Tumors of the central nervous system. Classification of the World Health Organization 2021. Towards a paradigm shift

Ramiro J. del Río*, Santiago E. Cicutti*, Javier D. González Ramos*

ABSTRACT
The study of central nervous system (CNS) tumors is a subject of great interest and such knowledge is of great importance in medical practice.

The classifications of CNS neoplasms began in the mid-19th century, until the World Health Organization (WHO) published, in 1979, the first edition of a useful systematic review for the purpose of establishing a common language for all medical specialties. To date, 5 updated editions of neoplastic taxonomy have been published.

The fifth edition, from 2021, consolidates the paradigm shift brought about by molecular advances, although the transition between morphological and molecular biological characterization is still in progress.

In this article, the new modifications introduced in the different most frequent families of tumors in pediatrics are analyzed, emphasizing useful information for pediatricians in their daily practice and multidisciplinary consultations.

Keywords: central nervous system neoplasms; International Classification of Diseases; World Health Organization; pediatrics.

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INTRODUCTION
Central nervous system (CNS) tumors are greatly relevant in pediatric practice because they are the most frequent solid neoplasms in this age group and are second only to leukemias among malignancies.1,2

Given the difference between this type of lesions and neoplasms found in other organs, it was not until 1979 that the World Health Organization (WHO) published the first classification of central nervous system tumors based on several previous systematic classifications by different authors. Therefore, an attempt was made to group the different entities according to their common characteristics;3-6 subsequently, over the years, several updates have been published,7-11 until the 5th edition was issued in 2021.12

Institutions with well-structured tumor banks are able to contribute to the establishment of molecular taxonomy, through the creation of information networks with multiple parameters used to modify and redirect diagnosis and treatment in order to improve prognosis.

The objective of this article is to summarize the most important aspects about the tumors that most frequently develop in pediatric patients, taking into account the information that may be useful for pediatricians.

GENERAL ASPECTS
• Central nervous system tumors are a heterogeneous group of entities with symptoms depending on their location, size, the patient’s age, and tumor lineage.13
• In the case of supratentorial lesions, intracranial hypertension syndrome with the typical triad of vomiting, headache, and papilledema is a common form of presentation in large lesions.
• In the case of infant patients whose cranial sutures have not yet fused, instead of the typical symptoms, a marked increase in head circumference, tense fontanelle, and sutural diastasis are more feasible.
• In the case of lesions in eloquent areas (motor, sensory, visual, etc.), focal syndromes may develop depending on the region involved.
• The presence of irritation in the cerebral cortex will lead to different types of seizures; seizures tend to be more frequent in neoplasms of the temporal bone and in certain tumor lineages (dysembryoplastic neuroepithelial tumor).
• In addition, tumors that occupy the posterior fossa in case of developing hydrocephalus will result in intracranial hypertension; vomiting due to irritation of the area postrema may occur in the occupation of the fourth ventricle, while alternating syndromes are typical in brainstem infiltration. Finally, cerebellar disorders may develop along cerebellar tumors.

• With a few exceptions, where imaging tests provide high diagnostic certainty and surgical resection is not indicated, tumor removal should be performed as far as possible without increasing morbidity; otherwise, biopsy sampling is practically mandatory. By analyzing the biopsy specimen, pathologists will be able to make a report based on the classification published by the WHO, which will guide the type of treatment and prognosis.

CHANGES IN THE 5TH EDITION OF THE WHO CLASSIFICATION
The new classification published in 2021 takes into account both molecular and histological components, resulting in a hybrid taxonomy indicative of a new paradigm that is still in flux.

First of all, the terms “entity” and “variant” were replaced by “type” and “subtype,” respectively, to standardize the books on the 5th edition of the WHO classification.12

The nomenclature of neoplasms attempts to be as simple as possible; the following terms are used to define them: location, age of presentation, or genetic modifiers with clinical utility11 (e.g.: diffuse midline glioma, K27M-altered). “Modifying” terms, such as “anaplastic” or “polymorphic,” were eliminated.

Tumor grading has also been changed in an attempt to resemble more closely the neoplasms present outside the CNS while retaining some classical features. For example, Roman numerals were removed in favor of Arabic numerals.14

Molecular biomarkers may be important prognostic indicators; for this reason, they were also included when determining certain tumor grades.

