Review Article

A Simplified Overview of World Health Organization Classification Update of Central Nervous System Tumors 2016

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Abstract

After 8 years, an update of central nervous system (CNS) tumors was published in 2016 after 2007. First time ever, molecular markers along with histology have been used in classification of any tumor. Major changes are seen in glioma and medulloblastoma groups. Few entities have been added such as diffuse midline glioma, H3 K27M-mutant, RELA fusion-positive ependymoma, embryonal tumor with multilayered rosettes, C19MC-altered, and hybrid nerve sheath tumors. Few variants and patterns that no longer have diagnostic and/or biological relevance and have been deleted such as glioblastoma cerebri, protoplasmic and fibrillary astrocytoma, and cellular ependymoma. Other changes include deletion of term "primitive neuroectodermal tumor," addition of criterion of brain invasion in atypical meningioma, separation of melanotic schwannoma from other schwannoma, and combination of solitary fibrous tumors and hemangiopericytoma as one entity. There is also expansion of entities in nerve sheath tumors and hematopoietic/lymphoid tumors of the CNS. In this review article, we tried to review CNS tumors 2016 classification update in a simplified manner; comparing the differences between 2016 and 2007 CNS tumors classifications with brief description of important molecular markers and finally utility as well as challenges of this classification.

Keywords: *Central nervous system tumor update, simplified overview, World Health Organization classification*

Introduction

The 2016 World Health Organization (WHO) classification of central nervous system (CNS) tumors is basically an updated version of 2007 classification, rather than a new version. 2007 WHO classification of CNS tumors was based mainly on the histological features of the tumor microscopically (light microscopy in hematoxylin- and eosin-stained sections, immunohistochemical [IHC] lineage-associated proteins, and ultrastructural characteristics) with different putative cells of origin and level of differentiation which lead to a lot of confusion and doubts among pathologists. Hence, there was a need for new classification to facilitate clinical, experimental, and epidemiological studies. In 2014, a meeting was held in Haarlem, the Netherlands, by International Society of Neuropathology, and attended by 117 contributors from twenty countries to formulate guidelines to introduce molecular findings into CNS tumor classification and diagnosis. Finally, the WHO classification of CNS tumors was updated in 2016 with addition of genetic basis of tumorigenesis or molecular marker. This classification provides prognostic or predictive data within diagnostic categories established by conventional histology which allow effective targeted treatments. This new classification will also aid researchers by helping them to make a more precise analysis of data in the laboratory and will also help in more accurate interlaboratory comparison.[1,2]

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2016 World Health Organization Classification Update of Central Nervous System Tumors

2016 WHO classification update includes both phenotypic and genotypic parameters, making it more objective than the previous classification. 2016 WHO classification update of CNS tumors and its comparison with 2007 WHO classification of CNS tumors, highlighting major modifications, are summarized in Table 1.[1-3]

Histological Grading of Central Nervous System Tumors

There are not many changes in WHO histological grading in 2016 update as compared to 2007 CNS tumor, only a new category "grade unknown" is added for diffuse leptomeningeal glioneuronal tumor. Grading of CNS tumors is mainly based on four morphologic criteria: cytological atypia, mitotic activity, microvascular proliferation (endothelial cell proliferation), and necrosis (St. Anne–Mayo grading system). According to above parameters, CNS tumors are classified in four grades. Table 2 shows the WHO histological grading of CNS tumors.

- Grade I: Tumors do not meet any of the criteria. These tumors are slow growing, nonmalignant, and associated with long-term survival
- Grade II: Tumors meet only one criterion, i.e., only cytological atypia. These tumors are slow growing but recur as higher-grade tumors. They can be malignant or nonmalignant
- Grade III: Tumors meet two criteria, i.e., anaplasia and mitotic activity. These tumors are malignant and often recur as higher-grade tumors
- Grade IV: Tumors meet three or four of the criteria, i.e., showing anaplasia, mitotic activity with microvascular proliferation, and/or necrosis. These tumors reproduce rapidly and are very aggressive malignant tumors.[1,4]

Features of 2016 World Health Organization Classification of Central Nervous System Tumors

New nomenclature

Standard terminology was introduced by combining histopathological and molecular features such as

- Histopathological name followed by the genetic features, for example, diffuse astrocytoma, isocitrate dehydrogenase (IDH)-mutant and medulloblastoma, and tumors in wingless (WNT)-activated
- For entities with more than one genetic determinant: Histopathological name followed by the multiple molecular features are included in the name, for example, oligodendroglioma, IDH-mutant, and1p/19q-codeleted
- For a tumor lacking a genetic mutation: The term wild type can be used, for example, glioblastoma and IDH-wild type
- For laboratory lacking any access to molecular diagnostic testing, the term not otherwise specified (NOS) can be used (i.e., NOS). NOS is also applicable to tumors, in which genetic assay testing is inconclusive. An NOS designation implies that there is insufficient information to assign a most specific code
- For tumor entities, in which a specific genetic alteration is present, the terms "positive" can be used is present, for example, ependymoma and RELA fusion-positive.[2]

Major changes in World Health Organization central nervous system tumor classification

Major changes have been introduced in the classification of two categories of tumors, based on molecular markers – diffuse gliomas (astrocytic, oligodendroglial, and glioblastoma tumors) and embryonal tumors particularly medulloblastoma.

