The 2016 WHO Classification of Tumours of the Central Nervous System: The Major Points of Revision

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Abstract

The updated 2016 edition of the World Health Organization (WHO) Classification of Tumours of the Central Nervous System (CNS) uses molecular parameters and the histology to define the main tumor categories for the first time. This represents a shift from the traditional principle of using neuropathological diagnoses, which are primarily based on the microscopic features, to using molecularly-oriented diagnoses. Major restructuring was made with regard to diffuse gliomas, medulloblastomas and other embryonal tumors. New entities that are defined by both the histological and molecular features include glioblastoma, isocitrate dehydrogenase (IDH)-wildtype and glioblastoma, IDH-mutant; diffuse midline glioma, H3 K27M-mutant; RELA fusion-positive ependymoma; medulloblastoma, wingless (WNT)-activated and medulloblastoma, sonic hedgehog (SHH)-activated; and embryonal tumor with multilayered rosettes, C19MC-altered. In addition, some entities that are no longer diagnostically relevant—such as CNS-primitive neuroectodermal tumor—have been deleted from this updated edition. The WHO2016 certainly facilitates clinical and basic research to improve the diagnosis of brain tumors and patient care.

Key words: World Health Organization (WHO), classification, histology, genetics, new entities

Introduction

In the past decades, the traditional approach to the diagnosis of tumors of the central nervous system, which was primarily based on the microscopic features, has shifted to a molecularly-oriented approach. This change has been driven by genetic as well as epigenetic discoveries.1) The updated 4th edition of the World Health Organization (WHO) Classification of Tumours of the Central Nervous System (WHO2016) has opened the door to a molecular era that the neuropathology/neuro-oncology community has never faced.2–4)

Since Bailey & Cushing introduced the histogenetic classification of the tumors of the central nervous system in 1926,5) the basic concept of classification has remained essentially unchanged, regardless of developments in the methods that are applied to the analysis of human tissue. Tumors are classified according to their similarity to the constituent cells of the central nervous system, such as astrocytes, oligodendrocytes and ependymal cells and are further sub-classified according to the presumed level of differentiation, which is determined based on morphological irregularities in comparison to their normal counterpart. Such similarities have been depicted by microscopic features on hematoxylin and eosin-stained sections, immunohistochemistry corresponding to lineage-specific proteins such as glial fibrillary acidic protein for the astrocytic lineage and ultrastructural findings that characterize histogenetic differentiation. Mitosis and cell cycle-specific antigens are used as markers to evaluate the proliferation activity and biological behavior (the WHO grading system).6)

These histogenetic classification and grading systems have been valid for near a century because they were roughly correlated with the prognosis and have remained beneficial to determining treatment strategies, including adjuvant therapies. Nonetheless, for the past 2 decades, these classification and grading systems have been challenged by genetic/epigenetic discoveries in at least three areas. First, histogenetic classification is no longer valid since it is clear that various differentiations can co-exist within the tissue of a single tumor. For example, astrocytic,7) oligodendrogial8) and ependymal tumors9–13) can co-exist with mature neurons and ependymal differentiation can be found across many different lineages beyond ependymomas. Second, the prognoses are less correlated with the WHO grade than the major molecular profiles.14–21) Third, when making a pathological diagnosis, inter-observer
differences are no longer acceptable since molecular testing offers better objectivity and reproducibility than subjective microscopic observation.22–24)

One of the first genetic alterations that led to the transformation of the diagnostic approach was a codeletion of chromosome 1p and 19q in oligodendroglioma.14,25,26) The term of oligodendroglioma was coined in remembrance of normal oligodendroglia, as defined by Baily & Cushing in the 1920s.5) Nonetheless, true oligodendrogial differentiation, such as myelin formation, has never been identified in ultrastructural studies and neither myelin-related protein nor messenger RNA has been consistently demonstrated in oligodendroglioma. Instead, oligodendroglia-like cells are often found in various neuroepithelial tumors with diverse differentiation and biological behavior—a situation that has caused significant diagnostic difficulties.27–31) On the other hand, the 1p/19q codeletion is well-correlated with both classic oligodendroglioma morphology and its clinical, radiological and biological characteristics,17,18,32,33) all of which indicate that gliomas harboring 1p/19q fall into a single entity.

Isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2, respectively) mutations are another type of genetic alteration that has had an impact on tumor classification.16–18,21,34) These mutations are found exclusively in infiltrating astrocytomas and oligodendrogliomas but not in circumscribed astrocytomas or ependymomas.34–36) A number of studies have shown that these mutations are strong prognostic makers and that they may well be the most upstream genetic event in the tumorigenesis of infiltrating astrocytomas and oligodendrogliomas.37) The discovery of IDH1/2 mutations is significant because it provides further evidence to rebut the traditional histogenetic classification systems and because it provides a common frame for two different entities beyond presumed lineages.

