmoplastic myxoid tumor of the pineal region SMARCB1-mutant, a rare neoplasm without histopathological signs of malignancy.[44]

Except for pinealocytomas and pinealoblastomas, the behavior of the remaining neoplasms is not completely understood, which makes it impossible to define their tumor grade.[22]

On the other hand, molecular groups based on methylation have been described for pinealoblastomas, showing different behaviors and prognoses. However, these groups were not included in the WHO 2021 classification.[17,35]

Craniopharyngioma

Craniopharyngioma constitutes a unique tumor with two variants: adamantinomatous and papillary. At present, they are classified as two different types of neoplasms due to their clinical, demographic differences, radiological features, histopathological findings, and molecular disorders.[10,30]

CONCLUSION

CNS tumor classifications have been described by several eminent professionals since the middle of the 19th century, resulting in the necessary publication by the WHO of a useful system to establish a common language worldwide. From 1979 up to the present day, five different editions have been released over the years.

The fifth edition consolidates the paradigm change thanks to molecular advances, even though the transition between morphological characterization and molecular biology is still in process. The advances, as described in the layer report from 2016, include the replacement of Roman numerals with Arabic ones, the exclusion of entities, the introduction of new family groups in the case of gliomas, and the description of tumor types and subtypes based on their molecular features. In addition, the incorporation of c-IMPACT-NOW reports marks a significant change, with special emphasis on neoplasms that affect younger patients.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

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

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

REFERENCES

1. Bailey P, Cushing H. A classification of tumors of the glioma group on a histogenetic basis with a correlation study of prognosis. Philadelphia, PA: Lippincott and Williams; 1926.
2. Banan R, Hartmann C. The new WHO 2016 classification of brain tumors-what neurosurgeons need to know. Acta Neurochir (Wien) 2017;159:403-18.
3. Becker AP, Scapulatempo-Neto C, Carloni AC, Paulino A, Sheren J, Aisner D, *et al*. KIAA1549: BRAF gene fusion and FGFR1 hotspot mutations are prognostic factors in pilocytic astrocytoma. J Neuropathol Exp Neurol 2015;74:743-54.
4. Chatwin HV, Cruz Cruz J, Green AL. Pediatric high-grade glioma: Moving toward subtype-specific multimodal therapy. FEBS J 2021;288:6127-41.
5. Clarke M, Mackay A, Ismer B, Pickles J, Tatevossian R, Newman S, *et al*. Infant high-grade gliomas comprise multiple subgroups characterized by novel targetable gene fusions and favorable outcomes. Cancer Discov 2020;10:942-63.
6. Cohen A. Brain tumors in children. N Engl J Med 2022;386:1922-31.
7. Daumas-Duport C, Scheithauer BW, O´Fallon J, Kelly P. Grading of astrocytomas. A simple and reproducible method. Cancer 1988;62:2152-65.
8. Ellison DW, Aldape KD, Capper D, Fouladi M, Gilbert M, Gilbertson R, *et al*. cIMPACT-NOW update 7: Advancing the molecular classification of ependymal tumors. Brain Pathol 2020;30:863-6.
9. Guerreros Stucklin AS, Ryall S, Fukuoka K, Zapotocky M, Lassaletta A, Li C, *et al*. Alterations in ALK/ROS1/NTRK/MET drive a group of infantile hemispheric gliomas. Nat Commun 2019;10:4343.
10. Holsken A, Sill M, Merkle J, Schweizer L, Buchfelder M, Flitsch J, *et al*. Adamantinomatous and papillary craniopharyngiomas are characterized by distinct epigenomic as well as mutational and transcriptomic profiles. Acta Neuropathol Commun 2016;4:20.
11. Jones DT, Kocialkowski LL, Pearson D, Bäcklund LM, Ichimura K, Collins V. Tandem duplication producing a novel oncogenic BRAF fusion gene defines the majority of pilocytic astrocytomas. Cancer Res 2008;68:8673-7.
12. Kernohan JW, Mabon RF, Svien HJ, Adson AW. A simplified classification of the gliomas. Symposium on a new simplified concept of gliomas. Proc Staff Meet Mayo Clin 1949;24:71-5.
13. Kleihues P, Burger PC, Scheithauer BW. Histological typing of tumors of the central nervous system. Heidelberg, New York: Springer Verlag; 1993.
14. Kleihues P, Cávenee WK. Pathology and genetics of tumors of the nervous system. Lyon: IARC Press; 2000.
15. Kristensen BW, Priesterbach-Ackley LP, Petersen JK, Wesseling P. Molecular pathology of tumors of the central nervous system. Ann Oncol 2019;30:1265-78.
16. Li BK, Al-Karmi S, Huang A, Bouffet E. Pediatric embryonal brain tumors in the molecular era. Expert Rev Mol Diagn 2020;20:293-303.
17. Li BK, Vasiljevic A, Dufour C, Yao F, Ho BL, Lu M, *et al*. Pineoblastoma segregates into molecular sub-groups with distinct clinico-pahtologic features: A Rare Brain Tumor Consortium registry study. Acta Neuropathol 2020;139:223-41.
18. Louis DN. The next step in brain tumor classification:" Let us now praise famous men". or molecules? Acta Neuropathol 2012;124:761-2.
19. Louis DN. Who classification of tumors of the central nervous system. Lyon: IARC Press; 2003.
20. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Ellision DW, Figarella-Branger D, *et al*. WHO classification and grading of tumors of the central nervous system. Lyon: IARC Press; 2016.
21. Louis DN, Perry A, Burger P, Ellison DW, Reifenberger G, von Deimling A, *et al*. International Society of Neuropathology-Haarlem consensus guidelines for nervous system tumor classification and grading. Brain Pathol 2014;24:429-35.
22. 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.
23. Louis DN, Wesseling P, Aldape K, Brat D, Capper D, Cree IA, *et al*. cIMPACT-NOW update 6: New entity and diagnostic principle recommendations of the cIMPACT-Utrecht meeting on future CNS tumor classification and grading. Brain Pathol 2020;30:844-56.
24. Louis DN, Wesseling P, Paulus W, Giannini C, Batchelor T, Cairncross JG, *et al*. cIMPACT-NOW update 1: Not otherwise specified (NOS) and not elsewhere classified (NEC). Acta Neuropathol 2018;135:481-4.
25. Marinoff AE, Ma C, Guo D, Snuderl M, Wright K, Manely P, *et al*. Rethinking childhood ependymoma: A retrospective, multi-center analysis reveals poor long-term overall survival. J Neurooncol 2017;135:201-11.
26. McKean-Cowdin R, Razavi P, Barrington-Trimis J, Baldwin RT, Asgharzadeh S, Cockburn M, *et al*. Trends in childhood brain tumor incidence, 1973-2009. J Neurooncol 2013;115:153-60.
27. Merchant TE, Bendel AE, Sabin ND, Burger P, Shaw D, Chang E, *et al*. Conformal radiation therapy for pediatric ependymoma, chemotherapy for incompletely resected ependymoma, and observation for completely resected, supratentorial ependymoma. J Clin Oncol 2019;37:974-83.
28. Millard NE, De Braganca KC. Medulloblastoma. J Child Neurol 2016;31:1341-53.
29. Mueller S, Chang S. Pediatric brain tumors: Current treatment strategies and future therapeutic approaches.

