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Review Article

A simplified overview of the World Health Organization classification of central nervous system tumors 2021

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ABSTRACT

Background: Building on the 2016 updated fourth edition and the work of consortium to inform molecular and practical approach to CNS tumor taxonomy, the major dramatic change occurs in 2021 fifth edition by advancing the role of molecular diagnostics in CNS tumor classification. The present review summarizes the major general changes in the 2021 fifth edition classification and the specific changes in each taxonomic category.

Methods: The review was designed in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis. Articles published in PubMed Central, Medline, and Embase databases till now were all searched. Only nonexperimental and nonanimal clinical studies were included in the study. Articles written only in the English language were considered.

Results: All IDH mutant diffuse astrocytic tumors are considered in a single type "astrocytoma IDH mutant" and then graded as CNS WHO Grades 2–4. Pediatric-type diffuse gliomas are now classified as separate entity. Anatomical site is also taken into consideration to classify ependymoma. The "Desmoplastic myxoid tumor of the pineal region, SMARCB1 mutant" and "Atypical neurofibromatous neoplasm of unknown biological potential" are new tumor type added to pineal and neurofibroma group, respectively. Mesenchymal tumor is now termed as only solitary fibrous tumor. Adamantinomatous and papillary subtype of craniopharyngioma are now classified as distinct tumor type. The new term "Pituitary neuroendocrine tumor" has been coined for pituitary adenoma.

Conclusion: The WHO CNS-5 introduces a new knowledge into the classification with progressive manner by introducing newly recognizing entities, by obsoleting tumor type, and by adjusting the taxonomic structure.

Keywords: Brain tumor, Central nervous system, Classification, Diagnosis, World Health Organization

INTRODUCTION

The fourth edition of the WHO classification of brain tumor, which emphasizes molecular criteria as a major role for diagnosis of CNS tumors, was reviewed and published in year 2016.[14] Since there was a rapid advancement in neurosciences, ongoing discovery of new biomarkers, as well as newer drug targets, there was a further need to accelerate the revision of classification of 2016. Hence, Consortium to Inform Molecular and Practical Approach to CNS Tumor Taxonomy (cIMPACT-NOW) was established to convey new updates time to time which guide for future WHO classification.[19] The aim of this review was to summarize the major general and specific changes in the recent WHO CNS classification 2021 (WHO CNS-5) to easily learn and understand these changes.

MATERIALS AND METHODS

The review was designed in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis. Articles published in PubMed Central, Medline, and Embase databases till now were all searched. In the relevant literature, references were manually searched for additional articles. We screened the title and abstract by combining the term "WHO [All Fields] AND 2021 [All Fields] AND ("classification" [Subheading] OR "classification" [All Fields] OR "classification" [MeSH Terms]) AND ("brain tumors" [All Fields] OR "brain neoplasms" [MeSH Terms] OR ("brain" [All Fields] AND "neoplasms" [All Fields]) OR "brain neoplasms" [All Fields] OR ("brain" [All Fields] AND "tumors" [All Fields]) OR "brain tumors" [All Fields]).

Only nonexperimental and nonanimal clinical studies were included in the study. Articles written only in the English language were considered. Results of the literature search were imported to EndNote X9 (Clarivate Analytics, Philadelphia, Pennsylvania). Software utilization sought to reduce data entry errors and bias (i.e., duplicating references).

RESULTS

Thirty-seven articles were identified on searching the PubMed Central, Medline, and Embase database. Out of 37, 21 articles were screened based on removal of duplicates. After screening for eligibility of potential articles, 11 studies were included in this review.

In the WHO 2021 classification of brain tumors, the newly recognized tumor types in each tumor category are given in Table 1.

The tumor types with their revised nomenclature or revised placement are given in Table 2.