According to new classification, the diffuse gliomas include the astrocytic tumors (WHO Grade II and III), oligodendrogliomas (WHO Grade II and III), oligoastrocytoma (WHO Grade II and III), and glioblastomas (WHO Grade IV). Earlier in 2007 classification, all astrocytic tumors had been grouped together, but now in new 2016 classification, all diffuse gliomas whether they are astrocytic or oligodendroglial are grouped under one heading, mainly based on their growth pattern, behavior as well as a mutation in IDH. This separates tumors especially astrocytomas that have more circumscribed growth, lack IDH gene alteration, or have BRAF mutation (i.e., pilocytic astrocytoma, subependymal giant cell astrocytoma, and pleomorphic xanthoastrocytoma).[5]

Main molecular markers used in gliomas

Isocitrate dehydrogenase

Main molecular makers in gliomas are IDH, 1p19qdeletion, MGMT, TERT, ATRX and p53 which are of diagnostic significance as shown in Table 3.

Two IDH variants have been used IDH 1 and IDH 2. Both are an enzyme in Krebs cycle which catalyzes the conversion of isocitrate to alpha-ketoglutarate.

IDH 1 mutations are heterozygous, involving an amino acid substitution (glycine to arginine) in the active site of the enzyme in codon 132 (R132H). This mutation results in the abnormal production of 2-hydroxyglutarate which causes histone and DNA methylation, hence promoting tumorigenesis.

Table 1: 2016 versus 2007 World Health Organization central nervous system tumors classifications and highlighting major changes in 2016 classification

	2016	2007	Major changes in 2016 classification
Diffuse astrocytic and oligodendroglial tumors	Diffuse astrocytoma, IDH mutant Gemistocytic astrocytoma, IDH mutant Diffuse astrocytoma, IDH wild type Diffuse astrocytoma, NOS Anaplastic astrocytoma IDH mutant IDH wild type NOS Diffuse midline glioma, H3 K27M-mutant	Pilocytic astrocytoma Pilomyxoid astrocytoma Subependymal giant cell astrocytoma Pleomorphic xanthoastrocytoma Diffuse astrocytoma Fibrillary astrocytoma Gemistocytic astrocytoma Protoplasmic astrocytoma Anaplastic astrocytoma	Astrocytic, oligodendroglioma and glioblastoma tumors combined under one heading of diffuse glioma Genetic classification of diffuse astrocytoma and anaplastic astrocytoma Pilocytic astrocytoma, subependymal giant cell astrocytoma and pleomorphic xanthoastrocytoma included under different heading Deletion Protoplasmic and fibrillary astrocytoma Addition Diffuse midline glioma, H3 K27M-mutant and anaplastic pleomorphic Xanthoastrocytoma, WHO Grade III, instead of pleomorphic Xanthoastrocytoma with anaplastic features
Diffuse astrocytic and oligodendroglial tumors	Glioblastoma, IDH wild type Giant cell glioblastoma Gliosarcoma Epithelioid glioblastoma Glioblastoma, IDH mutant Glioblastoma, NOS	Glioblastoma Giant cell glioblastoma Gliosarcoma Gliomatosis cerebri	Classification of glioblastoma genetically Addition of Epithelioid glioblastoma Glioblastoma with primitive neuronal component Removal of gliomatosis cerebri
Diffuse astrocytic and oligodendroglial tumors	Oligodendroglioma IDH mutant, and 1p19q co-deleted NOS Anaplastic oligodendroglioma IDH mutant and 1p19q co-deleted NOS	Oligodendroglioma Anaplastic oligodendroglioma	Genetic-based classification
Diffuse astrocytic and oligodendroglial tumors	Oligoastrocytoma, NOS Anaplastic oligoastrocytoma, NOS	Oligoastrocytoma Anaplastic oligoastrocytoma	Addition of NOS: Use of the diagnosis "oligoastrocytoma" is now discouraged in favor of astrocytoma or oligodendroglioma
Other astrocytic tumors	Pilocytic astrocytoma Pilomyxoid astrocytoma Subependymal giant cell astrocytoma Pleomorphic xanthoastrocytoma		Different heading
Ependymal tumors	Subependymoma Myxopapillary ependymoma Ependymoma Papillary Clear cell Tanycytic Anaplastic ependymoma Ependymoma, RELA fusion positive	Subependymoma Myxopapillary ependymoma Ependymoma Cellular Papillary Clear cell Tanycytic Anaplastic ependymoma	Addition of ependymoma, RELA fusion positive Removal of cellular ependymoma

Contd...

Table 1: Contd...

