Adult Diffuse Gliomas: Prevalence of the IDH1 Mutation in a University Hospital

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Gliomas Difusos do Adulto: Prevalência da Mutação IDH1 em um Hospital Universitário

Gliomas Difusos en Adultos: Prevalencia de la Mutación IDH1 en un Hospital Universitario

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ABSTRACT

Introduction: Gliomas are part of the primary tumors of the central nervous system and are neoplasms originating from glial cells. They are classified by the pattern of infiltration, histopathological grade, and molecular alterations. Mutations in the isocitrate dehydrogenase (IDH) enzyme identified in some glial tumors mark the beginning of carcinogenesis, increasing the functionality of the metabolic enzymes IDH1 and IDH2. Thus, adult diffuse gliomas are divided by the detection of this mutation, determining characteristics that can facilitate treatment, with specific targeted therapies such as vorasidenib and ivosidenib that improve patient prognosis. **Objective:** To analyze and correlate the prevalence of the IDH1-R132H mutation detected through tumor immunohistochemical examination and to evaluate the epidemiology of patients with gliomas who underwent surgical treatment between 2019 and 2023 at the Evangelical Mackenzie University Hospital (HUEM). **Method:** Cross-sectional and analytical study, with the collection of historical data from medical records at HUEM, analyzing the pathological anatomy report. The final sample consisted of 67 patients. **Results:** There was a higher prevalence of cases in white males, aged between 61-70 years. Regarding subtypes, the origin in astrocytes was the main one. IDH-wildtype glioblastomas of histological grade 4 prevailed. During the study period, the majority passed away. **Conclusion:** The presence of IDH1 mutations, combined with other genomic alterations, can define the prognosis and the strategy of choice for treating patients. Thus, it shows the importance of expanding immunohistochemical knowledge of gliomas, as this can lead to more effective therapeutic strategies.
Key words: Glioma/surgery; Mutation; Immuno-Histochemistry.

RESUMO

Introdução: Os gliomas pertencem aos tumores primários do sistema nervoso central e são neoplasias originárias nas células da glia. São classificados pelo padrão de infiltração, grau histopatológico e alterações moleculares. Mutações na enzima isocitrato desidrogenase (IDH), identificada em alguns tumores gliais, marcam o início da carcinogênese, aumentando a funcionalidade das enzimas metabólicas IDH1 e IDH2. Assim, dividem-se os gliomas difusos do adulto pela detecção dessa mutação, determinando características que podem facilitar o tratamento, havendo terapias-alvo específicas, como vorasidenib e ivosidenib, que melhoram o prognóstico dos pacientes. **Objetivo:** Analisar e correlacionar a prevalência da mutação IDH1-R132H, detectada por meio de exame imuno-histoquímico tumoral e avaliar a epidemiologia dos pacientes com gliomas submetidos a tratamento cirúrgico entre 2019 e 2023 no Hospital Universitário Evangélico Mackenzie (HUEM). **Método:** Estudo transversal e analítico, com coleta de dados históricos de prontuários médicos do HUEM, analisando o laudo anatomopatológico. A amostra final é composta por 67 pacientes. **Resultados:** Houve maior prevalência dos casos no sexo masculino, raça branca, com a faixa etária entre 61-70 anos. Quanto aos subtipos, a origem em astrócitos foi a principal. Os glioblastomas IDH-selvagem grau histológico 4 prevaleceram. No período estudado, a maioria veio a óbito. **Conclusão:** A presença de mutações IDH1, somada a demais alterações genômicas, pode definir o prognóstico e a estratégia de escolha para o tratamento dos pacientes. Dessa forma, evidencia-se a importância de ampliar o conhecimento imuno-histoquímico dos gliomas, visto que isso pode levar a estratégias terapêuticas mais efetivas.
Palavras-chave: Glioma/cirurgia; Mutação; Imuno-Histoquímica.