DISCUSSION

CNS tumor grading

CNS tumor grading is different from non-CNS tumor grading system. The WHO CNS-5 has moved CNS tumor grading much closer to how grading is done for non-CNS tumor, but has retained some traditional CNS tumor grading. Nonetheless, because CNS tumor grading system is still different from other tumor grading, the WHO CNS-5 endorses the use of term "CNS WHO grade" when assigning grade.[17]

Changes in the terminology and specific entities

(1) The WHO CNS-5 uses Arabic numerals in place of Roman numerals to become it more uniform as is currently done for all the other organ system grading.
(2) Tumors are graded within the types. This change was done for (i) to emphasize the biological similarities within tumor types rather than approximate clinical behavior, (ii) to provide more flexibility in using grade relative to the tumor type, and (iii) to conform with the WHO grading in non-CNS tumor type.[18]
(3) Types replace entities and subtypes replace variants. For examples, meningioma represents one type with numerous subtypes (Example – clear cells, chordoid, and rhabdoid).
(4) The term anaplastic, used extensively in the prior classification, has been dropped in favor of grading only.[17]
(5) Essential and desirable diagnostic criteria:

Each tumor type has been given certain essential diagnostic criteria necessary for a specific diagnosis as well as additional nonessential but nonetheless desirable criteria.[17]

(6) Not elsewhere classified (NEC):

In addition to not otherwise specified (NOS), which denotes tumors where complete molecular classification is not available, NEC has been added to denote tumors that have been fully characterized but that do not fit within the established classification system.[13,17]

Specific changes in the 5th edition

Diffuse gliomas

The WHO CNS-5 has divided the diffuse gliomas into adult- and pediatric-type diffuse glioma on the basis of their clinical and molecular distinction.

Adult-type diffuse gliomas:

In the 2016 WHO classification, IDH mutant diffuse astrocytic tumors were assigned to three different tumors type (diffuse astrocytoma, anaplastic astrocytoma, and glioblastoma) depending on histopathological parameters. In the present classification, however, all IDH mutant diffuse astrocytic tumors are considered a single type (astrocytoma and IDH mutant) and are then graded as CNS WHO Grades 2–4. Moreover, grading is no longer entirely histological, since the presence of cyclin-dependent kinase inhibitor (CDKN2A/B) homozygous deletion results in a CNS WHO grade of 4, even in the absence of microvascular proliferation or necrosis.

The WHO CNS-5 has divided adult-type diffuse gliomas into astrocytoma, IDH mutant; oligodendroglioma, IDH mutant, and 1p/19q codeleted; and glioblastoma, IDH wild type.[1,19] It is done to (1) address the poorly defined entity (such as oligoastrocytoma and IDH wild-type diffuse astrocytic tumors) and assign to more objectively defined entities, (2) use of grades with the types rather than requiring each grade to have different names, and (3) more ecumenical use of NOS and NEC terminology.

Table 1: Newly recognized tumor types in the 2021 WHO classification of CNS tumors.

S. No.	Tumor category		Newly recognized tumor types
A.	Pediatric-type diffuse low-grade glioma	1.	Diffuse astrocytoma, MYB or MYBL1 altered
		2.	Polymorphous low-grade neuroepithelial tumor of the young
		3.	Diffuse low-grade glioma, MAPK pathway altered
B.	Pediatric-type diffuse high-grade glioma	1.	Diffuse hemispheric glioma, H3 G34-mutant
		2.	Pediatric-type diffuse high-grade glioma, H3 wild type, and IDH wild type
		3.	Infant-type hemispheric glioma
C.	Glioneuronal and neuronal tumors	1.	Diffuse glioneuronal tumor with oligodendroglioma such as features and nuclear clusters (provisional type)
		2.	Myxoid glioneuronal tumor
		3.	Multinodular and vacuolating neuronal tumor
D.	Ependymal tumors	1.	Supratentorial ependymoma, YAP1 fusion positive
		2.	Posterior fossa ependymoma, group PFA
		3.	Posterior fossa ependymoma, group PFB
		4.	Spinal ependymoma, MYCN amplified
E.	Other CNS embryonal tumors	1.	Cribriform neuroepithelial tumor (provisional inclusion)
		2.	CNS neuroblastoma, FOXR2 activated
		3.	CNS tumor with BCOR internal tandem duplication
F.	Pineal tumors	1.	Desmoplastic myxoid tumor of the pineal region, SMARCB1 mutant
G.	Cranial and paraspinal nerve tumors	1.	A typical neurofibromatous neoplasm of unknown biological potential
		2.	Malignant melanotic nerve sheath tumor
H.	Mesenchymal, nonmeningothelial tumors	1.	Intracranial mesenchymal tumor, FET-CREB fusion positive (provisional inclusion)
		2.	Primary intracranial sarcoma, DICER1 mutant
		3.	CIC rearranged sarcoma
I.	Pituitary tumor	1.	Pituitary blastoma

Table 2: Tumor types with revised nomenclature or revised placement in the 2021 WHO classification of CNS tumors.

