Review Article

What Changed in CNS5? A Mini-Review on General Changes and Adult Diffuse Gliomas

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Abstract

The fifth edition of the WHO classification of tumors of the central nervous system (WHO CNS5) was published in 2021 which is the sixth version of the international standard for the diagnostics of CNS tumors. Regular updates of the consortium to inform molecular and practical approaches to CNS tumor taxonomy (cIMPACT-NOW) shaped the WHO CNS5 which continues the trend of incorporating the molecular characteristics of tumors into the histological and immunohistochemical findings. The various updates can be classified into general changes across all tumors and specific changes within the tumor groups. This mini-review highlights the general changes and the major changes in adult diffuse gliomas.

Keywords: Brain tumor classification, molecular pathology, WHO classification of tumors of the central nervous system

Résumé

La cinquième édition de la classification OMS des tumeurs du système nerveux central (WHO CNS5) a été publiée en 2021, soit la sixième version de la norme internationale pour le diagnostic des tumeurs du SNC. Mises à jour régulières du consortium pour informer les chercheurs moléculaires et pratiques les approches de la taxonomie des tumeurs du SNC (cIMPACT-NOW) ont façonné le CNS5 de l'OMS, qui poursuit la tendance à incorporer la méthodologie moléculaire caractéristiques des tumeurs dans les résultats histologiques et immunohistochimiques. Les différentes mises à jour peuvent être classées en modifications générales dans toutes les tumeurs et les changements spécifiques au sein des groupes de tumeurs. Cette mini-revue met en évidence les changements généraux et les changements majeurs dans gliomes diffus de l'adulte.

Mots-clés: Classification des tumeurs cérébrales, pathologie moléculaire, classification OMS des tumeurs du système nerveux central

Introduction

Gliomas are tumors arising from the glial cells of the brain and the spinal cord. Gliomas make up approximately 30% of all brain and central nervous system (CNS) tumors and 80% of all malignant brain tumors.[1] Among them, adult-type diffuse gliomas are the most common malignant tumors of the CNS.[2] However, it must be remembered that the term glioma encompasses a myriad of entities of varying histogenesis, morphology, and genetic alterations and the prognosis depends upon the types, variants, and grades of tumors. While low-grade gliomas (LGG) have a 5-year survival rate as high as 80%, high-grade gliomas (HGG) have 5-year survival rates of <5%.[2]

In 2021, the fifth edition of the WHO classification of tumors of the CNS (WHO CNS5) was published which is the sixth version of the international standard for diagnostics of CNS tumors, as a continuum of the prior publications of 1979 (1st edition), 1993 (2nd edition),

Access this article online

Quick Response Code:

Website: www.annalsafrmed.org

DOI: 10.4103/aam.aam_63_23

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How to cite this article: Chakrabarti I, Mazumder S. What changed in CNS5? A mini-review on general changes and adult diffuse gliomas. Ann Afr Med 2024;23:255-61.

Submitted: 27-Apr-2023 **Revised:** 20-Sep-2023
Accepted: 03-Oct-2023 **Published:** 20-Jul-2024

2000 (3rd edition), 2007 (4th edition), and 2016 (revised 4th edition).

The categorization of gliomas for the past century has been based largely on histogenesis and microscopic features. However, 2016 WHO classification (based on the Haarlem consensus guidelines) resulted in a paradigm shift in the classification of these tumors by formally incorporating the molecular characteristics into the definition of many of these tumors, discontinuing many entities, variants, and terms and introducing several newly recognized entities, variants, and patterns. It encouraged an integrated and layered diagnosis in which histopathology and molecular information were included which will narrow down the diagnosis and hence affect the clinical management of these tumors. The International Society of Neuropathology created the consortium to inform molecular and practical approaches to CNS tumor taxonomy (cIMPACT-NOW) to keep pace with the rapidly evolving molecular updates. Inputs from the 7 updates of cIMPACT-NOW shaped the WHO CNS5 which still continues the trend of incorporating the molecular characteristics of tumors into the histological and immunohistochemical findings.[3]

WHO CNS5 carries forward what was started in the revised 4th edition of the classification of CNS tumors with some major and minor changes. These may be grouped as general changes across all tumors and specific changes within the tumor groups. The present mini-review aims to highlight all the general changes of CNS tumors along with the major changes in adult diffuse gliomas of CNS5.