The suffix NOS (not otherwise specified), which used to group all those tumors that could not be assigned a specific type, is now divided into 2. On the one side, the term NOS continues to be used for those entities that cannot be classified according to the WHO because specific tests cannot be performed, either due to shortage of material, specimen deterioration, or lack of methods to do the necessary molecular tests. On the other side, the expression NEC (not elsewhere classified) is introduced in relation
to neoplasms where the required tests were performed, but their report is uncertain when it comes to classifying the specimen according to any of the types established by the WHO.\textsuperscript{15}

**LAYERED INTEGRATED DIAGNOSIS**

Since the 2016 revision, based on a successful adaptation for hematopoietic tumors,\textsuperscript{16} Davis Louis proposed to integrate molecular and histological information in the form of layers, which was accepted by experts and approved in the Haarlem consensus.\textsuperscript{15,17} Such systematic classification serves as a guideline for pathologists when preparing the corresponding reports.

The concept involves successive levels, where the first layer indicates the integrated diagnosis; the second layer, the histological type; the third layer, the grade; and the fourth layer, the molecular characteristics. The premise “molecular biology beats histology” emerges from this model.\textsuperscript{18} For example, a midline glioma demonstrating an alteration in histone K27 will be considered grade 4, even if the lesion does not exhibit any morphological feature of aggressive behavior. As can be inferred, the lower levels give way to the higher levels until reaching the first level, where the integrated diagnosis is finally expressed (Figure 1).

**2021 CLASSIFICATION OF PEDIATRIC TUMORS**

The following is a description of CNS tumors in children, with emphasis on those that underwent changes in the latest classification.

**Gliomas**

The 5\textsuperscript{th} edition of the WHO took a new approach to the classification of glial, glioneuronal, and neuronal tumors. They were divided into 6 different 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 (Table 1 and Figure 2).

Choroid plexus tumors were eliminated from this category.\textsuperscript{12}

As can be seen in such division, there is a great separation between pediatric-type and adult-type diffuse gliomas, which may have a similar histology, but their behavior entails important differences; for example, pediatric gliomas rarely progress to higher grades. However, youth and adolescents show an overlap, so it is feasible to find entities corresponding to both age groups.

Pediatric-type diffuse low-grade gliomas include 4 types: diffuse astrocytoma, \textit{MYB}- or \textit{MYBL1}-altered; angiocentric glioma; polymorphous low-grade neuroepithelial tumor of the young (PLNTY); and diffuse low-grade glioma, MAPK pathway-altered. Of these, only the angiocentric glioma describes a typical morphological characteristic, while the rest are defined by their biomarkers (\textit{MYB}, \textit{MYBL1}, \textit{BRAF}, \textit{FGFR}). The latter, in turn, may have astrocytic or oligondedrocytic morphology.\textsuperscript{15} Unlike circumscribed gliomas, diffuse gliomas may be difficult to resect completely, especially deeply located tumors. Alterations in the MAPK pathway require particular attention, including \textit{BRAF} oncogene mutation or fusion, \textit{NF1} mutation, \textit{FGFR1} mutation, and fusion in the \textit{NTRK} gene family.\textsuperscript{19,20} This allows to focus on targeted therapies, such as \textit{BRAF} inhibitors (dabrafenib) or MEK pathway inhibitors (trametinib).\textsuperscript{21}

![Figure 1. Example of layered integrated diagnosis as per the Haarlem consensus](image-url)
Diffuse high-grade gliomas also include 4 types: diffuse midline glioma, $H3\ K27$-altered; diffuse hemispheric glioma, $H3\ G34$-mutant; diffuse pediatric-type high-grade glioma, $H3$-wildtype and $IDH$-wildtype; and infant-type hemispheric glioma. These account for 10% of brain tumors in children and have a poor prognosis.\textsuperscript{22} Diffuse midline glioma, $H3\ K27$-altered, includes a relatively frequent tumor formerly known as diffuse intrinsic pontine glioma (DIPG). The other 3 types correspond to new entities that require molecular biology for characterization. Infant-type hemispheric glioma is a new entity occurring in newborns and infants with a typical molecular profile ($ALK$, $ROS1$, $NTRK1/2/3$, or $MET$).\textsuperscript{23,24}