The incorporation of the sonic hedgehog (SHH) and wingless (WNT) pathways in medulloblastomas also has prognostic and predictive implications.38,39) Medulloblastoma with alterations in the WNT pathways is associated with a significantly indolent prognosis while medulloblastoma with group 3 and 4 has the worst prognosis. Most WNT-activated tumors exhibit classic medulloblastoma morphology but not all tumors with classic medulloblastoma morphology show WNT activation. Thus, medulloblastomas are classified according to their genetic and histological features.

The basic principles of the revision of WHO2016

The Haarlem consensus guidelines

Before the consensus meeting for WHO2016 in Heidelberg, a meeting was held in Haarlem, the Netherlands, to discuss how non-histological data such as molecular information could be incorporated into the next WHO classification of brain tumors. A consensus was reached that molecular information should be incorporated into the next WHO classification in accordance with a set of guidelines provided by the “International Society of Neuropathology-Haarlem meeting”.40) The main recommendations were that (i) diagnostic entities should be defined as narrowly as possible in order to optimize interobserver reproducibility, the clinicopathological predictions and therapeutic planning; (ii) diagnoses should be “layered” with a histological classification, the WHO grade and molecular information should be listed below an “integrated diagnosis” (Table 1); and (iii) determinations should be made for each tumor entity as to whether molecular information is required, suggested, or not needed for its definition.

Histology-based molecular classification

In WHO2016, the conventional histological results obtained using H&E-stained sections remain the initial stratifier. After determining the major category (such as infiltrating glioma, neuronal tumor or embryonal tumor) based on the histology, a subset is applied based on the results of molecular testing (Table 2).40,41)

<table>
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<td>II</td>
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<tr>
<td>Layer 4 Molecular information</td>
<td>IDH1R132H+, 1p/19q non-deleted, p53+, ATRX loss</td>
</tr>
</tbody>
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IDH: isocitrate dehydrogenase, mt: mutant.

| Table 2 Tumor categories requiring molecular information for classification |
|-----------------------------|-----------------------------|
| Adults or supratentorial location | Child and adolescence or infratentorial location |
| Diffuse astrocytic and oligodendrogial tumors | IDH1/2 1p19q codeletion | H3 K27M |
| Ependymal tumors | RELA fusion |
| Embryonal tumors | WNT/SHH |
| Embryonal tumors | INI-1, C19MC |

IDH: isocitrate dehydrogenase.
In terms of discordant results such as “a diffuse glioma that histologically appears astrocytic but proves to have IDH mutation and 1p/19q codeletion” or “a tumor that resembles oligodendroglioma by light microscopy but has IDH, ATRX and TP53 mutations in the setting of intact 1p and 19q”, it is clearly stated in the review article written by the senior editors of the WHO2016 that the genotype trumps the histological phenotype. Nevertheless, it remains possible that ‘not otherwise specified (NOS)’ designations can be applied to discordant examples since the WHO2016 is predicated on the basis of combined phenotypic and genotypic classification and on the generation of “integrated” diagnoses.

The ‘not otherwise specified’ (NOS) status

In accordance with the Haarlem guidelines, the NOS status was introduced in WHO2016 to define entities as narrowly as possible. NOS is applied when (i) genetic testing is not available, (ii) genetic testing does not show diagnostic genetic alterations that are compatible with the histological findings or (iii) when there is uncertainty about a tumor’s architectural or cytological features due to insufficient tissue sampling or the presence of tissue artifacts.

The Major Points of Revision

The revised entities and variants are listed in Table 3.

Oligodendrogliomas: The histology of oligodendroglialoma has to be ‘classic’, since this nomenclature is intended to define 1p19q codeleted glioma. More than 90% of classic oligodendrogliaoma show IDH mutation and 1p19q codeletion; which is now considered a genetic signature of oligodendroglioma. Given the high frequency of R132H mutations in IDH1 that are detectable by immunohistochemistry, molecular testing for another locus in IDH1/2 may be required in less than 10% of classic oligodendrogliaomas. If it becomes anaplastic, the classic histology will be unclear and genetic testing for codeletion will be mandatory in that setting. When a classic oligodendrogliaoma is classified as IDH wildtype, the final diagnosis is oligodendrogliaoma, NOS, after other mimicking entities are excluded (Table 4).