General Changes of Central Nervous System Tumors

Changes in taxonomy

One of the changes made in the taxonomy of tumors is that "type" has now replaced "entity" and "subtype" has replaced the "variant." This has been done in line with the changes made in the classification of tumors of other organ systems. The word variant has been removed to ensure that there is no confusion with a variant indicating a genetic alteration. Only the types are listed in the main WHO classification, while subtypes are mentioned under the individual type of tumors.[4] For example, under the classification of medulloblastoma, sonic hedgehog signaling molecule (SHH)-activated and TP53 wild-type medulloblastoma is mentioned as a type, but the subtype provisional molecular subgroup SHH-1 is mentioned only under the relevant chapter of medulloblastoma.[5] Similarly, meningioma is mentioned in the main classification but its subtypes like meningothelial meningioma, transitional meningioma etc. are mentioned only in the chapter on meningioma.[4] The term anaplastic has been removed from oligodendroglioma and astrocytoma (both WHO Grade 3 tumors) for clarity, but the qualifier anaplastic is still retained in anaplastic meningioma.[6] The term anaplastic ependymoma also does not find a place in this new classification. In some tumors, the anatomical site has been omitted as they are not limited to those areas, e.g. for choroid glioma the qualifier "of the third ventricle" has been omitted.[7]

Gene and protein nomenclature

WHO CNS5 has standardized and updated reporting of gene symbols, names, and chromosomal alterations using the Hugo Gene Nomenclature Committee system for gene symbols and names (https://www.genenames.org/) and the recommendations from Human Genome Variation Society (https://www.hgvs.org/) for sequence variants. The gene symbols are written in italics but proteins and gene groups are not italicized (e.g., Isocitrate dehydrogenase (*IDH*) is italicized but the family of *IDH* genes is not italicized).[5,7]

A sequence alteration, in WHO CNS5, is reported using a "c." prefix for the coding deoxyribonucleic acid (DNA) sequence, followed by the nucleotide number and nucleotide change. The predicted protein sequence change follows a "p." prefix with the reference amino acid, the amino acid number, and the variant amino acid resulting from the mutation. For example, the most common BRAF variant is *BRAF*: c.1799T>A p.Val600Glu (or *BRAF*: c.1799T>A p.V600E if single-letter amino acid codes are preferred).[5,8]

For Histone protein alterations, the WHO CNS5 uses the legacy protein numbering system in parentheses after the protein-level variant description, e.g., *H3-3A*: c.103G>A p.Gly35Arg (G34R), or *H3-3A*: c.83A>T p.Lys28Met (K27M).[5,8]

CNS tumor grading

WHO CNS5 has adopted Arabic numerals (1, 2, 3, and 4) to assign to various grades rather than Roman numerals (I, II, III, and IV) which were used previously to reduce typographical and interpretive errors and also to maintain uniformity with other tumor grading systems.

For instance, as per the WHO 2021; CNS 5 nomenclature, diffuse astrocytoma CNS WHO Grade II will now be reported as Astrocytoma IDH mutant WHO Grade 2. Similarly, anaplastic astrocytoma CNS WHO Grade III is now to be reported as Astrocytoma IDH mutant WHO Grade 3.

Traditionally, the WHO CNS tumor grading has differed from the grading of other non-CNS tumors as grades have been applied across different entities and not within a single tumor type with the exception of solitary fibrous tumor/hemangiopericytoma (which had Grades I, II, and III).[4,5,9] This has led to confusion in clarity. For example, as per WHO 2016 edition, the astrocytoma group of tumors had WHO grades II and III and they also had different names like diffuse astrocytoma and anaplastic astrocytoma, respectively. To add to the confusion, anaplastic astrocytomas and anaplastic meningiomas were both placed under the same WHO Grade III although they have different biological behaviors and treatment outcomes. Similarly, WNT-activated medulloblastoma (an embryonal tumor with aggressive behavior, if left untreated) and a diffuse midline glioma H3K27-altered, both shared the

same WHO Grade IV. However, the former is responsive to current therapeutic regimens with long-term survival while the latter is a poor responder to present treatment options.