RESUMEN

Introducción: Los gliomas pertenecen a los tumores primarios del sistema nervioso central y son neoplasias originadas en las células de la neuroglia. Se clasifican por el patrón de infiltración, grado histopatológico y alteraciones moleculares. Las mutaciones en la enzima isocitrato deshidrogenasa (IDH) identificadas en algunos tumores gliales marcan el inicio de la carcinogénesis, aumentando la funcionalidad de las enzimas metabólicas IDH1 e IDH2. Así, se dividen los gliomas difusos del adulto por la detección de esta mutación, determinando características que pueden facilitar el tratamiento, existiendo terapias dirigidas específicas como vorasidenib e ivosidenib que mejoran el pronóstico de los pacientes. **Objetivo:** Analizar y correlacionar la prevalencia de la mutación IDH1-R132H, detectada a través de un examen inmunohistoquímico tumoral, y evaluar la epidemiología de los pacientes con gliomas sometidos a tratamiento quirúrgico entre 2019 y 2023 en el Hospital Universitario Evangélico Mackenzie (HUEM). **Método:** Estudio transversal y analítico, con recolección de datos históricos de historias clínicas del HUEM, analizando el informe anatomopatológico. La muestra final está compuesta por 67 pacientes. **Resultados:** Hubo mayor prevalencia de casos en el sexo masculino, raza blanca, con el grupo de edad entre 61-70 años. En cuanto a los subtipos, el origen en astrocitos fue el principal. Los glioblastomas IDH salvaje de grado histológico 4 prevalecieron. En el periodo estudiado, la mayoría falleció. **Conclusión:** La presencia de mutaciones IDH1, junto con otras alteraciones genómicas, puede definir el pronóstico y la estrategia de elección para el tratamiento de los pacientes. De esta forma, se evidencia la importancia de ampliar el conocimiento inmunohistoquímico de los gliomas, ya que esto puede llevar a estrategias terapéuticas más efectivas.
Palabras clave: Glioma/cirugía; Mutación; Inmunohistoquímica.

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INTRODUCTION

Gliomas are neoplasms derived from glial cells and are part of the heterogeneous group of primary tumors of the central nervous system (CNS). They constitute 30% of all brain neoplasms and 80% of cancers in this region. Gliomas are subdivided and classified according to: Histological type, degree of aggressiveness and molecular characteristics[1]. The incidence of gliomas varies around the world, with an average global rate of 3.4 cases per 100 thousand inhabitants a year. The occurrence in the South of Brazil is considerably higher, with 10.17 cases in men per 100 thousand inhabitants and 8.52 cases in women for every 100 thousand inhabitants each year[2].

The isocitrate dehydrogenase 1 (IDH1) and 2 (IDH2) enzymes are part of the Krebs cycle, responsible for cellular processes of glucose, glutamine metabolism and lipogenesis[3]. The identification of the *IDH* gene mutation revolutionized the classification of adult diffuse gliomas in the World Health Organization (WHO) 2016 protocols and recently in the 2021 protocols[3,4]. All oligodendrogliomas, by definition, are known to have this genetic alteration. Moreover, from this analysis, it is possible to divide astrocytomas into IDH-mutant and IDH-wild type[4].

The use of genetic tests for this finding is still not very accessible, so the most used technique is the immunohistochemical study of tumors[5]. The mutation identified by this method is *IDH1*-R132H and is widely used as a diagnostic medium for correct sub-classification. About 25% of patients with gliomas present an *IDH1/IDH2* mutation, providing better prognostic and therapeutic results to patients[5,6], since therapies directed to gliomas with the IDH1-R132H mutation are being developed and have been focused mainly on the use of IDH-mutant inhibitors, which aim to reduce the production of oncometabolite 2-hydroxyglutarate (2-HG), associated with tumor progression[6]. In this context, the general objective of the research is to evaluate the prevalence of the IDH1-R132H mutation in gliomas in a Paraná hospital, cataloging population epidemiological characteristics and relating them to prognostic factors.

METHOD

Cross-sectional and retrospective study with a quantitative approach, carried out in the State of Paraná, in the city of Curitiba, in which medical records of the Mackenzie Evangelical University Hospital (HUEM) were reviewed. Data collection took place between November 2019 and June 2023 through the survey of anatomopathological and immunohistochemical reports of surgical pieces for assessing the IDH1-R132H mutation of patients over 18 years old undergoing neurosurgery. Pediatric patients, patients with no data on the medical record and/or incomplete immunohistochemical analysis were excluded. In addition, several variables were listed, such as sex, age, race, histological type/degree and clinical outcome.