	2016	2007	Major changes in 2016 classification
Choroid plexus tumors	Choroid plexus papilloma	Choroid plexus papilloma	No change
	Atypical choroid plexus papilloma	Atypical choroid plexus papilloma	
	Choroid plexus carcinoma	Choroid plexus carcinoma	
Other gliomas	Astroblastoma	Other neuroepithelial tumors	Heading changed
	Chordoid glioma of the third ventricle	Astroblastoma	
	Angiocentric glioma	Chordoid glioma of the third ventricle	
		Angiocentric glioma	
Neuronal and mixed neuronal-glial tumors	Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)	Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)	Addition of diffuse leptomeningeal glioneuronal tumor
	Desmoplastic infantile astrocytoma/ganglioglioma	Desmoplastic infantile astrocytoma/ganglioglioma	
	Dysembryoplastic neuroepithelial tumor	Dysembryoplastic neuroepithelial tumor	
	Gangliocytoma	Gangliocytoma	
	Ganglioglioma	Ganglioglioma	
	Anaplastic ganglioglioma	Anaplastic ganglioglioma	
	Central neurocytoma	Central neurocytoma	
	Extraventricular neurocytoma	Extraventricular neurocytoma	
	Cerebellar liponeurocytoma	Cerebellar liponeurocytoma	
	Papillary glioneuronal tumor	Papillary glioneuronal tumor	
	Rosette-forming glioneuronal tumor of the fourth ventricle	Rosette-forming glioneuronal tumor of the fourth ventricle	
	Paraganglioma	Paraganglioma	
	Diffuse leptomeningeal glioneuronal tumor		
Tumors of the pineal region	Pineocytoma	Pineocytoma	No change
	Pineal parenchymal tumor of intermediate differentiation	Pineal parenchymal tumor of intermediate differentiation	
	Pineoblastoma	Pineoblastoma	
	Papillary tumor of the pineal region	Papillary tumor of the pineal region	
Embryonal tumors	Medulloblastoma, genetically defined	Medulloblastoma	Reclassified genetically, histologically and as NOS
	WNT activated	Desmoplastic/nodular medulloblastoma	Combined anaplastic and large cell variety
	SHH activated and TP53 mutant	Medulloblastoma with extensive nodularity	
	SHH activated and TP53 wild type	Anaplastic medulloblastoma	
	Non-WNT/non-SHH	Large cell medulloblastoma	
	Group 3		
	Group 4		
	Medulloblastoma, histologically defined		
	Classic		
	Desmoplastic/nodular		
	Extensive nodularity		
	Large cell/anaplastic		
	Medulloblastoma, NOS		

Contd...

Table 1: Contd...

	2016	2007	Major changes in 2016 classification
	Medulloepithelioma CNS neuroblastoma CNS ganglioneuroblastoma AT/RT CNS embryonal tumor, NOS CNS embryonal tumor with rhabdoid features Embryonal tumor with multilayered rosettes, C19MC altered Embryonal tumor with multilayered rosettes, NOS	CNS PNET CNS neuroblastoma CNS ganglioneuroblastoma Medulloepithelioma Ependymoblastoma AT/RT	Addition of CNS embryonal tumor, NOS CNS embryonal tumor with rhabdoid features Embryonal tumor with multilayered rosettes, C19MC altered Embryonal tumor with multilayered rosettes, NOS Removal of term PNETs and now replaced by ETMRs
Tumors of cranial and paraspinal nerves	Schwannoma (neurilemoma, neurinoma) Cellular Plexiform Melanotic Neurofibroma Plexiform Atypical Perineurioma Hybrid nerve sheath tumors MPNST Epithelioid MPNST MPNST with perineurial differentiation	Schwannoma (neurilemoma, neurinoma) Cellular Plexiform Melanotic Neurofibroma Plexiform Perineurioma Perineurioma, NOS Malignant perineurioma MPNST Epithelioid MPNST MPNST with mesenchymal differentiation Melanotic MPNST MPNST with glandular differentiation	Addition Atypical neurofibroma Hybrid nerve sheath tumors MPNST with perineurial differentiation Deletion of MPNST with mesenchymal differentiation Melanotic MPNST MPNST with glandular differentiation Nerve sheath tumors are expanded, with incorporation of hybrid nerve sheath tumor and separation of melanotic schwannoma from others
Meningioma	Meningioma Meningothelial Fibrous (fibroblastic) Transitional (mixed) Psammomatous Angiomatous Microcystic Secretory Lymphoplasmacyte-rich Metaplastic Chordoid Clear cell Atypical Papillary Rhabdoid Anaplastic (malignant)	Meningioma Meningothelial Fibrous (fibroblastic) Transitional (mixed) Psammomatous Angiomatous Microcystic Secretory Lymphoplasmacyte-rich Metaplastic Chordoid Clear cell Atypical Papillary Rhabdoid Anaplastic (malignant)	No change except introduction of brain invasion as a criterion for the diagnosis of atypical meningioma, WHO Grade II

Contd...

Table 1: Contd...