Thus, in order to avoid confusion using grades across the various CNS tumor types , WHO CNS5 has employed within-tumor-type grading, e.g. Astrocytomas IDH mutant will now have Grades 2, 3, and 4 just like the grading of tumors of other organ systems, However, it still retains the term "CNS WHO grade" because CNS tumor grading still differs, in some aspects, from other tumor grading systems. This is due to the fact that traditionally, the grades of CNS tumors somewhat reflect the overall clinical-biological behavior of the tumors.

The third important change is the introduction of combined histological and molecular grading. Because of its implications in biological behavior and in treatment outcomes, molecular parameters have been added as biomarkers for grading in WHO CNS5. The grading of CNS tumors had long been dependent on morphological features like atypia, mitosis, endovascular proliferation, and necrosis. However, with the advent of some robust molecular markers, the WHO CNS5 recommends that these molecular markers can even supersede the requirements of histological criteria. For example, an IDH wild-type diffuse astrocytoma with *TERT* (Telomerase reverse transcriptase) promoter mutation/ *EGFR* (epidermal growth factor receptor) amplification/gain of chromosome 7 with concomitant loss of chromosome 10, would still qualify as IDH-wild type Glioblastoma even without the presence of microvascular proliferation/necrosis on light microscopy.

Integrated and layered diagnoses

In line with the Haarlem consensus guidelines,[10] the WHO CNS5 has adopted the layered reporting format, presenting a full range of diagnostic information, including histopathological features, CNS WHO grade, and molecular alterations[3,4] [Table 1]. This layered format has become a part of the International Collaboration on Cancer Reporting dataset[11] and provides vital information to the treating surgeon.

Essential and desirable criteria for diagnosis

Each chapter in CNS5 gives a systemically structured text box describing the "Essential and desirable diagnostic criteria" for each tumor type. The essential diagnostic criteria are the minimum or must-have requirements needed for diagnosis, while the desirable diagnostic criteria are the nice-to-have criteria that support but are not mandatory for diagnosis. In some tumors, not all criteria listed under the essential criteria need to be met for diagnosis, and in those cases, the designation "OR" is mentioned.[4,5]

For example:

For diagnosing Astrocytoma IDH mutant, the essential criteria are: [5]

A diffusely infiltrating glioma

AND

IDH1 codon 132 or IDH2 codon 172 missense mutation

AND

Loss of nuclear alpha-thalassemia/mental retardation, X-linked (ATRX) expression or ATRX mutation

OR

Exclusion of combined whole-arm deletions of 1p and 19q.

This indicates that any one, either the loss of nuclear ATRX expression/mutation or exclusion of combined whole-arm deletions of 1p and 19q, when combined with a diffusely infiltrating glioma and IDH 1/2 missense mutation, will qualify as astrocytoma IDH mutant.

The desirable criteria of astrocytoma IDH mutant include

- TP53 mutation or strong nuclear expression of p53 in >10% of tumor cells
- Methylation profile of astrocytoma, IDH-mutant
- Astrocyte differentiation by morphology.

Not otherwise specified and not elsewhere classified diagnoses

WHO CNS5 uses the term not otherwise specified (NOS) when the molecular information is not available or not performed or not successful. In addition, not elsewhere classified (NEC) diagnosis has been adopted to indicate cases in which a precise WHO diagnosis cannot be rendered in spite of successfully performing the necessary diagnostic testing. This may be due to a mismatch between the clinical, histological, immunohistochemical, and/or genetic features.[4] Such cases are often given a descriptive diagnosis.[12] It is to be noted that NOS and NEC can be used for any tumor type.[3]

Table 1: Layered reporting format

		Brain (left frontal mass)
Layer 1	Integrated diagnosis	GBM, IDH wild type, CNS WHO grade 4
Layer 2	Histologic diagnosis	GBM
Layer 3	WHO grade	CNS WHO grade 4
Layer 4	Molecular information	IDH-wild type (R132H IHC and IDH1/2 sequencing)
		p53-rare positive cells, consistent with wild type (IHC)
		ATRX retained nuclear expression- consistent with wild-type (IHC)
		TERT promoter mutation-PCR
		EGFR amplified (FISH)

CNS=Central nervous system, WHO=World Health Organization, IHC=Immunohistochemistry, PCR=Polymerase chain reaction, GBM=Glioblastoma

Changes in measurements and mitotic count assessment

In CNS5, the length units have been changed, so tumor size is now given in millimeters (mm) rather than centimeters (cm) to avoid using decimals.[6]