<table>
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<th>Table 1. World Health Organization classification of glial tumors (5th edition, 2021)</th>
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<td><strong>Classification of gliomas, glioneuronal tumors, and neuronal tumors</strong></td>
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<td>Diffuse astrocytoma, $MYB$- or $MYBL1$-altered</td>
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<td>Angiocentric glioma</td>
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<td>Polymorphous low-grade neuroepithelial tumor of the young (PLNTY)</td>
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<td><strong>Circumscribed astrocytic gliomas</strong></td>
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<td>Ganglioglioma</td>
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<td>Desmoplastic infantile ganglioglioma (DIG) / desmoplastic infantile astrocytoma</td>
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<td>Dysembryoplastic neuroepithelial tumor</td>
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<td>Multinodular and vacuolating neuronal tumor</td>
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<td>Extraventricular neurocytoma</td>
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<td>Cerebellar liponeurocytoma</td>
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Therefore, the disappearance of 2 pediatric tumor lineages may be inferred: oligodendroglioma and glioblastoma, tumors that have become adult-type tumors.

Circumscribed astrocytic gliomas differ from diffuse tumors in that they are well-limited solid lesions. Their name erroneously leads to believe that they are low-grade; however, among the numerous entities observed, not all of them are necessarily not very aggressive, nor are they exclusive to pediatric patients.

This tumor family includes pilocytic astrocytoma, the most frequent CNS tumor in children (20% of CNS neoplasms in patients younger than 20 years),25–27 most commonly located in the cerebellum and suprasellar region. The most usual molecular marker is the KIAA1549-BRAF fusion (MAPK pathway).

Another lesion in this group preferentially found in children is pleomorphic xanthoastrocytoma, which may be grade 2 or 3 and is one of the few examples of tumor progression. The alteration usually found is the BRAF V600 mutation, which may be treated with a targeted therapy, as mentioned above.12

Glioneuronal and neuronal tumors

All tumors with a neural component were grouped together in the new classification. The most frequent tumors are gangliogliomas and dysembryoplastic neuroepithelial tumor (DNT). Gangliogliomas are located in the brainstem, supratentorial area, and bulbomedullary junction and are generally grade 1, although, in a few cases, signs of aggressive behavior (grade 3) are observed. DNT is a benign, grade 1, supratentorial lesion that usually manifests with seizures. In addition to previously known entities, 3 new types were introduced (although the first one is still provisional): diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters (DGONC), myxoid glioneuronal tumor, and multinodular and vacuolating neuronal tumor.12

Ependymomas

Ependymomas are the third most frequent type of CNS tumors in children, after gliomas and medulloblastomas (5–10%); 90% of ependymomas are intracranial at the expense of the posterior fossa.28,29

To group them, histopathological and molecular characteristics and the anatomic site were combined30 (Figures 3 and 4).

This type of neoplasms is usually grade 1, 2, or 3. Subependymoma (rare lesion) is the only...
grade 1 tumor, since myxopapillary ependymoma became grade 2 given its potential for recurrence, similar to the rest of the ependymomas.

In relation to these entities, as mentioned above, the term anaplastic was successfully eliminated; this variant no longer exists.\(^{31}\)

Supratentorial tumors are categorized according to 2 molecular fusions. On the one side, the \(C11orf95-RELA\) fusion, present in 70% of cases and now called \(ZFTA\) fusion (designation of the \(C11orf95\) gene)\(^ {12}\) and, on the other side, the fusion involving the \(YAP1\) gene. It remains to define a small number of tumors that do not present any of these alterations, which, for the moment, would be defined as NEC.\(^ {12}\) Although the \(ZFTA\) fusion is associated with a worse prognosis, patients who received radiotherapy did not have a uniform course, so the true value of this marker...
is yet unclear.\textsuperscript{30,31}

In relation to posterior fossa ependymomas, the division according to the methylation profile into the 2 most common subtypes (A and B) was finally introduced. Posterior fossa ependymomas, subtype A (PFA) present a relative loss of H3K27 trimethylation, an epigenetic marker, and have a worse outcome. Posterior fossa ependymomas, subtype B (PFB) occur in older children and are associated with a better survival rate.\textsuperscript{30–33}

**Choroid plexus tumors**

The main change in this type of entity was that it was categorized within a family of its own, separated from the group of primary neuroepithelial tumors. Papillomas or carcinomas may develop in these organs, with a lesion of intermediate malignancy called atypical papilloma.\textsuperscript{12}