	2016	2007	Major changes in 2016 classification
Mesenchymal, nonmeningothelial tumors	Lipoma	Lipoma	Addition
	Angiolipoma	Angiolipoma	Hemangioblastoma (in previous classification, 2007 it was classified in separate heading "other neoplasm related to the meninges")
	Hibernoma	Hibernoma	Desmoid type fibromatosis
	Liposarcoma	Liposarcoma	Myofibroblastoma
	Fibrosarcoma	Solitary fibrous tumor	Inflammatory myofibroblastic tumors
	Malignant fibrous histiocytoma/ undifferentiated pleomorphic sarcoma	Fibrosarcoma	Benign fibrous histiocytoma
	Leiomyoma	Malignant fibrous histiocytoma	Solitary fibrous tumor and hemangiopericytoma are now considered a combined diagnosis (solitary fibrous tumor/hemangiopericytoma)[po]
	Leiomyosarcoma	Leiomyoma	
	Rhabdomyoma	Leiomyosarcoma	
	Rhabdomyosarcoma	Rhabdomyoma	
	Chondroma	Rhabdomyosarcoma	
	Chondrosarcoma	Chondroma	
	Osteoma	Chondrosarcoma	
	Osteosarcoma	Osteoma	
	Osteochondroma	Osteosarcoma	
	Hemangioma	Osteochondroma	
	Epithelioid hemangioendothelioma	Haemangioma	
	Angiosarcoma	Epithelioid haemangioendothelioma	
	Kaposi sarcoma	Haemangiopericytoma	
	Ewing sarcoma - PNET	Anaplastic haemangiopericytoma	
	Solitary fibrous tumor/ hemangiopericytoma: Grade 1, 2, 3	Angiosarcoma	
	Hemangioblastoma	Kaposi sarcoma	
	Desmoid-type fibromatosis	Ewing sarcoma - PNET	
	Myofibroblastoma		
	Inflammatory myofibroblastic tumors		
	Benign fibrous histiocytoma		
Melanocytic tumors	Meningeal melanocytosis	Diffuse melanocytosis	Mainly addition of meningeal word
	Meningeal melanocytoma	Melanocytoma	
	Meningeal melanoma	Malignant melanoma	
	Meningeal melanomatosis	Meningeal melanomatosis	
Lymphomas	Diffuse large B-cell lymphoma of the CNS	Malignant lymphomas	
	Immunodeficiency-associated CNS lymphomas	Plasmacytoma	
	AIDS-related diffuse large B-cell lymphoma	Granulocytic sarcoma	
	EBV-positive diffuse large B-cell lymphoma, NOS		
	Lymphomatoid granulomatosis		
	Intravascular large B-cell lymphoma		
	Low-grade B-cell lymphomas of the CNS		
	T-cell and NK/T-cell lymphomas of the CNS		

Contd...

Table 1: Contd...

	2016	2007	Major changes in 2016 classification
	Anaplastic large cell lymphoma		
	ALK positive		
	ALK negative		
	MALT lymphoma of the dura		
Histiocytic tumors	Erdheim-Chester disease		New addition
	Histiocytic sarcoma		
	Juvenile xanthogranuloma		
	Langerhans cell histiocytosis		
	Rosai-Dorfman disease		
Germ cell tumors	Germinoma	Germinoma	No change
	Embryonal carcinoma	Embryonal carcinoma	
	Yolk sac tumor	Yolk sac tumor	
	Choriocarcinoma	Choriocarcinoma	
	Teratoma	Teratoma	
	Mature	Mature	
	Immature	Immature	
	Teratoma with malignant transformation	Teratoma with malignant transformation	
	Mixed germ cell tumor	Mixed germ cell tumor	
Tumors of the sellar region	Craniopharyngioma	Craniopharyngioma	No change
	Adamantinomatous	Adamantinomatous	
	Papillary	Papillary	
	Granular cell tumor	Granular cell tumor	
	Pituicytoma	Pituicytoma	
	Spindle cell oncocytoma	Spindle cell oncocytoma of the adenohypophysis	
Metastatic tumors			No change

CNS: Central nervous system, IDH: Isocitrate dehydrogenase, NOS: Not otherwise specified, WHO: World Health Organization, SHH: Sonic hedgehog, ETMRs: Embryonal tumors with multilayered rosettes, MPNST: Malignant peripheral nerve sheath tumor, PNET: Primitive neuroectodermal tumor, EBV: Epstein-Barr virus, ALK: Anaplastic lymphoma kinase, MALT: Mucosa-associated lymphoid tissue, WNT: Tumors in wingless, TP53: Tumor protein p53

IDH 2 mutations occur in codon 172. Mutations in IDH 2 are associated with 2-hydroxyglutaric aciduria (D-2-hydroxyglutaric aciduria [D-2-HGA], L-2-HGA, and combined D, L-2-HGA), which results in seizures, weak muscle tone (hypotonia), and progressive damage to the cerebrum.

IDH is a most important diagnostic marker as it can differentiate glioma from gliosis. It is positive in astrocytoma, oligodendroglioma, and even in 10% glioblastoma, especially secondary.