S. No.	Tumor types	Revised nomenclature or revised placement
1.	Astrocytoma, IDH mutant	Divided into Grades 2–4
2.	Diffuse midline glioma, H3 K27 altered	Term "mutant" is replaced with "altered"
3.	Chordoid glioma	Removes site designation
4.	Astroblastoma, MN1 altered	Adds genetic modifier
5.	Embryonal tumor with multilayered rosettes	Removes genetic modifier to allow for genetic subtypes
6.	Solitary fibrous tumor	Remove the term "hemangiopericytoma"
7.	Mesenchymal chondrosarcoma	Distinct tumor type (formerly as a subtype)
8.	Adamantinomatous craniopharyngioma	Distinct tumor type (formerly as a subtype)
9.	Papillary craniopharyngioma	Distinct tumor type (formerly as a subtype)
10.	Pituicytoma, granular cell tumor of the sellar region, and spindle cell oncocytoma	Included in 1 section as a related group of tumor
11.	Pituitary adenoma	Add the new term "PitNET"

IDH wild-type diffuse astrocytic tumors in adult:

The WHO CNS-5 incorporates three genetic criteria to assign highest WHO grade (glioblastoma IDH wild type).[2,31] These are as follows:

(1) Telomerase reverse transcriptase (TERT) promoter mutation or
(2) Epithelial growth factor receptor (EGFR) gene amplification or
(3) Combined gain of whole chromosome 7 or loss of whole chromosome 10
(4) Glioblastoma IDH wild type should be diagnosed in the setting of an IDH wild-type diffuse glioma in the adult if there is[2,31]

(1) Microvascular proliferation or necrosis or
(2) TERT promoter mutation or
(3) EGFR amplification or

(4) Gain in entire chromosome 7 or loss in entire chromosome 10.

Hence, "Glioblastoma, IDH mutant" has removed from the new WHO CNS-5 classification.

Pediatric-type diffuse gliomas

Pediatric-type diffuse gliomas are classified as separate entities to differentiate it from others diffuse gliomas. The requirement of this update was that (1) it carry distinct molecular alteration, despite histological similarities to adult glioma. Common genetic alterations in adult infiltrating glioma such as IDH mutation and 1p/19q codeletion are rare in children whereas other characteristic mutations are more common. (2) It occurs mostly in brainstem whereas in adults are mostly supratentorial. (3) It carry different prognosis and respond to different chemotherapeutic regimen than do adult gliomas. Hence, appropriate molecular testing is essential for accurate classification and the identification of potential therapeutic target.[17]

Pediatric-type low-grade diffuse gliomas

These tumors had diffuse growth in the brain but have overlapping or less specific histological features. Molecular features help to characterize these tumors for each other.[16] These are

(1) Diffuse astrocytoma, MYB, or MYBL-1 altered
(2) Angiocentric glioma
(3) Polymorphous low-grade neuroepithelial tumors of the young
(4) Diffuse low-grade glioma, MAPK pathway altered.

Pediatric-type high-grade diffuse gliomas

It consists of four subtypes.[3,30]

(1) Diffuse midline glioma H3K27 altered (previously mutant). As multiple mechanism may involve other than mutation so altered term used
(2) Diffuse pediatric-type high-grade glioma, H3 wild type, and IDH wild type are specified as being wild type for both H3 and IDH gene families and, such as many other CNS tumor types, requires molecular characterization and integration of histopathological and molecular data for diagnosis purposes
(3) Diffuse hemispheric glioma, H3 G34 mutant
(4) Infant-type hemispheric glioma: it is a novel type of HGG that occurs in newborn and infant and has a distinct molecular profile with fusion gene involving 4LK, ROS-1, NTRK1/2/3, or MET.

