



Case Report

Isocitrate dehydrogenase 1 and 2 gene mutation status – a critical parameter in the diagnosis and prognosis of adult gliomas

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ABSTRACT

Isocitrate dehydrogenase 1 and 2 mutations are known to be early events in gliomagenesis and have a definite role in tumor progression. Isocitrate dehydrogenase 1/2 mutation status is considered to be one of the most powerful independent positive predictor of outcome amongst all molecular markers described in association with gliomas. The inclusion of this parameter in the 2016 update of the World Health Organization Classification of Tumors of The Central Nervous System reinforced its importance in glioma classification and prognostication. As a result, now there is enough evidence to prove that Isocitrate dehydrogenase-mutant and Isocitrate dehydrogenase-wildtype gliomas are two biologically distinct categories of gliomas with likely different pathways of tumorigenesis, different clinical outcomes, and respond differently to similar treatment strategies. Increasing knowledge about the role of IDH1/2 mutation in gliomagenesis has resulted in many novel targeting strategies being developed and evaluated for usefulness in the clinical setting. This literature review aims to highlight the diagnostic and prognostic importance of Isocitrate dehydrogenase 1/2 gene mutations in adult gliomas.

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INTRODUCTION

Gliomas, tumors that originate from the glial cells in the brain and spinal cord, account for the most common type of primary brain tumor.¹ Traditionally, they have been classified based on histogenesis, that is - their morphological similarities with their putative cells of origin, into astrocytomas, oligodendrogliomas, and ependymomas.¹ They are further graded into WHO grades I to IV based on well-defined morphologic and clinical criteria; grade I tumors are considered benign with a good clinical outcome, grade II/ III tumors are more invasive with an intermediate to poor clinical outcome and grade IV tumors are the most aggressive with the worst clinical outcomes.²

Over the past decade, several studies furnished evidence related to the genetic basis of tumor formation and progression in gliomas.¹ Some of these findings were found to be so impactful that they have now been incorporated in the recently updated 2016 WHO Classification of Tumors of the Central Nervous System.¹ This update is extremely significant because it depicts a paradigm shift from the age-old concept of morphology-based tumor classification to an integrated morpho-molecular system that gives importance to well-established genetic parameters in addition to histology.¹ The incorporation of such objective molecular parameters in the diagnostic criteria is expected to be useful in experimental modeling and therapeutic discovery, ultimately leading to accurate prediction of patient outcome.¹

Molecular parameters of notable importance related to gliomas, that have been incorporated within the 2016 WHO Classification of Tumors of the Central Nervous System are the IDH1/2 mutation status, 1p/19q codeletion status, and H3K27M mutation status.¹ Based on the IDH1/2 mutation status, adult gliomas have been grouped into three biologically distinct categories – IDH mutant with 1p/19q codeletion, IDH mutant with 1p/19q intact, and IDH wildtype.^{3,4} This review will specifically focus on the role of IDH1/2 mutation in gliomagenesis, prognostication, and therapeutics.

IDH1/2 mutation status - role in gliomagenesis & detection:

The importance of IDH1/2 mutation status in gliomas came to light when Parsons et al, in 2008, demonstrated a recurrent heterozygous mutation at R132H (substitution of arginine by histidine at amino acid 132), the active site of the IDH1 gene, in 12% of the glioblastomas.^{2,5} Subsequently, they demonstrated that this substitution occurred in >90% of the Grade II/III gliomas.^{2,5} This substitution was by far the most common mutation identified in gliomas. A few other rarer mutations in IDH1 and IDH2 genes were also reported in this study.^{2,5} This study reshaped the way these tumors were viewed and this parameter was found to be so impactful both diagnostically and prognostically that it was incorporated within the updated WHO CNS tumor classification system.

IDH1/2 mutations in gliomas have been established to be early and definite events in gliomagenesis.⁶ The famous study by Watanabe et al studied multiple biopsies from the same 321 patients over time and demonstrated that IDH1 mutation preceded TP53 mutation and/or 1p/19q loss in Grade II/III and secondary gliomas. This finding suggested that grade II/III gliomas originate from a common progenitor glial cell with IDH mutation and then go on to acquire additional mutations. If they acquire TP53 mutation, then they would differentiate into astrocytic tumors, while if they acquire 1p/19q loss then they would differentiate into oligodendroglial tumors.⁶

IDH mutation status & its role in gliomagenesis:

The IDH genes 1 and 2 encode for NADP+ dependent enzymes IDH1 and IDH2.⁷ These enzymes play key roles in energy metabolism, DNA damage repair, and epigenetic gene regulation. These enzymes are critical in Krebs' cycle for the oxidative carboxylation of isocitrate to alpha-ketoglutarate (alpha-KG). Mutation at R132 in IDH1 or R172 in IDH2 genes induces a neo-enzymatic activity that causes the conversion of alpha-ketoglutarate (alpha-KG) to 2-hydroxyglutarate (2-HG).⁷ This 2-HG is an intermediate metabolite that has been implicated in tumorigenesis. Extremely high levels of 2-HG competitively inhibit a number of enzymes including hydroxylases, DNA repair enzymes like AlkB homolog (ALKBH7), a histone demethylase, and TET27 which are closely linked to epigenetic regulation of gene expression. Epigenetic dysregulation is thought to cause CpG hypermethylation in IDH mutant gliomas which renders them susceptible to additional genomic alterations including p53 mutation and 1p/19q loss, thus implying that IDH1/2 mutation is an important driver of oncogenesis in gliomas.⁸ Noshmeh et al demonstrated that many IDH mutant glioblastomas had a DNA hypermethylation signature, also known as the "Glioma-CpG Island Methylator Phenotype" (G-CIMP). This phenotype is associated with a younger age at diagnosis and favorable prognosis.^{9,10} IDH mutation initiates tumor progression by destabilizing hypoxia-inducible factor 1 α (HIF1 α), which in turn activates a downstream cascade of events that promotes cell proliferation, invasion, angiogenesis, and metastasis.^{8,11}

Detection of IDH1/2 mutation status

With the incorporation of IDH1/2 mutation status in the diagnostic criteria of WHO Grade II/III gliomas, analysis of gliomas for IDH1/2 mutation status has now become mandatory for the classification of gliomas.¹ IDH mutations are clinically detected by immunohistochemistry (IHC) testing with anti-R132 IDH1 antibodies which detects the most common mutation – a point missense mutation at R132, the active site of IDH1 gene.¹²

IHC is widely employed in clinical practice for detecting IDH mutations as it is a cost-effective and highly sensitive method. However, the downside is that using IHC alone for detection of IDH mutation status is not entirely reliable because many of the rarer non-R132H-IDH1 mutations are missed because of the mutation-specific antibody (usually anti-R132-IDH1) that is used in most centers.³ Using sequencing technology, especially in those cases that are negative for IDH mutation by IHC, can improve the efficacy of diagnosis. Kurian et al used this combined approach in their study and found a higher detection rate (24%) of rare IDH mutations than when compared to using IHC alone.¹²

Because of the diagnostic, prognostic, and therapeutic significance of IDH1/2 mutation status in gliomas, it is important for standardized protocols to be developed for the analysis of IDH-mutant status. Using protocols that rationally combine IHC with sequencing (wherever necessary) will prove to be more effective in sub-typing of gliomas based on their IDH-mutant status.

PROGNOSTIC SIGNIFICANCE OF IDH1/2 MUTATION IN GLIOMAS

Amongst all the molecular markers identified in relation to adult gliomas, IDH1/2 mutation status is considered the single most significant independent diagnostic and prognostic parameter.^{8,12} Several independent studies have reported that IDH1/2-mutated gliomas have an improved clinical outcome as well as overall survival when compared to the IDH-wild-type tumors.^{8,13} A meta-analysis of 55 observational studies reporting IDH mutation status and survival in gliomas reported that IDH1/2 mutation in WHO grade II/III gliomas was strongly associated with better overall survival and outcomes.⁸ Olar et al studied the prognostic effect of the mitotic index after stratification by IDH mutation status, and reported that the mitotic index was positively associated with outcome in IDH wild-type gliomas but not in IDH-mutated gliomas.¹⁴ All these unique features of IDH-mutant tumors reinforced the fact the IDH-mutant gliomas and IDH-wild-type gliomas constituted two distinct biological categories of gliomas. This difference in biological behavior between the two groups may also reflect distinct sets of prognostic significations as well as very different therapeutic responses.

Although the current updated edition of the WHO CNS tumor classification system does a better job at predicting clinical outcomes than its previous edition, many experts in the field are of opinion that there is scope for further improvement in this direction and have been pushing for expansion of the classification system to include more objective parameters which will precisely predict treatment response and patient outcome.¹ In this context, several additional molecular biomarkers are being investigated in relation to gliomas and many researchers have attempted to further stratify IDH mutated gliomas in order to identify additional clinically significant prognostic biomarkers.^{2,13,15,16} This review will briefly discuss some of the common molecular markers evaluated for potential prognostic significance in IDH-mutant gliomas.