IDH can be demonstrated by IDH 1 or IDH 2 mutation by immunohistochemistry using mutation-specific antibody against R132H mutant IDH 1, if immunostaining is negative, then it should be followed by IDH 1/2 DNA genotyping.

Mutation in both IDH 1 and IDH 2 entity is known as IDH mutant. Both are negative then it is known as IDH wild type. If IDH testing is not available or cannot be fully performed or is inconclusive, then it is labeled as IDH NOS.[6,7]

1p/19q co-deletion

In 1p/19q co-deletion, there is complete deletion of both the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q). 1p/19q co-deletion can be demonstrated by fluorescent *in situ* hybridization (FISH), polymerase chain reaction, chromogenic *in situ* hybridization, or molecular genetic testing. It is definitive for the diagnosis of Grade II and Grade III (anaplastic) oligodendroglioma. It is a strong prognostic factor associated with improved survival and also a predictive factor for response to chemotherapy as well as radiotherapy.[5]

O6-methylguanine-DNA methyltransferase methylation (MGMT)

The O^6-methylguanine-DNA methyltransferase (MGMT) gene encodes a DNA repair enzyme that can nullify

Table 2: World Health Organization histological grading of 2016 central nervous system tumors

	I	II	III	IV	Grade unknown
Diffuse astrocytic and oligodendroglial tumors		Diffuse astrocytoma IDH mutant IDH wild type Oligodendroglioma IDH mutant, and1p19q co-deleted	Anaplastic astrocytoma IDH mutant IDH wild type Anaplastic oligodendroglioma, IDH mutant, and1p19q co-deleted	Diffuse midline glioma, H3 K27M-mutant Glioblastoma, IDH wild type Glioblastoma, IDH mutant	
Other astrocytic tumors	Pilocytic astrocytoma Subependymal giant cell astrocytoma	Pleomorphic xanthoastrocytoma Pilomyxoid astrocytoma	Anaplastic pleomorphic xanthoastrocytoma		
Ependymal tumors	Subependymoma Myxopapillary ependymoma	Ependymoma Papillary Clear cell Tanycytic Ependymoma, RELA fusion positive	Anaplastic ependymoma		
Choroid plexus tumors	Choroid plexus papilloma	Atypical choroid plexus papilloma	Choroid plexus carcinoma		
Other gliomas	Angiocentric glioma	Chordoid glioma of the third ventricle	Astroblastoma		
Neuronal and mixed neuronal-glial tumors	Dysplastic gangliocytoma of cerebellum Desmoplastic infantile astrocytoma/ganglioglioma Dysembryoplastic neuroepithelial tumor Gangliocytoma Ganglioglioma Papillary glioneuronal tumor Rosette-forming glioneuronal tumor of the fourth ventricle Paraganglioma	Central neurocytoma Extraventricular neurocytoma Cerebellar liponeurocytoma	Anaplastic ganglioglioma		Diffuse leptomeningeal glioneuronal tumor
Tumors of the pineal region	Pineocytoma	Pineal parenchymal tumor of intermediate differentiation Papillary tumor of the pineal region (could be Grade III also)		Pineoblastoma	
Embryonal tumors				Medulloblastoma (all subtypes) Medulloepithelioma CNS neuroblastoma CNS ganglioneuroblastoma AT/RT CNS embryonal tumor, NOS	

Contd...

Table 2: Contd...

	I	II	III	IV	Grade unknown
				CNS embryonal tumor with rhabdoid features	
				Embryonal tumor with multilayered rosettes, C19MC altered	
				Embryonal tumor with multilayered rosettes, NOS	
Tumors of cranial and paraspinal nerves	Schwannoma		MPNST		
	Perineurioma		Epithelioid MPNST		
	Hybrid nerve sheath tumors		MPNST with perineurial differentiation (could be I, II, IV)		
Meningiomas	Meningioma	Atypical	Anaplastic (malignant)		
Mesenchymal tumors	Solitary fibrous tumor/ hemangiopericytoma: Grade 1, 2, 3				
	Hemangioblastoma				
Tumors of the sellar region	Craniopharyngioma				
	Granular cell tumor				
	Pituicytoma				
	Spindle cell oncocytoma				

IDH: Isocitrate dehydrogenase, CNS: Central nervous system, NOS: Not otherwise specified, MPNST: Malignant peripheral nerve sheath tumor, AT/RT: Atypical teratoid/rhabdoid tumor

Table 3: Molecular markers in diagnosis of glioma

Tumors	Molecular marker
Astrocytoma	IDH1/2, TP53, ATRX
Oligodendroglioma	IDH1/2, 1p/19q co-deletion, TERT
Glioblastoma	IDH1/2, TERT, MGMT methylation
Diffuse midline glioma, H3 K27M-mutant	H3 K27M, ATRX, TP53