Term glioblastoma is no longer used for pediatric-type gliomas.

Ependymoma

In the WHO CNS 5, anatomic locations are also used in addition to histopathological and molecular features to classify ependymoma.[6,25] These are three types.

(A) Supratentorial ependymoma: it has two subtypes.
    (1) Supratentorial ependymoma with ZFTA fusion: it is more representative of tumor type than RELA because it may be fused with partners more than RELA
    (2) Supratentorial ependymoma with YAP1fusion:

Overall supratentorial ependymoma has more favorable prognosis.

(B) Posterior fossa ependymoma: it has two subtypes.
    (1) PFA (Pediatric type)
    (2) PFB (Adult type): has better prognosis.
(C) Spinal ependymoma:

Ependymomas in the spinal cord have four subtypes.

(1) Spinal ependymoma
(2) Spinal ependymoma, MYCN amplified: it is clinically aggressive subtypes.

Molecular classification does not provide added clinicopathological utility for myxopapillary ependymoma and subependymoma, so NOS and NEC suffix are used to describe these tumors. In light of frequent recurrence, myxopapillary ependymoma has now been upgraded to the WHO Grade 2. Papillary, clear cell, and tanycytic are no longer used as subtypes of ependymoma, being included instead as patterns in the histopathological description of ependymoma. The term anaplastic ependymoma is no longer in use. A pathologist can still choose to assign either CNS WHO Grade 2 or 3 ependymoma, according to histopathological features.[6]

Medulloblastoma

In the WHO 2016 classification, medulloblastoma was divided into four principal molecular groups. In the WHO CNS 5, these groups are represented same and new subgroups have emerged at a more granular level below the four principal molecular groups: four subgroups of SHH and eight subgroups of non-WNT/non-SHH medulloblastomas.[9,10]

In the WHO CNS 5, medulloblastoma is divided into two types.[4,20-22]

(A) Medulloblastoma molecularly defined: it has four subtypes.
    (1) Medulloblastoma WNT activated: histologically, it includes all classic variants

        Medulloblastoma SHH activated and TP53 wild type
    (2) Medulloblastoma SHH activated and TP53 mutant

Histologically, medulloblastoma SHH activated includes desmoplastic/nodular and medulloblastoma with extensive nodularity (MBEN) variants

(3) Medulloblastoma non-WNT/non-SHH-Groups 3 and 4: histologically, it includes large-cell anaplastic variants.
(B) Medulloblastoma histologically defined

The morphological types of medulloblastoma, such as classic, desmoplastic/nodular, MBEN, and large-cell anaplastic type are now been combined into one section that describes them as morphological pattern of an inclusive tumor type, "Medulloblastoma histologically defined." The morphologic differences have their own specific clinical associations and molecularly defined medulloblastoma demonstrate distinct association with the morphologic patterns.[9,10]

Choroid plexus tumors

These tumors are separated from the family of the primary neuroepithelial tumors that feature more glial and/or neuronal differentiation and less epithelial differentiation.

Other embryonal tumors

The WHO 2016 classification included two other embryonal tumors such as atypical teratoid/rhabdoid tumor (AT/RT) and embryonal tumor with multilayered rosettes (ETMR). The WHO CNS 5 recognizes three molecular subtypes of AT/RT and ETMR with DICER1 alteration.

The new one added to this classification is as follows:[13,15,19]
(i) CNS neuroblastoma, FOXR2 activated
(ii) CNS tumor with BCOR internal tandem duplication
(iii) Cribriform neuroepithelial tumor has been introduced as a provisional entity
(iv) CNS embryonal tumor: it includes those embryonal tumors that defy a more specific diagnosis, that is, NEC or NOS.