**Embryonal tumors**

Embryonal tumors are a heterogeneous type of CNS malignant neoplasms\textsuperscript{21} of the highest aggressive behavior (grade 4 in all types and subtypes) and account for 20% of pediatric brain neoplasms\textsuperscript{34} (Figure 5). Typically defined as small, round, blue cells, they were originally named primitive neuroectodermal tumors (PNETs).\textsuperscript{1,35} Embryonal tumors located in the posterior fossa corresponded to medulloblastomas; those in the pineal region, pineoblastomas (these names are still used); and those in the anterior or middle fossa, supratentorial PNETs.\textsuperscript{35,36}

In 2016, these types of entities were reclassified according to their molecular profiles and combined with histological features. The term “PNET” thus disappeared and they are now all grouped into a single family of CNS embryonal tumors. Based on an integrated taxonomy with a strong emphasis on molecular profiling, the 5th edition of the WHO classification associated 2 groups: medulloblastomas and other embryonal tumors.\textsuperscript{21}

**Medulloblastomas**

Medulloblastomas are the most frequent malignant solid tumor in pediatrics;\textsuperscript{37} 70% of cases occur in children younger than 10 years, with one third being younger than 3 years. They originate exclusively in the posterior fossa and account for more than 60% of childhood embryonal tumors.\textsuperscript{38–41}

Typically, the factors associated with a poor outcome were dissemination at the time of presentation, young age (younger than 3 or 5 years), and post-surgical tumor residue greater than 1.5 cm\textsuperscript{3}.\textsuperscript{37}

Four morphologic variants were originally described: classic, desmoplastic/nodular, medulloblastoma with extensive nodularity (MBEN), and large cell/anaplastic.\textsuperscript{42}

Subsequently, with the advent of molecular biology, 4 subtypes were established: WNT-activated, sonic hedgehog (SHH) activated, group 3, and group 4.\textsuperscript{40}

In turn, the SHH subtype can be subdivided into 2 subgroups according to their \textit{TP53} status (mutant versus wildtype), with different clinicopathological characteristics.\textsuperscript{12}

Although there is a correlation between morphological and molecular variants, based on the new classification, they are reported according to the characteristics analyzed, i.e. histologically defined medulloblastoma or genetically defined medulloblastoma.\textsuperscript{12}

**Figure 5. Magnetic resonance imaging tests of patients with embryonal tumors**
Given the heterogeneity of these tumors and the need to group them according to a combination of histological and molecular features, it is highly necessary to report them according to the layered and integrated diagnosis method described above, with the terms NOS and NEC when necessary.

**Other embryonal tumors**
- The remaining embryonal tumors comprise the following types: atypical teratoid/rhabdoid tumor (AT/RT), embryonal tumor with multilayered rosettes (ETMR), CNS neuroblastoma, FOXR2-activated, and CNS tumor with BCOR internal tandem duplication. AT/RT and ETMR were present in previous classifications, whereas the last 3 were included in the latest one.
- However, many times, not all diagnostic methods are available to establish the type, so they could be reported as NOS or NEC embryonal tumors if they do not have molecular characteristics that would allow them to be classified as any of those described above.\(^4\)\(^3\),\(^4\)\(^4\)

**Pineal tumors**
This group still includes the types of pineal tumors included previously: pineocytoma, pineal parenchymal tumor of intermediate differentiation (PPTID), and pineoblastoma. The 2021 classification added desmoplastic myxoid tumor of the pineal region SMARCB-1-mutant, a rare neoplasm lacking histopathological signs of malignancy.\(^4\)\(^5\)

Except for the classically known pineocytomas and pineoblastomas, the rest of the neoplasms do not have an entirely certain behavior; tumor grade cannot yet be defined.\(^1\)\(^2\)

In addition, molecular variants of pineoblastomas defined by methylation with different behavior and prognosis have been described without being included in the classification.\(^4\)\(^6\),\(^4\)\(^7\)

**Craniopharyngiomas**
Craniopharyngioma was considered a single tumor with 2 variants: adamantinomatous craniopharyngioma and papillary craniopharyngioma. Today they are classified as 2 different types of neoplasms, given their clinical demographic differences, radiological features, histopathological findings, and molecular alterations.\(^4\)\(^8\),\(^4\)\(^9\)

**CONCLUSIONS**
Given the frequency of CNS tumors, they should be taken into account in the diagnostic algorithm of patients presenting with suspicious symptoms.

The large heterogeneous group of this type of tumors led several eminent professionals to make various classifications since the mid-19th century; the latest is the 5th edition of the WHO classification, published in 2021.

The knowledge and systematic characterization of the different entities allows addressing the most important aspects of these neoplasms and understanding their diagnostic, prognostic, and therapeutic characteristics.

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