Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2023.202612.2777 Volume 30, Issue 1.3, April 2024, Supplement Issue
Manuscript ID ZUMJ-2303-2777
DOI 10.21608/ZUMJ.2023.202612.2777
REVIEW ARTICLE

Prognostic Value of Isocitrate Dehydrogenase and Mismatch Repair Genes in Gliomas

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Submit Date 03-04-2023
Accept Date 2023-04-19

ABSTRACT

Background: Gliomas are considered the most prevalent malignancies of the central nervous system. These tumors are diffusely infiltrative and behave destructively toward the nearby brain tissue. Based on histological grading, gliomas were previously categorized. Histopathology and molecular characteristics are now included in the classification of brain tumors. Glioma prognosis can be predicted, which allows patients to choose an effective course of treatment. It is crucial to look for fresh prognostic indicators in cancer biopsy samples that might indicate prognosis. IDH mutation is a crucial component for the subclass categorization of diffuse gliomas and is just one of many molecular parameters. Significantly, all forms of IDH-mutant gliomas seem to have a much better prognosis than malignant diffuse IDH wild type (IDH-wt) gliomas such as glioblastoma.

Conclusions: We concluded that IDH1 and MMR genes immunohistochemical expression could help in the prediction of gliomas outcomes. More large-scale multicenter investigations are needed to back up our findings.

Keywords: Gliomas; Mismatch; Isocitrate; Dehydrogenase

INTRODUCTION

Gliomas are considered the most prevalent malignancies of the central nervous system. Gliomas are classified as grade one 'the most popular subtype is pilocytic astrocytoma', grade two 'diffuse astrocytoma, oligodendroglioma, and oligoastrocytoma', grade three 'anaplastic astrocytoma, anaplastic oligodendroglioma' while grade four is glioblastoma **[1].** A whole-exome sequencing analysis of 22 glioblastomas revealed recurrent mutations in the isocitrate dehydrogenase gene IDH1. Following research, it was shown that IDH1 mutations are very relevant in a variety of cancers **[2].**

Molecular aspects of gliomas:

IDH-mutant gliomas account for roughly forty percent of adult gliomas. Regarding IDH and ATRX mutations, grade three gliomas could be separated into other three distinct categories. Those molecular variants are therapeutically significant because treatment methods can be devised based on molecular type and WHO classification **[3].** Immunohistochemistry is a well-established, low-cost, robust, and widely available method. As a result, immunohistochemistry techniques using established protocols and materials have become a crucial component of current practice for detecting molecular genetic alterations **[4].**

The important molecule in differentiating diffuse gliomas' subtypes is IDH mutation, which is one of numerous molecular criteria. Significantly, all forms of IDH-mutant gliomas seem to have a much better prognosis than malignant diffuse IDH wild-type (IDH-wt)

gliomas such as glioblastoma **[5].** During the cell cycle, DNA replication is a highly conserved and controlled process. The DNA polymerases that duplicate the DNA during the S-phase are not error-free. Single-nucleotide variants indicate integrated base mistakes, yet polymerase slippages lead to insertions and deletions, particularly in repeated sequences known as microsatellites. Likewise, replication repair failure is characterized by point mutations and microsatellite instability. Exonuclease domains in DNA polymerases and the mismatch repair (MMR) mechanism control replication fidelity **[6].** Mutations in the MMR genes can cause multiple disorders and patients with them are exposed to acquiring a variety of cancer types **[7].**

IDH in glioma and its prognostic role:

Isocitrate is subjected to oxidative decarboxylation by the enzyme IDH, which results in the production of alpha-ketoglutarate and CO2. Isocitrate is first converted to oxalosuccinate through oxidation, and then alpha-ketoglutarate is created by decarboxylating the carboxyl group of beta to a ketone **[8].**

Isocitrate IDH 1 or 2 genes are typically the target of mutations in gliomas **[9].** Therefore, mutations in both genes may result in silencing tumor-suppressor genes like MGMT and ERCC1 and hypermethylating their promoters. IDH1 or IDH2 mutations can also lead to an increase in oxidative stress. Increasing DNA oxidative damage may cause mutations. IDH1 or IDH2 mutations therefore function as drivers of glioma carcinogenesis, however, the primary mechanism is unknown **[10].**

The discovery and characterization of IDH mutations led to a fundamental conceptual breakthrough in our knowledge of the molecular etiology of glioma. Compared to glioblastomas, grade two and three gliomas have a significantly higher prevalence of IDH mutations **[11].** IDH1 and IDH2 encode crucial Krebs cycle enzymes. A-ketoglutarate (a-KG) is converted into the oncometabolite D-2-hydroxyglutarate (2HG) when these mutations exist in the catalytic domains of the enzymes **[12].**

The median OS or PFS of GBM cases having IDH 1/2 mutations are typically longer than those with IDH wild-type GBM, according to extensive clinical assessments of the disease **[9].** Also, this inclination was validated in individuals with anaplastic astrocytoma included in other investigations **[13].**

MMR genes in glioma and its prognostic role:

Immunohistochemistry analysis is typically used to identify the DNA mismatch repair (MMR) complex proteins. Biallelic mismatch repair deficiency (bMMRD) is marked by an extensive spectrum of early onset. The most frequent brain tumors linked to bMMRD are high-grade gliomas (HGG), which are also the main cause of death in these kids **[11].**

Immunohistochemistry for the four MMR proteins has been shown in numerous studies to be a reliable screening technique. A genetic diagnosis can be guided by the absence of expression of 1 or more MMR proteins **[15].** Furthermore, low-grade gliomas seem to be markedly prevalent in NF1 patients, and the majority of them do not advance. Hence, late detection of malignant lesions and probable survival effects result from misinterpretation of people with bMMRD as NF1 **[14].**

CONCLUSIONS

We concluded that IDH1 and MMR genes immunohistochemical expression could help in the prediction of gliomas outcomes. More large-scale multicenter investigations are needed to back up our findings.

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To Cite:

Ahmed, D., Rashed, H., Mohamed, A., Saeed, N., Elmosalamy, W. Prognostic value of Isocitrate Dehydrogenase And Mismatch Repair Genes In Gliomas. *Zagazig University Medical Journal*, 2024; (378-380): -. doi: 10.21608/zumj.2023.202612.2777