Pineal tumors

The new tumor type added to pineal tumor is desmoplastic myxoid tumor of the pineal region, SMARCB1 mutant.[32] The WHO CNS-5 also defines the KBTBD4 in frame insertion as a molecular diagnostic criterion for pineal parenchymal tumor of intermediate differentiation.[11] Pineoblastoma has now divided into four molecular subtypes.
(1) Pineoblastoma miRNA processing altered 1: found in children
(2) Pineoblastoma miRNA processing altered 2: found mostly in older children and had a good prognosis
(3) Pineoblastoma, MYC/FOXR2 activated: found in infants
(4) Pineoblastoma, RB1 altered: found in infants and had the similarity to retinoblastoma.[12,26]

Meningioma

In the new classification, meningioma is considered as a single type with its broad morphological spectrum reflected in 15 subtypes. It is now emphasized that the criteria defining atypical or anaplastic (the WHO Grade 2 or 3) meningioma should be applied regardless of the underlying subtype. Grading of these tumor should not be entirely based on rhabdoid cytology and papillary architecture alone, as papillary and rhabdoid features are often seen in combination with other aggressive features.[33] Certain molecular markers are needed to define these meningioma subtypes. These are BAP-1 for rhabdoid and papillary subtype, and KLF4/TRAF7 for secretary subtype.[7,28,29]

Mesenchymal/nonmeningothelial tumors

The WHO CNS 5 now covers only those mesenchymal tumors that occur uniquely in the CNS or, though similar to their soft-tissue counterparts, are encountered regularly in the CNS. Leiomyoma is no longer included in this group, given that their diagnostic features are identical to their soft-tissue counter parts. The hybrid term "Solitary fibrous tumor/Hemangiopericytoma" is no longer use, the tumor now termed as only solitary fibrous tumor and the term "Hemangiopericytoma" has been retired.

The new tumor type that had been added is as follows:
(1) Intracranial mesenchymal tumor
(2) FET-CREB fusion positive (provisional)
(3) CIC rearranged sarcoma and
(4) Primary intracranial sarcoma, DICER1 mutant.

Nerve tumors

The new subtype added to the neurofibroma group is "Atypical Neurofibromatous Neoplasm of Unknown Biological Potential." It is an NF1 associated tumor with increased malignant transformation behavior that is still quantitatively insufficient for a definitive diagnosis of malignant peripheral nerve sheath tumor. The tumor "Melanotic Schwannoma" has been renamed as malignant melanotic nerve sheath tumor due to its aggressive behavior and genetic under printing that distinguishes it from all other schwannoma. Paraganglioma of the cauda equina/filum terminale region is now recognized as distinct tumor type due to immunohistochemical and DNA methylation differences and the lack of familial association. Hence, paragangliomas are now included with nerve tumors.

Lymphoma and other histiocytic tumors

The WHO CNS-5 includes only those lymphoid and histiocytic tumors that occur relatively often in the CNS or that have special histological or molecular features when they occur in the CNS.

Sellar region tumors

The WHO CNS-5 had coined the new term for pituitary adenoma as "Pituitary Neuroendocrine Tumor."[27] Pituicytoma,

granular cell tumor, and spindle cell oncocytoma are included in single section as related group of tumor types,[5,23] as they represent the morphologic variation of same tumor. Adamantinomatous and papillary subtype of craniopharyngioma are now classified as distinct tumor type, given their different clinicodemographic, radiologic, histopathologic, and genetic alteration profiles.[8,24] A new tumor type has been added to this group as pituitary blastoma. It is a rare embryonal neoplasm of infancy composed of primitive blastemal cells, neuroendocrine cells, and Rathkes epithelium.

Metastatic tumor

It is divided into two groups:

(1) Those that preferentially affect the brain and spinal cord parenchyma and
(2) That preferentially affects the meninges.

Further emphasis has been given to those molecular markers that are helpful for diagnosis and/or for guiding therapies for these tumors.

CONCLUSION

The WHO CNS-5 introduces a new knowledge into the classification with progressive manner by introducing newly recognizing entities, by obsoleting tumor type, and by adjusting the taxonomic structure. The changes and their simplified explanations provide a practical approach to specialists in neuro-oncology and pathologists and such progress becomes more beneficial to patients who are suffering from CNS tumors.

Declaration of patient consent

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

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Conflicts of interest

There are no conflicts of interest.

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