IDH: Isocitrate dehydrogenase, TP53: Tumor protein p53, ATRX: Alpha-thalassemia/mental retardation syndrome X-linked, MGMT: O^6-methylguanine-DNA methyltransferase

the effects of alkylating chemotherapy such as temozolomide. The alkylating chemotherapy damages DNA by adding methyl groups. Therefore, a tumor with a high degree of MGMT activity will be resistant to chemotherapies which target DNA at this location. If the promoter region of the MGMT gene is unmethylated, the gene will be active, whereas if the promoter region of MGMT is hypermethylated, the gene will be silenced. However, if the MGMT gene is active, the damage is rapidly repaired. Methylation of the MGMT gene promoter is a favorable prognostic and predictive factor in glioblastoma patients, but it is not a diagnostic marker for the same.[8]

TERT (Telomerase reverse transcriptase) promoter mutations

TERT mutations often involve C228T and C250T mutations of the promoter region. TERT promoter mutations and long telomere length predict poor survival and radiotherapy resistance in gliomas. It occurs mainly in glioblastoma and oligodendroglioma.[9,10]

Alpha-thalassemia/mental retardation syndrome X-linked (ATRX)

It is chromatin remodeling protein important in DNA replication, telomere stability, gene transcription, chromosome congression, and cohesion during cell division. Alpha-thalassemia/mental retardation syndrome X-linked (ATRX) mutation results in lengthening of telomerase which helps in chromatin maintenance and remodeling. All cells are ATRX positive. If ATRX mutation is present, then there will be a loss of staining in the cells.

ATRX mutations are almost always accompanied by other mutations in the histone regulation (IDH, H33 K27M, tumor protein p53 [TP53], etc.). Loss of ATRX expression is seen in 45% of anaplastic astrocytomas, 27% of anaplastic oligoastrocytomas, and 10% of

anaplastic oligodendrogliomas and also in pediatric and adult high-grade astrocytoma.[10,11]

Tumor protein p53

p53 is a tumor suppressor gene located on the short arm of chromosome 17. Loss of p53 leads to DNA damage, hypoxia, oncogene activation, microtubule disruption, and oxidative damage which in turn contributes to the CNS tumors pathogenesis mainly medulloblastoma, glioblastoma, and in 56%–58% of IDH-mutant astrocytomas. Copy number-neutral loss of heterozygosity of chromosome 17p (CNLOH 17p) was nearly exclusively associated with IDH 1 mutant astrocytomas with TP53 mutations. "CNLOH" means that one copy of the chromosomal has been deleted whereas the remaining copy has been duplicated. The net result is that the cell still has a total of two copies of the gene or chromosomal segment, but instead of having two different copies [one from the mother and one from the father], a single copy has been duplicated). CNLOH 17p was found to be a significant prognostic factor, with better survival outcomes for those with the CNLOH 17p alteration.[12,13]

Molecular markers used in embryonal tumors

Tumors in wingless and sonic hedgehog activation

WNT-activated and sonic hedgehog active groups show activation cell signaling pathways which lead to tumorigenesis in medulloblastoma. In 2016 WHO classification update, medulloblastoma is classified according to molecular characteristics as well as histological features. Molecular classification is based on transcriptome, microRNA (miRNA), and methylome profiling for clinical treatment and histological classification has also been retained due to its clinical utility when molecular analysis is not feasible.[14]

C19MC alteration

Amplification of the C19MC region on chromosome 19 is noted in embryonal tumor with multilayered rosettes (ETMR). The presence of a focal amplification at chromosome region 19q13.42 associated with an upregulation of the oncogenic miRNA cluster.[15]

Other new molecular markers are

H3 K27M-mutation

Histone H3 K27M is a mutation in the H3F3A gene, encoding for histone H3.3. The lysine is substituted to methionine at 27 position in histone variant H3.3 (H3.3-K27M). This mutation leads to a global reduction of H3K27 trimethylation by sequestering an enzymatic subunit of the polycomb repressive complex 2. As a consequence, the epigenetic setting of the cell including DNA methylation is altered and drives gene expression toward tumorigenesis.[16,17]

RELA fusion

C11orf95-RELA fusions result from chromothripsis involving chromosome 11q13.1. C11orf95-RELA fusion proteins translocated spontaneously to the nucleus to activate members of the nuclear factor-κB family of transcriptional regulators that are central mediators of the cellular inflammatory response and which rapidly transform neural stem cells to form tumors, i.e., ependymoma.[18]

Newly added entities, variants, and patterns

- New entities have been added such as diffuse midline glioma, H3 K27M-mutant, diffuse leptomeningeal glioneuronal tumor, and ependymoma RELA-positive tumors, and some variants have been added, especially in glioblastoma such as epithelioid glioblastoma. As well as some patterns such as glioblastoma with a primitive neuroectodermal tumor (PNET) component have been included in 2016 CNS tumor classifications
- Some entities, variants, and patterns have been deleted such as gliomatosis cerebri (now considered a pattern instead of an entity) and "PNET" terminology for embryonal tumors.[2,19]