1p/19q co-deletion

The importance of 1p/19q co-deletion in gliomas is so well established that this parameter has found a place in the updated WHO Classification of Tumors of The CNS as a major diagnostic criterion alongside IDH1/2 mutation status for classifying gliomas.¹ In fact, 1p/19q co-deletion was the first molecular biomarker of significance discovered

in relation to gliomas.^{17,18} This co-deletion is frequently associated with IDH1/2 mutation and is strongly associated with oligodendrogliomas, a subtype of glioma. The IDH-mutant 1p/19q co-deleted gliomas are associated with a significantly better overall survival when compared to tumors with only IDH mutation.^{17,18} This biomarker is also important because its presence predicts improved response to certain alkylating agents.¹⁸ Because the traditional histological criteria for subtyping and grading of gliomas with oligodendroglial morphology has poor reproducibility among pathologists, this marker is especially helpful in identifying tumors with oligodendroglial morphology reliably, especially given its prognostic significance.¹⁸

CDKN2A/B

CDKN2A/B has emerged as a powerful indicator of poor clinical outcome in IDH mutated gliomas.¹⁶ Shirahata et al aimed to establish a grading system with prognostic impact for gliomas, in which they studied 211 cases of adult gliomas.¹⁶ CDKN2A/B deletion emerged as a single most powerful parameter for predicting poor prognosis in this study. They reported that CDKN2A/B deletion correlated with a higher proliferation rate in tumor cells because the loss of p16 removes the inhibitory influences on the cell cycle and causes unchecked cell proliferation.¹⁶ Interestingly, in this study, tumor mitotic count (traditionally used as a marker of tumor proliferation index) and necrosis, which were among the key prognostic parameters in the 2016 WHO grading system, were not found to have any prognostic significance.¹⁶ CDKN2A/B has the potential to be incorporated within the CNS tumor classification system as it could be considered a marker of tumor proliferation, given its role in cell cycle regulation. This biomarker could potentially replace traditionally used markers of tumor proliferation like mitotic index, which is associated with a high degree of inter-observer variability.

Loss of 9p, Trisomy 7, and TERT mutations

Loss of 9p, trisomy 7, and TERT mutation in correlation with IDH1/2 mutant status have been documented to be associated with poor clinical outcomes.^{15,17} Wijnenga et al demonstrated that loss of 9p and trisomy 7 were frequent findings in IDH-mutated gliomas and correlated with poor prognosis.¹⁴ Eckel-Passow et al studied a large cohort of gliomas stratified based on 3 molecular parameters – IDH mutation, TERT mutation, and 1p/12q codeletion.¹⁷ They demonstrated that the so-called ‘triple-positive tumors’ (IDH mutated-1p/19q codeleted-TERT mutated) have the best prognosis, while tumors with only TERT mutations (without IDH mutation and 1p/19q codeletion) had the worst prognosis.¹⁷ This stresses the need for further stratification studies in correlation with IDH-mutation status because of how a certain prognostic biomarker behaves in IDH-mutated gliomas as opposed to IDH-wild-type gliomas.

MGMT promoter methylation status

MGMT gene promoter methylation status in gliomas is important because of its role in predicting patient response to certain chemotherapeutic agents.^{19,20} Juralti et al demonstrated that the patients with IDH mutation along with MGMT promoter methylation status had the longest survival compared to IDH mutated gliomas with unmethylated MGMT promoter status, while patients without IDH mutation had the worst prognosis irrespective of their MGMT promoter status.²¹ The landmark clinical trial which established temozolomide, an alkylating agent, as the treatment of choice in glioblastomas, documented that gliomas with methylation of MGMT promoter were the most sensitive to treatment with temozolomide.¹⁸⁻²⁰ This biomarker is therefore useful to predict treatment response to chemotherapy with alkylating agents in patients with IDH-mutated gliomas.

Limitations

Although the results from some of these studies are impressive, there are certain limitations to the interpretation of these results. Some of these stratification studies for potential prognostic biomarkers were retrospective studies and hence selection bias cannot be excluded. Also, some of them were univariate studies whose findings could not be confirmed on multivariate studies. Certain confounding factors like location of glioma and involvement of vital brainstem structures, which can influence treatment protocol, need to be taken into account while considering the patient outcome. Hence, although some of these biomarkers look promising concerning prognostic relevance in IDH-mutant gliomas, there is still a need for validation of these results in other large studies with longer follow-up periods before any definitive conclusions can be made.