Neurotherapeutics 2009;6:570-86.
30. Müller HL, Merchant TE, Warmuth-Metz-M, Martinez-Barber JP, Puget S. Craniopharyngioma. Nat Rev Dis Primers 2019;5:75.
31. Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2011-2015. Neuro Oncol 2018;20(suppl_4):iv1-86.
32. Packer RJ, Cogen P, Vezina G, Rorke LB. Medulloblastoma: Clinical and biologic aspects. Neuro Oncol 1999;1:232-50.
33. Panwalkar P, Clark J, Ramaswamy V, Hawes D, Yang F, Dunham C, *et al*. Immunohistochemical analysis of H3K27me3 demonstrates global reduction in group A childhood posterior fossa ependymoma and is a powerful predictor of outcome. Acta Neuropathol 2017;134:705-14.
34. Paulina AC, Wen BC, Buatti JM, Hussey D, Zhen WK, Mayr NA, *et al*. Intracranial ependymomas: An analysis of prognostic factors and patterns of failure. Am J Clin Oncol 2002;25:117-22.
35. Pfaff E, Aichmüller C, Sill M, Stichel D, Snuderl M, Karajannis MA, *et al*. Molecular subgrouping of primary pineal parenchymal tumors reveals distinct subtypes correlated with clinical parameters and genetic alterations. Acta Neuropathol 2020;139:243-57.
36. Rorke LB. The cerebellar medulloblastoma and its relationship to primitive neuroectodermal tumors. J Neuropathol Exp Neurol 1983;42:1-15.
37. Rutkowski S, von Hoff K, Emser A, Zwiener I, Pietsh T, Figarella-Branger D, *et al*. Survival and prognostic factors of early childhood medulloblastoma: An international meta-analysis. J Clin Oncol 2010;28:4961-8.
38. Santarpia L, Lippman SM, El-Naggar AK. Targeting the MAPK-RAS-RAF signaling pathway in cancer therapy. Expert Opin Ther Targets 2012;16:103-19.
39. Sturm D, Pfister SM, Jones DT. Pediatric gliomas: Current concepts on diagnosis, biology, and clinical management. J Clin Oncol 2017;35:2370-7.
40. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, *et al*. WHO classification of tumors of haematopoietic and lymphoid tissues. Lyon: IARC Press; 2008.
41. Taylor MD, Northcott PA, Korshunov A, Remke M, Cho YJ, Clifford S, *et al*. Molecular subgroups of medulloblastoma: The current consensus. Acta Neuropathol 2012;123:465-72.
42. Virchow R. Die krankhaften geschwulste. Berlin: Hirschwald; 1863.
43. Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics. CA Cancer J Clin 2014;64:83-103.
44. Wefers A, Bens S, Nemes K, Agaimy A, Oyen F, Vogelgesang S, *et al*. Desmoplastic myxoid tumor, SMARCB1-mutant clinical, histopathological and molecular characterization of a pineal region tumor encountered in adolescents and adults. Acta Neuropathol 2020;139:277-86.
45. Wu J, Armstrong TS, Gilbert MR. Biology and management of ependymomas. Neuro Oncol 2016;18:902-13.
46. Zülch KJ. Histological typing of tumors of the central nervous system. Geneva: World Health Organization; 1979.

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