CLINICAL RELEVANCE OF MOLECULAR MARKERS IN GLIOMAS

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SUMMARY

Molecular markers are increasingly being utilized in diagnosing, prognosticating and predicting response to therapy of gliomas. The 4th edition of the World Health Organization (WHO) Classification of Tumours of the Central Nervous System (CNS) was updated in 2016 and incorporates multiple molecular markers in combination with histology to arrive at an integrated pathological diagnosis (1). Newer entities were defined and some were removed based on biological and clinical relevance. Clinical trials have retrospectively incorporated molecular markers and reported patient outcomes based on them, which have showed significant survival differences for specific subtypes of gliomas. Challenges with respect to interobserver variability in diagnosis based on histology alone or availability of minimal diagnostic brain tissue can now be addressed with the use of molecular markers.

Key words: Brain tumor, glioma, molecular markers.

BRIEF OVERVIEW OF CHANGES

The WHO 2016 classification integrated genotypic and phenotypic parameters that add to diagnostic accuracy of CNS tumors. This in turn will facilitate more accurate determination of prognosis and development of targeted treatments. An algorithm beginning with histology and followed by addition of molecular testing for diagnosing different subtypes of gliomas has been suggested. Isocitrate dehydrogenase (*IDH*) mutation testing either by immunohistochemistry or sequencing will now be part of routine testing and will classify gliomas as *IDH*-mutant or -wildtype. As shown in several studies, *IDH*-mutant gliomas are generally associated with good response to treatment and a better prognosis (2,3). Oligoastrocytoma grade II or III as a diagnosis has been a subject of high interobserver variability (4,5), which can now be better designated as either oligodendroglioma or astrocytoma with the use of molecular markers *IDH*, ATRX, and chromosomes 1p and 19q. However, given the chance of discordant results and the non-availability of molecular testing, these diagnostic entities are kept in the new classification system as oligoastrocytoma and anaplastic oligoastrocytoma NOS (not otherwise specified), although in general this diagnosis is being discouraged. The NOS designation has also been added as a possibility to grades II and III oligodendrogliomas and astrocytomas and grade IV glioblastomas. The use of NOS is to be used in two situations: if molecular testing has not been performed or if molecular testing was not conclusive. Gliomatosis cerebri, an entity that was defined in the original WHO 4th edition from 2007 (6), has now been deleted from the 2016 classification as it indicates a pattern of spread better defined on imaging. It is reportedly seen in *IDH*-mutant astrocytoma and oligodendroglioma as well as *IDH*-wildtype glioblastoma (7,8). Two diffuse astrocytoma variants, namely protoplasmic and fibrillary astrocytomas have also been deleted from the new

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classification; however, gemistocytic astrocytoma has kept its defined place, but only as an *IDH*-mutant subtype. This once again shows the importance of associated molecular component in making the diagnosis. Diffuse midline glioma characterized by a K27M mutation in the histone H3 genes H3F3A or HIST1H3B/C is a newly defined entity. These tumors have a diffuse growth pattern, have midline location, occur in both children and adults, and are associated with a very poor prognosis1. Diffuse intrinsic pontine glioma (DIPG) is considered a part of this new entity. This molecular definition will facilitate development of therapies directed against this mutation. Other molecular markers in non-glioma tumors that have now been incorporated in the new WHO classification include RELA fusion-positive supratentorial ependymoma, mostly occurring in children; C19MC-altered embryonal tumors with multilayered rosettes; and restructuring of medulloblastomas based on WNT, SHH (sonic hedgehog), and TP53 mutations. For the purpose of this review we will focus on molecular markers in diffuse gliomas only (Table 1).

SUMMARY OF MOLECULAR MARKERS ISOCITRATE DEHYDROGENASE (*IDH*) MUTATIONS

IDH is a cytosolic enzyme that catalyzes the oxidative decarboxylation of isocitrate into alpha-ketoglutarate and nicotinamide adenine dinucleotide phosphate (NADPH) in normal cells (9). The most common mutation involves amino acid 132 of *IDH1* (R132H) in more than 70% of WHO grade II and III astrocytomas, oligodendrogliomas, and in secondary glioblastomas. As a surrogate to molecular genetic testing, a mutation-specific antibody can be used clinically to identify R132H mutations in glioma tumor tissue by immunohistochemistry (Figure 1). *IDH2* (functions in the mitochondria) mutations noted in R172 amino acid are much less common (~3%) and associated with oligodendroglial histology (2,10). The mutated *IDH* enzymes convert isocitrate to 2-hydroxyglutarate, which is believed to function as an oncometabolite and cause tumorigenesis. Although the exact mechanisms of this process remain to be elucidated, epigenetic mechanisms causing development of hypermethylated phenotype, thereby

TABLE 1. CHANGES IN CLASSIFICATION OF GLIOMAS BETWEEN 2007 AND 2016 WHO CLASSIFICATION SYSTEMS

WHO 2007	WHO 2016
Diffuse astrocytoma	Diffuse astrocytoma, IDH-mutant
	Gemistocytic astrocytoma, IDH-mutant
	Diffuse astrocytoma, IDH-wildtype
	Diffuse astrocytoma, NOS
Anaplastic astrocytoma	Anaplastic astrocytoma, IDH-mutant
	Anaplastic astrocytoma, IDH-wildtype
	Anaplastic astrocytoma, NOS
Glioblastoma	Glioblastoma, IDH-wildtype
	Glioblastoma, IDH-mutant
	Glioblastoma, NOS
Oligodendroglioma	Oligodendroglioma, IDH-mutant and 1p/19q-codeleted
	Oligodendroglioma, NOS
Anaplastic oligodendroglioma	Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted
	Anaplastic oligodendroglioma, NOS
Oligoastrocytoma	Oligoastrocytoma, NOS
Anaplastic oligoastrocytoma	Anaplastic oligoastrocytoma, NOS
Did not exist	New Diffuse midline glioma H3 K27M-mutant
Gliomatosis cerebri	Deleted
Protoplasmic astrocytoma Fibrillary astrocytoma	Deleted

NOS: Not otherwise specified