IDH1/2 MUTATION STATUS, ITS ROLE IN THERAPEUTICS & FUTURE DIRECTIONS

IDH1/2 has certain unique properties that make them attractive targets for novel therapeutic strategies and experimental modeling.¹⁸ Ranking high among these properties are longer overall survival and better treatment response associated with IDH-mutant gliomas. IDH1 plays a critical role against reactive oxygen species (ROS) induced oxidative damage.⁷ IDH mutant cells lose their protective effect against damage by ROS and hence are more sensitive to oxidative damage than IDH-wildtype cells.⁷ IDH-mutant tumors respond better to certain anticancer drugs (rich sources of ROS) than IDH-wildtype tumors. This may partly explain the longer survival observed in IDH mutant gliomas treated with chemo/radiotherapy compared to the wild-type IDH gliomas.⁷ Further, mutational uniformity within these tumors is useful in the therapeutic context since this ensures maximum treatment efficacy, minimal side effects, low

risk of resistance to therapy, and fewer chances of relapse/recurrence.⁷

Inhibitors of mutant IDH1/2

The basic strategy is to design small molecules that will prevent the conversion of alpha-KG to 2-HG by binding to the active site of the mutant IDH1/2, thus resulting in decreased production and accumulation of 2-HG.²² AG-120 is a highly selective inhibitor of mutant IDH1/R132H that is currently being evaluated for the treatment of patients with gliomas. The preliminary phase I clinical trial data showed no toxicity or serious side effects associated with its use. BAY-1436032, a pan mutant IDH1 inhibitor, also being evaluated for treatment in advanced solid tumors including gliomas, has been documented to reduce 2-HG levels to near-normal levels.²² AG-881, a pan-IDH1/2-mutant inhibitor, is thought to be very promising because of its propensity to cross the blood-brain barrier. This unique property of this molecule may prove to have superior therapeutic benefit in IDH1/2-mutant gliomas.²² Currently, all these new therapeutic agents mentioned are at different phases of preclinical trials.

IDH MUTANT-SPECIFIC VACCINE

A mutation-specific vaccine has been proposed as a possible therapeutic strategy for IDH1/R132H mutant tumors. Schumacher et al reported the presence of an immunogenic epitope on IDH1 (R132H) and demonstrated that peptides within the mutant region induced immune responses against the mutated IDH1. They derived a peptide vaccine from IDH1/R132H and vaccinated mice models with IDH1 mutant gliomas. The mice models treated with the peptide vaccine survived longer than controls. This vaccine is currently in phase I clinical trials and initial reports have demonstrated safety and tolerance to the peptide vaccine.²³

FUTURE DIRECTIONS

The property of higher chemo/radiosensitivity that IDH mutation status confers on gliomas has great potential to be explored for therapeutic purposes. Inducing an IDH-mutation-like status in IDH-wildtype tumors could prove useful in improving patient outcomes which are otherwise poor in IDH-wildtype tumors. This could be achieved by building therapeutic strategies which will inhibit the activity of IDH1/2 in IDH wildtype tumors.⁶ This strategy could be tried in aggressive grade IV primary glioblastomas, a subtype of glioma which usually lacks IDH1/2 mutations. Such an approach could contribute to sensitize wildtype IDH1 tumor cells to the cytotoxic effects of radio/chemotherapy and help improve patient outcomes in these very tumors which otherwise have a high degree of mortality and morbidity.²⁴

Given the deficit in IDH-mutant tumor cells to effectively

repair DNA damage by homologous recombination, treatment strategies using poly(ADP-ribose) polymerase (PARP) inhibitors can be tried. In preclinical trials, IDH-mutant status has been found to confer the tumor with higher sensitivity to PARP inhibitors when compared to IDH-wild-type.²⁵ It may be worthwhile to explore the usefulness of existing FDA-approved PARP inhibitors (which are currently in use for other cancers) in the treatment of IDH1/2 mutated solid tumors including gliomas.⁷

CONCLUSIONS

The landmark discovery of IDH1/2 mutation status in gliomas and its well-established role in predicting patient outcome has redefined how these tumors are classified. With the inclusion of this genetic parameter in the recent WHO classification of tumors of the Central Nervous System, it is expected that there will be a greater appreciation of the role of IDH1/2 mutation status in gliomagenesis and this will set the stage for further research and discovery of novel efficient treatment strategies that will help treat these tumors better. This will also hopefully lead to the discovery of many more molecular parameters of prognostic significance that can accurately predict treatment response, help in tailoring patient therapy, and function as effective therapeutic targets all of which ultimately translates to improved clinical outcomes and better quality of life in patients with brain tumors

Conflict of Interest: None

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