In WHO 2016 edition, mitotic counts were expressed per 10 high-power fields (HPFs). Since various microscopes have different field sizes of high-power objectives, CNS5 has attempted to standardize the mitotic counts by expressing the number of mitosis per a predefined area in mm^2 as well as expressing it as per 10 HPFs. Unlike many other non-CNS tumors, standardization and optimization of the antigen retrieval protocol for Ki-67 across various centers have been poor.[9] Establishing a reliable cut-off value for the Ki-67/MIB-1 proliferating index has also been difficult. These nuclear antigens are often weakened due to long storage duration and higher storage temperature.[13] However, the Ki-67/MIB-1 proliferating index is mentioned in many of these CNS tumors and appears as a useful biomarker for grading and prognostication.[6]

Novel diagnostic technologies

In addition to histomorphology, newer techniques like immunohistochemistry (IHC) and molecular studies have reshaped the classification of CNS tumors over the years. Another novel technology known as DNA methylation array uses arrays for genome-wide profiling of DNA methylation patterns across tumor types. This methylome profiling has emerged as a powerful tool for the diagnosis and hence the classification of CNS tumors.[8,9]

Almost all (but not all) tumor types are assumed to have distinct methylation patterns or signatures and hence, in CNS5, information about diagnostic methylation profiling has been included in definitions as well as essential and desirable diagnostic criteria of some tumors.[8]

It is particularly helpful in diagnostically challenging tumors with atypical histomorphology or discordant genetic features and may be the only method available presently to identify some rare tumor types and subtypes. Twenty-two new tumor types have been recognized by DNA methylation profiling and few tumors like "high-grade astrocytoma with piloid features" are defined only by DNA methylation profiling.[4]

It is also helpful when the tissue obtained is very limited for employing other diagnostic tests.

However, due to the lack of availability in all centers, optimal methodologies, and standardization of regulatory factors,[14] CNS5 has not made DNA methylation profiling mandatory for diagnosis, but it is more likely to gain further importance in the near future by adding to the diagnostic precision of CNS tumors.

Newly recognized types and revised nomenclature of some existing tumor types

Twenty-two new tumor types have been added - 7 gliomas, 3 glioneuronal tumors, 4 ependymomas, 3 embryonal tumors, 3 sarcomas, 1 pineal gland tumor, and 1 pituitary tumor, mostly based on DNA methylome profiling [Table 2]. Among these twenty-two tumors, 3 tumors viz. diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters (DGONC), cribriform neuroepithelial tumor (CRINET), and intracranial mesenchymal tumor FET-CREB fusion-positive, have been accepted as provisional types but more published studies are needed before accepting them as clinicopathologically distinct tumors within the classification.

Thirteen tumors have now a modified nomenclature [Table 3] with modification of various qualifiers in the terminologies. Some nonbrain tumors under the sections mesenchymal, nonmeningothelial and hematolymphoid tumors have also been removed from the new classification as they are rarely encountered in CNS.

Changes in the classification of diffuse glial tumors

The gliomas can be diffuse or circumscribed. The diffuse gliomas have now been restructured as adult-type diffuse gliomas which occur primarily in adults and pediatric-type

Table 2: Newly recognized types in central nervous system 5[5,8]

Gliomas
Diffuse astrocytoma, MYB- or MYBL1-altered
PLNTY
Diffuse low-grade glioma, MAPK pathway-altered
Diffuse hemispheric glioma, H3 G34-mutant
Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
Infant-type hemispheric glioma
High-grade astrocytoma with piloid features
Glioneuronal tumors
DGONC (provisional type)
Myxoid glioneuronal tumor
MVNT
Ependymomas
Supratentorial ependymoma, YAP1 fusion-positive
Spinal ependymoma, MYCN amplified
Posterior fossa ependymoma group PFA
Posterior fossa ependymoma group PFB
Embryonal tumors
Cribriform neuroepithelial tumor (provisional type)
CNS neuroblastoma, FOXR2-activated
CNS tumor with BCOR internal tandem duplication
Sarcomas
Primary intracranial sarcoma, DICER mutated
Intracranial mesenchymal tumor, FET-CREB fusion-positive (provisional type)
CIC-rearranged sarcoma
Pineal gland tumor
Desmoplastic myxoid tumor of the pineal region, SMARCB1 mutant
Pituitary tumor
Pituitary blastoma