New entities introduced in the 2016 World Health Organization classification

Diffuse midline glioma, H3 K27M-mutant

- Epidemiology: Predilection for young adults and children
- Etiology: Histone H3 K27M is a mutation in the H3F3A gene, encoding for histone H3.3
- Localization: Brain stem (previously known as brain stem glioma), thalamus, and spinal cord (previously known as diffuse intrinsic pontine glioma)
- Radiographic features: Diffuse growth with hypointense on T1 and hyperintense on with contrast enhancement along with necrosis and hemorrhage
- Spread: Leptomeningeal dissemination
- Gross: Distortion and enlargement of anatomical structures systemically with areas of hemorrhage and necrosis
- Microscopy: Tumor cells are small monomorphic with microvascular proliferation and necrosis
- IHC: Positive for strongly nuclear positivity for H3 K27M and also positive for neural cell adhesion molecule 1, S-100, OLIG2, MAP2, and Nuclear p53 Negative for Neu N and Chromogranin A
- Prognosis: Prognosis: Poor.[16,20]

Diffuse leptomeningeal glioneuronal tumor (also known as disseminated oligodendroglial-like leptomeningeal tumor of childhood)

- Epidemiology: Children and adolescents
- Localization: Posterior fossa, spinal, intracranial leptomeninges

- Clinical features: Increased intracranial pressure due to obstructive hydrocephalus (headache, nausea and vomiting), opisthotonos, and sign of meningeal or cranial nerve damage
- Radiographic features: Magnetic resonance imaging (MRI) shows meningeal enhancement with thickening and hyperintense T2
- Spread: Cerebrospinal fluid (CSF) examination: high protein and negative cytology
- Gross: Intraparenchymal, circumscribed, solid/cystic nodules. Multifocal extension of tumor along Virchow–Robin space
- Microscopy: Tumor is low-to-moderate cellularity neoplasm composed of cells with perinuclear haloes similar to oligodendroglial cells, they have round-to-oval nuclei with finely granular dispersed chromatin and inconspicuous nucleoli with intense desmoplastic fibrous response. They have low mitotic index (<1%)
- IHC: Positivity for BRAF fusion (common), synaptophysin (diffuse immunoreactivity), OLIG2 (patchy immunoreactivity), S-100 (diffuse immunoreactivity), and glial fibrillary acidic protein (GFAP) (patchy immunoreactivity).

Negative for neurofilament and epithelial membrane antigen (EMA) and no IDH mutations

- Prognosis: Moderate prognosis
- Differential diagnosis: In contrast to oligodendrogliomas, diffuse leptomeningeal glioneuronal tumors do not have IDH IDH mutations.[21,22]

Embryonal tumor with multilayered rosettes (also known as embryonal tumor with abundant neuropil and true rosettes)

- Epidemiology: Predilection for children and females
- Etiology: Amplification of the C19MC region on chromosome 19 in both CNS PNET and embryonal tumor with abundant neuropil and true rosettes, suggesting that these are the one entity with variable growth patterns
- Localization: Cerebrum, cerebellum, brain stem
- Clinical features: Increased intracranial pressure, seizures, hemiparesis, cerebellar signs, cranial nerve palsies, and other neurologic deficits
- Radiographic features: MRI - The tumor appears as a large, demarcated, solid mass featuring patchy or no contrast enhancement, with surrounding edema, often with significant mass effect. A minority of the reported cases have shown cystic components and microcalcifications. T1: Decreased intensity, T2: Increased intensity, and T1 (gadolinium): Patchy or no contrast enhancement
- Magnetic resonance spectroscopy shows choline peak and a high ratio of choline/aspartate suggesting hypercellularity of the tumor
- Gross: Large involve multiple lobes can protrude to cerebellopontine cistern. They are well circumscribed, grayish pink with area of necrosis, hemorrhage, and calcification
- Microscopy: It is rare small round blue cell tumor of the CNS. They are multilayered, pseudostratified neuroepithelium with central, round, or slit-like lumen. The lumen is either empty or filled with eosinophilic debris. Nucleus of cells is pushed away from the lumen
- Spread: Locally infiltrative, leptomeningeal dissemination, extraneural metastasis
- IHC: Positivity: Vimentin, nestin, focal positive for EMA, cytokeratin, and CD99. Neutrophil is positive for synaptophysin, NeuN, and NFPs.
  Negative: Glial and neuronal marker
- Prognosis: Aggressive tumors with poor prognosis
- Differential diagnosis: Medulloblastoma (unlike medulloblastoma, ETMR has no epithelial-like formation), medulloepithelioma, atypical teratoid/rhabdoid tumor (AT/RT).[15]