Diffuse astrocytomas (Fig. 1)

After the histological confirmation of astrocytoma, the second stratifier for adult patients is the presence or absence of IDH1 or IDH2 mutations. If TP53 as well as ATRX mutations (both of which are mutually exclusive to 1p19q codeletion) are present in IDH-mutant gliomas, the diagnosis of oligodendrogliaoma is immediately excluded. Either TP53 or ATRX mutations can be detected by immunohistochemistry (Table 5). If the tumor is located in the thalamus or pons, an H3 K27M mutation, which is mutually exclusive of IDH1/2 mutations, should be considered. When a 1p19q codeletion is present, the tumor is further classified as oligodendroglioma, regardless of the histology. All IDH1/2-mutant gliomas without codeletions are now classified as astrocytoma. Oligoastrocytoma, anaplastic oligoastrocytoma and glioblastoma with an oligodendrogliial component were deleted from the classification, since they are no longer genetically relevant. Gliomas in pediatric patients, particularly patients under ten years of age, are unlikely to possess IDH1/2 mutations or 1p19q codeletions and generally fall into the category of diffuse or anaplastic astrocytoma, IDH wildtype. The nosological positions of pediatric- and adult-type IDH-wildtype gliomas are currently ambiguous; most of the latter behave like glioblastoma, and are transcribed in italics. Although some data suggest that the prognosis of WHO grade II IDH-mutant glioma does not differ from that of WHO grade III IDH-mutant glioma, the grading scheme was not changed in this revision. Nonetheless some amendments will be required in the next revision.

Glioblastomas

The definition of this nomenclature remains histological rather than genetic, i.e. a high-grade glioma with predominantly astrocytic differentiation, featuring nuclear atypia, cellular pleomorphism as well as microvascular proliferation and/or necrosis. Depending on the absence or presence of IDH1/2 mutations, glioblastomas are divided into glioblastoma, IDH-wildtype, which corresponds to clinically-defined primary or de novo glioblastoma, and glioblastoma, IDH-mutant, which corresponds to so-called secondary glioblastoma. It was decided that the terms, primary and secondary, would not be used in WHO2016, since they are clinically defined. Glioblastomas with negative R132H IDH1 immunohistochemistry are quite important clinically and are considered to be equivalent to glioblastoma, IDH-wildtype in patients older than 55 years of age, since no mutations other than IDH1 R132H have been reported in glioblastomas in that age group.

One new glioblastoma variant is epithelioid glioblastoma, which has been designated as rhabdoid or epithelioid/rhabdoid. To avoid confusion with true rhabdoid tumors such as atypical teratoid/rhabdoid tumor (AT/RT), which harbors INI1 or BRG1 mutations, the term ‘rhabdoid’ is abandoned to describe this variant; in approximately half of the cases, it lacks either mutation but harbors a BRAF V600E mutation.
Table 3  Major points of revision

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<td>Pleomorphic xanthoastrocytoma</td>
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<td>Anaplastic pleomorphic xanthoastrocytoma</td>
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Table 4  WHO grade II adult diffuse gliomas

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IDH: isocitrate dehydrogenase.
Table 5  Immunohistochemical surrogates for molecular alterations required in WHO2016

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<td>Correlation with C11orf95–RELA fusion and NF-Kappa B activation</td>
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<td>A177, #3978</td>
<td>ETMR</td>
<td>Diffuse cytoplasmic staining</td>
</tr>
</tbody>
</table>

IDH: isocitrate dehydrogenase.

Pediatric diffuse astrocytomas and oligodendrogliomas

These tumors, which share a common histology, are grouped with their adult counterparts in WHO2016, despite the clear difference in clinical behavior between the tumors in pediatric and adult patients.

This is partly because WHO2016 is an upgrade of the previous edition, which did not allow the coining of a new framework, such as pediatric glioma subgroup within the classification but also because no single genetic alteration is sufficient to create a new entity in these pediatric gliomas.\textsuperscript{51,52} The only
exception is a newly defined entity, diffuse midline glioma, H3 K27M-mutant.\(^2\)

**Diffuse midline glioma, H3 K27M-mutant (Fig. 2)**

This is an infiltrative, high-grade glioma with predominately astrocytic differentiation that occurs in a midline location, i.e., the thalamus, brainstem or spinal cord, harboring a K27M mutation in either \(H3F3A\) or \(HIST1H3B/C\).\(^48,50\) This tumor predominately affects children but can also be seen in adults. It is classified as WHO grade IV regardless of the presence or absence of anaplastic features.\(^2\)

**Ependymomas**

There have been few changes in the nomenclature related to ependymomas in this revision, since the recently proposed molecular classification of ependymomas is based on DNA methylation profiling, which is only available in restricted institutions.\(^58\) One genetically-defined ependymoma subtype, ependymoma, \(RELA\) fusion-positive, has been accepted. The genetic alteration of this subtype is detectable by fluorescence in situ hybridization (FISH).\(^59,60\)

This variant accounts for the majority of supratentorial examples. The expression of L1 cell adhesion molecule (CAM) is well correlated with the presence of a \(RELA\) fusion in supratentorial ependymomas but this is also expressed by other tumors.\(^59\)