MVNT=Multinodular and vacuolating neuronal tumor, DGONC=Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters, PLNTY=Polymorphous low-grade neuroepithelial tumor of the young, CNS=Central nervous system, PFA=Posterior fossa group A, PFB=Posterior fossa group B

Table 3: Revised nomenclature of tumor types in central nervous system 5[5,8]

Astrocytoma, IDH-mutant (the term GBM, IDH mutated has been removed)
Diffuse midline glioma, H3 K27-altered ("mutant" changed to "altered")
Chordoid glioma (the site "of third ventricle" has been removed)
Astroblastoma, MN1-altered (genetic modifier "MN1-altered" added)
Supratentorial ependymoma, ZFTA fusion-positive (change in fusion partner and gene nomenclature; replaces old terminology ependymoma, RELA fusion positive)
Embryonal tumor with multilayered rosettes (genetic modifier removed so that subtypes can be added; replaces the older term embryonal tumor with multi-layered rosettes, C19MC-altered
Solitary fibrous tumor (replaces the hybrid term solitary fibrous tumor/hemangiopericytoma, in line with soft tissue tumors)
Mesenchymal chondrosarcoma (previously a subtype)
Adamantinomatous craniopharyngioma (previously a subtype)
Papillary craniopharyngioma (previously a subtype)
Pituicytoma, granular cell tumor of the sellar region, and spindle cell oncocytoma (grouped together)
Pituitary adenoma/PitNET (PitNET added)

GBM=Glioblastoma

diffuse gliomas which occur primarily in children. It is important to understand that the words adult-type and pediatric-type indicate prognostically and biologically distinct groups of tumors with representative molecular alterations and not just a particular age group as pediatric-type diffuse gliomas can sometimes occur in adults and adult types can rarely occur in children or young adults as well.[8,15]

The adult diffuse gliomas are subdivided into a) astrocytoma IDH-mutant, b) oligodendroglioma IDH-mutant and 1p/19q-codeleted and c) glioblastoma IDH-wildtype. These are further graded as per CNS WHO grades.

The pediatric-type diffuse gliomas may further be classified into HGG and LGG [Table 4].

The pediatric-type diffuse LGG include (i) diffuse LGG, MAPK pathway-altered, (ii) diffuse astrocytoma, *MYB*-or *MYBL1*-altered, (iii) angiocentric glioma, and (iv) polymorphous low-grade neuroepithelial tumor of the young. Other than the angiocentric glioma, the other three tumors included in this group are newly recognized entities.

The pediatric-type diffuse HGG include (i) diffuse midline glioma, H3 K27-altered, (ii) diffuse hemispheric glioma, H3 G34-mutant, (iii) diffuse pediatric-type HGG, H3-wildtype, IDH-wildtype and (iv) Infant-type hemispheric glioma.

Among these, the diffuse midline glioma, H3 K27 mutated has been changed to H3 K27 altered to account for possible epigenetic changes other than mutations. The rest are newly recognized types.

The circumscribed gliomas are enlisted in Table 5.

Changes in adult diffuse gliomas

Some of the major changes in this category have been mentioned in the previous sections.

Table 4: Diffuse gliomas; adult-type and pediatric-type with central nervous system world health organization grades

	CNS WHO grades
Adult-type diffuse gliomas	
Astrocytoma, IDH-mutant	2/3/4
Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted	2/3
GBM, IDH-wildtype	4
Pediatric-type diffuse LGG	
Diffuse low-grade glioma, MAPK pathway-altered	NA
Diffuse astrocytoma, MYB-or MYBL1-altered	1
Angiocentric glioma	1
PLNTY of the young	1
Pediatric-type diffuse HGG	
Diffuse midline glioma, H3 K27-altered	4
Diffuse hemispheric glioma, H3 G34-mutant	4
Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype	4
Infant-type hemispheric glioma	NA

CNS=Central nervous system, WHO=World Health Organization, NA=Not available, PLNTY=Polymorphous low-grade neuroepithelial tumor, HGG=High-grade gliomas, LGG=Low-grade gliomas, GBM=Glioblastoma

In CNS5, as mentioned earlier, the adult-type diffuse gliomas have been classified are of 3 types:

- Astrocytoma, IDH-mutant
- Oligodendroglioma, IDH-mutant and 1p/19q codeleted
- Glioblastoma, IDH-wildtype.