Ependymoma RELA fusion positive

- Epidemiology: Predilection for children
- Localization: Supratentorial (ependymoma in posterior fossa and spinal compartment do not harbor RELA fusion gene)
- Clinical features: Headache, seizures, or location-dependent focal neurologic deficits
- Radiographic features: MRI - gadolinium-enhanced MRI: well-circumscribed mass with contrast enhancement, intratumoral hemorrhage, and calcification
- Spread: Cerebrospinal spread
- Gross: Well circumscribed, arising in or near ventricular system, tan colored, soft spongy, occasionally with gritty calcium deposits
- Microscopy: Demonstrate classical (well-delineated glioma with monomorphic cells characteristics but round to oval nuclei with speckled nuclear chromatin, key features are perivascular anucleated zone/pseudorosettes, and true ependymal rosettes), or anaplastic morphology (high nuclear-to-cytoplasmic ratio with brisk mitotic activity, delicate network capillary blood vessels, and focal clear cells
- IHC: Positivity: GFAP, EMA, S-100, Vimentin, and L1CAM with C11or95 rearrangement
- The presence of the RELA fusion gene can be assessed with FISH
- Prognosis: Worst
- Differential diagnosis: Astrocytoma and medulloblastoma.[18]

New variants introduced in the 2016 World Health Organization classification of glioblastoma

Epithelioid glioblastoma

- Epidemiology: Predilection for young adults and children
- Etiology: *De novo* (most of them expressed SMARCB1). They frequently have BRAF V600E mutations
- Localization: Cerebral cortex (temporal and frontal lobes) and diencephalon
- Radiographic features: MRI - gadolinium-enhanced solid mass with hemorrhage and leptomeningeal seeding
- Gross: Unifocal, prominent hemorrhage, and necrosis
- Microscopy: Uniform population of large epithelioid cells that have abundant eosinophilic cytoplasm, vesicular chromatin, and prominent nucleoli. These cells are reminiscent of melanoma cells. Rhabdoid cells are also sometimes encountered
- Spread: Leptomeningeal dissemination
- IHC: Positivity vimentin, S-100, synaptophysin, GFAP and also expresses cytokeratin AE1/AE3, EMA Negative for melanA, desmin, myoglobin, and smooth muscle actin
- Prognosis: Aggressive tumors with poor prognosis
- Differential diagnosis: In children, the main differential is AT/RT, distinguished by universal lack of INI1 expression in AT/RT.[23,24]

New patterns introduced in the 2016 World Health Organization classification of glioblastoma

Glioblastoma with a primitive neuroectodermal tumorcomponent

- Epidemiology: Elderly
- Microscopy: The tumor consisted of two different components which were histologically distinct. Immunohistochemically, GFAP positivity was found in the astrocytic cells and fibrillary network. This supported the glial nature of the tumor. Another component of the tumor showed a multifocal distribution and consisted of cellular areas of small cells with narrow cytoplasms and hyperchromatic nuclei. The cells in these areas occasionally formed pseudorosettes, and their mitotic activity was high
- Spread: High rate of CSF dissemination.[25]

Integrated Reporting of Central Nervous System Tumors

Now, emphasis has been laid down on integrated reporting of CNS tumous. Diagnosis should be "layered" with histological classification, WHO grade, and molecular information and reported as "integrated diagnosis."[2]

- Layer 1: Integrated diagnosis (incorporating all tissue-based information)
- Layer 2: Histological classification, for example, diffuse glioma (such as astrocytoma or oligodendroglioma)
- Layer 3: WHO grade, for example, Grade II
- Layer 4: Molecular information, for example, IDH mutant, 1p/19q-co-deleted, ATRX Negative, p53: Negative
- Integrated diagnosis would be oligodendroglioma, IDH-mutant, and 1p/19q-co-deleted.

Advantages And Challenges Of 2016 Central Nervous System Update

Advantages

The main advantages of this classification are:

- Diagnostic criteria, pathological features, and associated genetic alterations are explained in disease-oriented manner leading to more homogenous and specific disease entities with increased objectivity
- New genetically defined entities are described separately
- Pediatric tumors are separated and described independently from its adult counter part
- Improvement in diagnostic accuracy, patient management, and treatment response due to targeted therapies.

Challenges

Some challenges in this classification are:

- Even though molecular assays are included in diagnostic criteria, methods to obtain them have not been specified leading to interobserver as well as interinstitutional variations
- Many institutions or regions still are devoid of access to genetic diagnostic tools
- Adoption of tests to determine genetic alterations and increased availability of IHC markers is a time-consuming process
- The term "NOS" indicates insufficient information which can create "wastebasket" category in future for research purposes
- Diagnosis of oligoastrocytoma is still difficult to define as oligoastrocytoma and anaplastic oligoastrocytoma are now designated as NOS categories. Their diagnosis should be made in the absence of diagnostic molecular marker tests or in the absence of a dual genotype classification which is done
- Actual format for reporting integrated diagnoses in lacking
- The use of both histology and molecular features increases the possibility of incongruous results, for

example, a tumor that appears astrocytic histologically but has IDH mutation, and 1p19q co-deletion would preferably be reported as oligodendroglioma as the genotype overrides the phenotype according to new classification

- Even now, classification cannot proceed purely on the basis of genotype alone because WHO grading is still based on histological criteria.[1,2,26]

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Conflicts of interest

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