**Neuronal and mixed neuronal-glial tumors (Fig. 3)**

Two lesions, diffuse leptomeningial glioneuronal tumor (DLGNT)\(^61-63\) and multinodular and vacuolating neuronal tumor (MVNT)\(^64-66\) both of which are considered to be unique lesions, have been described by various similar

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**Fig. 2** Diffuse midline glioma, H3 K27M-mutant. (a) Axial FLAIR MRI shows an ill-defined high intensity area in the left thalamus. (b) Thalamic tumor shows diffuse astrocytic morphology with anaplasia. (c) The tumor cells show strong GFAP expression. (d) Sagittal FLAIR MRI shows a diffusely infiltrating pontine glioma expanding the pons. (e) IDH1 R132H immunohistochemistry is negative. (f) Strong nuclear staining for K27M-mutant H3 is present.
Fig. 3 Diffuse leptomeningial glioneuronal tumor (DLGNT) (a–d) and vacuolating neuronal tumor (MVNT) (e–j). (a) Expansion by tumor tissue of the cerebellar leptomeninges without apparent intraparenchymal masses (Klüver-Barrera staining). (b) Showing the mixture of small, round oligodendroglia-like cells and irregularly oriented neuronal cells. (c) Occasionally tumor tissue shows mucin-rich microcystic background. (d) Neuronal cells as well as the neoplastic stroma show positive synaptophysin immunoreactivity. (e, f) Axial FLAIR MRIs show an irregular cortical lesion in the right medial temporal lobe. (g) Multiple nodular or patchy lesions in the subcortical white matter are evident in Klüver-Barrera staining. (h) Dysplastic cells having an abundant amphiphilic to eosinophilic cytoplasm with peripheral Nissl substance showed focal clustering. (i) Tumor cells are strongly positive for α-internexin on the cell membranes. (j) The dysplastic neurons were intensely stained by HuC/Hu.
terms in the literature. DLGNT is characterized by the diffuse involvement of the leptomeninges, particularly those of the spinal cord, with or without recognizable parenchymal components. The major constituent of DLGNT is oligodendroglia-like cells with variable neuronal components (from neurocytes to ganglioid cells). DLGNT often poses BRAF fusions as well as chromosome 1p deletions. MVNT is a quasi-tumor that is characterized by multiple nodules composed of vacuolating dysplastic neurons in the subcortical white matter. A relatively restrictive—either nodular or ribbon-like—growth pattern suggests that MVNT has a hamartomatous nature.

Embryonal tumors

The main changes in this category included the addition of medulloblastomas, which are genetically defined, and embryonal tumor with multilayered rosettes (ETMR), C19MC-altered. Central Nervous System (CNS)-primitive neuroectodermal tumor (PNET) was eliminated. For medulloblastoma, the most popular 4-type classification was not adopted in this revision; however, WNT-activated, SHH-activated and non-WNT/SHH have been accepted instead. The SHH-activated tumors were divided into those with and without TP53 mutations that can be detected by immunohistochemistry. Multilayered rosettes are characterized by a pseudostratified neuroepithelium with a central lumen covered by a defined apical surface with an internal limiting membrane; rosettes of this type always lack a defined outer membrane. Multilayered rosettes are not always present in ETMR, C19MC-altered but medulloepithelioma-type rosettes may be present. Of note, a small portion of medulloepithelioma may harbor C19MC-alteration. If no diagnostic genetic alteration is identified, the tumor is classified as plain “medulloepithelioma”.

DNA methylation profiling has revealed that majority of CNS-PNETs display molecular profiles indistinguishable from those of various other well-defined CNS tumor entities, which strongly suggests that CNS-PNETs are not an entity. In the remaining fractions, in which well-defined entities were excluded, some unknown tumors, one of which resembles CNS neuroblastoma, have been reported, the details of those unknown tumors remain unclear.

Immunohistochemical surrogates in a clinical setting

Although WHO2016 does not allow the use of surrogate markers to detect molecular alterations, some hospitals/medical centers, particularly those located in areas other than Europe and North America, do not have full access to methods to detect the signature molecular alterations. In the clinical setting, the use of immunohistochemical surrogates is necessary. Since Sanger sequencing, the most standard method to detect point mutations on IDH1/2, requires at least 20% of mutant alleles for identifying mutations, immunohistochemistry can be more sensitive than genetic tastings. Nonetheless, it is important to bear in mind that no surrogate markers can be used as a substitute for an official WHO diagnosis and we have to facilitate departmental and institutional molecular testing to improve the diagnosis of brain tumors. The immunohistochemical surrogates that fulfill the WHO2016 diagnoses are shown in Table 5.

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Conflicts of Interest Disclosure

The author declares no conflicts of interest.

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