All IDH-mutant astrocytomas are now termed as astrocytoma, IDH-mutant and are further graded into CNS WHO Grades 2, 3, and 4 based on histological features and molecular markers. As mentioned earlier, the molecular markers can supersede the histological criteria for grading, e.g. even if there is the absence of necrosis or microvascular proliferation, the presence of CDKN2A or CDKN2B homozygous deletion will upgrade an astrocytoma, IDH-mutant to WHO CNS Grade 4. In astrocytoma IDH-mutant, ATRX and/or P53 expression can be used as surrogate immunohistochemical markers of the absence of 1p/19q codeletion.[14]

The terms like diffuse astrocytoma, anaplastic astrocytoma, glioblastoma *IDH* mutant, and anaplastic oligodendroglioma have been discontinued in the new WHO classification.

Many of the signature molecular characteristics like IDH1 p.R132H, p53, BRAF V600E, H3K27M, H3 G34R/V, and ATRX can be demonstrated on IHC, while Fluorescence in situ hybridization (FISH) is used for the detection of other molecular parameters like CDKN2A/B homozygous deletion, EGFR amplification, and 1p/19q codeletion.[3] However, next-generation sequencing is the way forward to detect many of these mutations and fusions.

Oligodendrogliomas are diffuse gliomas characterized by IDH mutations and codeletion of chromosome 1p and 19q. They are termed as oligodendroglioma, IDH-mutant and

Table 5: Circumscribed gliomas
Subependymal giant cell astrocytoma
High-grade astrocytoma with piloid features
Astroblastoma, MN1-altered
Pilocytic astrocytoma
Pleomorphic xanthoastrocytoma
Chordoid glioma

1p/19q-codeleted. As this is part of the diagnostic criteria, all IDH-mutant diffuse gliomas should be tested for 1p/19q codeletion. Even if the histological appearance is favoring an astrocytic tumor, the presence of IDH mutation coupled with 1p/19q codeletion will render a diagnosis of oligodendroglioma. ATRX mutations are mutually exclusive of 1p/19q codeletion, and thus, unlike astrocytomas, ATRX is retained in 1p/19q codeleted oligodendrogliomas. The retention of ATRX helps in the diagnosis of oligodendrogliomas.

The subtypes of oligodendroglioma include:

- Oligodendroglioma, IDH-mutant and 1p/19q-codeleted CNS WHO Grade 2
- Oligodendroglioma, IDH-mutant and 1p/19q-codeleted CNS WHO Grade 3.

The histological criteria of increased cellularity, cytological atypia, brisk mitosis, microvascular proliferation, and necrosis with/without palisading are the criteria to assign the higher grade.

Rare cases of oligodendroglioma, on which IDH mutation and codeletion study of chromosome 1p and 19q are unsuccessful/could not be completed, are referred to as oligodendroglioma NOS.[15] Like the 2016 edition, the use of the term oligoastrocytoma is increasingly discouraged as most of them are either classified into astrocytomas or oligodendrogliomas based on molecular analysis.

The 2021 WHO incorporates the molecular criteria for the diagnosis of glioblastoma in IDH-wildtype astrocytic gliomas as well.

In IDH - wildtype diffuse astrocytic tumors in adults, even in the absence of high-grade histopathologic features of microvascular proliferation and necrosis, the presence of ≥1 of the 3 following genetic parameters will qualify them as glioblastomas, IDH wildtype. They are as follows:

- TERT promoter mutation
- EGFR gene amplification
- Concurrent gain of entire chromosome 7 and loss of entire chromosome 10 (+7/−10).

Hypermethylation of the O^6-methylguanine-DNA-methyltransferase (MGMT) gene has been shown to be associated with improved response to treatment with alkylating agents (like temozolomide) and improved outcome in patients of glioblastoma , CNS WHO grade 4.[14,16] Hence, methylation study of the MGMT gene is helpful to predict the response and overall survival in these patients.

Conclusion

WHO CNS5 incorporates the current understanding and research of brain tumors. It has phased out many tumor types, introduced newer entities, and attempted to make the classification more uniform and simpler. However, the present classification will again be updated and modified in light of new information. Till then, it will act as a practical guidance for neuropathologists and neuro-oncologists around the world.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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