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The 2021 WHO Classification of Tumors of the Central Nervous System: clinical implications

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See the article by Louis et al. pp. 1231–1251.

The fifth edition of the World Health Organization (WHO) Classification of Tumors of the Central Nervous System (CNS) (WHO CNS5) was recently released and summarized by Louis et al in this issue of Neuro-Oncology.[1] This builds on the 2016 WHO CNS tumor update which for the first time incorporated molecular data with histology in classifying CNS tumors, as well as the subsequent work of the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW). The changes in WHO CNS5 group tumors into more biologically and molecularly defined entities with better characterized natural histories, as well as introducing new tumor types and subtypes, especially in the pediatric population. Most importantly, these updated classifications will enable clinicians to have a better understanding of the prognosis and optimal therapy for patients with specific CNS tumors. It will also allow more homogeneous populations of patients to be enrolled into clinical trials, facilitating the evaluation of novel therapies.

Adult Connotations

Some of the most important changes in WHO CNS5 involve the classification of gliomas, differentiating gliomas that occur primarily in adults from those that occur mainly in children. For clinicians, the change in the classification of glioblastomas has the greatest practical implications. Previously, glioblastomas were diagnosed based on the histologic findings of microvascular proliferation and/or necrosis and included both *IDH-mutated* (10%) and *IDH wild-type* (90%) tumors with very different biologies and prognoses. In WHO CNS5, glioblastomas will comprise only IDH wild-type tumors. In addition, IDH wildtype diffuse astrocytic tumors in adults without the histologic features of glioblastoma but have one or more of 3 genetic parameters (TERT promoter mutation, EGFR gene amplification, or combined gain of entire chromosome 7 and loss of entire chromosome 10 [+7/–10]) will also be classified as glioblastomas. In the new classification, all *IDH*-mutant diffuse astrocytic tumors are considered a single type (astrocytoma, *IDH*-mutant) and are graded as 2, 3, or 4. Grading of these tumors will also take into account other molecular findings such as the presence of CDKN2A/B homozygous deletion which results in a worse prognosis. IDH-mutant astrocytomas with these molecular alterations will have a WHO CNS grade of 4, even in the absence of microvascular proliferation or necrosis. While this separation of astrocytomas into IDH wild-type and -mutated tumors is an important advance, it places particular emphasis on neuropathology laboratories to have access to adequate molecular testing and to be able to obtain results in a timely manner in order to identify the 10% of astrocytomas that have noncanonical *IDH* mutations that will not be detected by *IDHR132H* immunohistochemistry and to be able to identify astrocytomas with molecular features of glioblastoma. Payors will also have to be educated on the importance of these molecular tests and provide adequate reimbursement. The restriction of the diagnosis of glioblastoma to IDH wild-type tumors only allows a more homogenous population to be studied in clinical trials. However, *IDH*-mutant astrocytomas, especially the grade 4 tumors, will have fewer trial options and it will be important to develop clinical trial options for this population of patients also.

Pediatric Connotations

The pediatric clinical implications of WHO CNS5 are significant and the most welcome modification is the separation of gliomas into pediatric-type and adult-type, given

their well-established molecular genetic differences. The subgroupings are important, but likely of greater clinical importance are the associated common molecular genetic changes. Differences in molecular profiles have already been embraced for pediatric low-grade gliomas treatment planning, as separation of patients on basis of tumors with specific BRAF mutations and fusions is an accepted tenet in ongoing clinical trials.[2] An added consideration is the recent recognition that some gliomas, such as pilocytic astrocytomas with complex histological features, termed high-grade astrocytomas with piloid features, may have concomitant mutations (CDKN2A/B, ATRX, etc.) in addition to BRAF alterations which affect prognosis.[3] The subclassifications of pediatric-type low-grade gliomas on the basis of different histological features associated with characteristic genetic changes are crucial for their better clinical understanding but are also challenging for clinicians. Different molecularly targeted approaches are likely required for each tumor type and thus result in the need to create rational clinical trials directed toward relatively rare tumor subtypes.[4]

For pediatric high-grade gliomas, WHO CNS5 also builds on the 2016 classifications schema which identified the frequent epigenetic changes which help define these tumors. The recognition of an infant-type hemispheric gliomas associated with neurotrophic receptor tyrosine kinase (NTRK) family or other genetic aberrations, is an important component of this classification, with major therapeutic implications.

The ganglion cell tumors and mixed glial-neuronal tumors remain moving targets. The incorporation of both histologic and molecular features has led to better classification and understanding of these tumors. How this will be translated into more effective treatments is still to be seen, but the increasing use of molecular-targeted therapies has certainly changed the therapeutic approach to such tumors in pediatrics; especially given the hesitancy to utilize radiotherapy early in childhood.

The modifications in the classification of the ependymal tumors based on histological and molecular features, as well as anatomic site, has important connotations. This is especially true for the posterior fossa tumors, as specific molecular alterations, such as chromosome 6q loss, are of differing predictive value dependent on the subtype of posterior fossa ependymoma in which the mutation is present.[5] How the modified ependymal tumor subgrouping will impact therapeutic approach is unclear, including whether some subgroups can be treated with less aggressive surgery, radiation, or chemotherapy.

WHO CNS5 builds on the 2016 WHO classification of medulloblastoma and embraces the clinical and biological heterogeneity of medulloblastomas.[6] The overlap between Group 3 and Group 4 medulloblastoma was accepted in the 2016 version and the most common type of medulloblastoma continues to be non-WNT/non-SHH category. SHH-driven tumors remain split into TP53 wild-type and TP53-mutant subgroups, acknowledging the different prognosis of these 2 subsets of SHH-associated tumors. The layered reporting of medulloblastoma tumors, incorporating molecular information, remains a crucial component of classification and is mandatory to better conceptualize these tumors; 13 or more subgroups are now identified. However, it increases the challenge to develop molecularly based clinical studies. How to best cluster together individual splinter groups for biologically based therapy remains a work in progress. The risk of identifying biologically defined groups so small that studies cannot be mounted for them is real and has to be balanced against the possibility that important therapeutic signals will be lost if molecularly different tumors are treated homogenously.

The non-medulloblastoma embryonal tumors remain tremendous therapeutic challenges. For the non-medulloblastoma embryonal tumors, with the possible exception of atypical teratoid/rhabdoid tumors, many issues persist including the impact of surgery on survival, whether focal or craniospinal radiation is required, the utility of chemotherapy, and what are the most effective molecular-targeted therapies to incorporate. It seems clear that without at least some degree of biologic separation, it is unlikely significant strides will be made in developing better treatments. An issue shared by medulloblastoma and other embryonal tumors are their relatively frequent underlying germline abnormalities. The present classification does not take into account the cancer predisposition syndromes that occur in subsets of patients; germline aberrations that likely impact response to therapy and outcomes.

Clearly, any classification system including the WHO CNS5 has to be considered a work in progress, and the update provides both great opportunities and therapeutic challenges. Finding the correct balance between instantly utilizing the classifications to direct molecular-targeted therapy versus the potential detrimental impact of adding ineffective molecular-targeted therapies based on incomplete biologic understandings is a great challenge. The natural tendency to jump to the newest, shiniest treatment is one that has to be carefully tempered, especially in pediatrics, given the lack of detailed understanding of the impact of altering molecular pathways crucial in normal development. No doubt future information concerning cancer pathway activation, the immunologic aspects of the brain tumor and its microenvironment and, as stated previously, the underlying genetic predispositions of these tumors, will alter "layered" classification. To simplify the translational challenge, to paraphrase a conflicted Danish prince… "to lump or split, that is the question!"

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