Immunohistochemical analysis of gliomas is an essential tool for molecular characterization of these tumors[7]. The commonly used immunohistochemical markers include IDH1, alpha thalassemia X-linked intellectual disability syndrome (ATRX), tumoral protein P53 and Ki-67, all performed in the determined sample[7]. For microscopic diagnostic interpretation, the following parameters are defined by the literature:

- ATRX: The loss of expression (absence of immunostaining) of tumor cells is often associated with mutant IDH gliomas, particularly those of astrocytic lineage[7]. Loss of ATRX, along with the TP53 mutation, can help differentiate mutant astrocytomas from other subtypes[7].
- p53: Used as a substitute for mutations in the TP53[7] gene. Overexpression (strong and diffuse immunostaining) of p53 is often observed in mutant IDH gliomas, especially in those without codeletion 1p/19q[7].
- Ki-67: The Ki-67 marking index is a predictor of cell proliferation, being used to evaluate tumor aggressiveness[7]. The nuclear positivity of immunoreaction is quantified in percentage values[7].
- IDH1-R132H: Use of monoclonal antibodies that are effective in detecting mutant protein[7]. In microscopic analysis, when it shows strong cytoplasmic staining and, to a lesser extent, nuclear staining in tumor cells, it favors the mutant pattern of the studied gliomas[7]. If staining is negative, but clinical suspicion is present, there is a recommendation for complementary genetic analysis to seek other mutations in IDH1 or IDH2, but not available in the service in question[7].

For data analysis, the information was exported to a Microsoft Office Excel software spreadsheet, in which they were treated by descriptive statistics in absolute numbers and percentages. In the applicable data, Fisher's test was performed with a significance of 0.05.

This research has been approved by the Research Ethics Committee, report number 6082856 (CAAE (submission for ethical review): 69638223.9.0000.0103), in compliance with Resolution No. 466/12[8] of the National Research Council, which regulates scientific research in human beings. Subsequently, the data obtained were compared with the literature surveyed on the subject.

RESULTS

From November 2019 to June 2023, 67 cases of cerebral gliomas were recorded at the hospital's High-Complexity Care Center and met the criteria for inclusion of the research. Table 1 presents the characterization of the sample distributed by sex. The distribution shows prevalence of males, which totaled 59.7% of the cases. The table also records the distribution of patients with gliomas according to age group (ten-year range). The 61-70 years range was the most affected, with 29.85% of the cases. Regarding race, there was a significant predominance in the white population in 88.06% of the sample (Table 1).

Regarding the distribution of histopathological aspects, astrocytomas were the highlight in 91.9% of the cases, including those identified as glioblastoma in this group. For categorization regarding the group of tumors, they were divided into low degree (corresponds to WHO grade 2) and high degree (including grades 3 and 4), according to the literature described[8]. High-grade neoplasms were the most frequent, representing 88.7% of the sample, while low-grade neoplasms represented 11.3%.

Table 1. Distribution according to clinical data of patients with gliomas: Sex, age and race (n=67)

Clinical data			
n=67	**Profile**	**n**	**%**
Sex	Male	40	59.70%
	Female	27	40.30%
Age	11-20 years-old	2	2.99%
	21-30 years-old	1	1.49%
	31-40 years-old	10	14.93%
	41-50 years-old	9	13.43%
	51-60 years-old	15	22.85%
	61-70 years-old	20	29.85%
	71-80 years-old	8	11.94%
	81-90 years-old	2	2.99%
Race	White	59	88.06%
	Brown	5	7.46%
	No information	3	4.48%

Table 2 presents the results of immunohistochemical analysis for the expression of IDH1-R132H, besides the analysis of antibodies for P53 and ATRX, added to the evaluation of the proliferative index (Ki-67). Cases where there was positivity in the IDH1-R132H antibody are defined as mutated and are usually accompanied by abnormal P53 pattern and loss of ATRX expression. In 21% of the sample, the searched IDH mutation was detected. Regarding Ki-67, expressed in general mean, the higher the percentage evaluated microscopically, the more aggressive the neoplasm indicated, with accelerated growth rate, values above 20% are already considered high[9].

From the joint analysis of histopathology and immunohistochemical results, considering WHO's most up-to-date classification[9], Table 3 shows all pathological entities diagnosed in the studied population. The most predominant neoplasm was glioblastoma IDH-wild type, grade 4, representing 75.8% of the cases.

Regarding the clinical outcome of patients with gliomas (Table 4), they were categorized into two groups: Living and deceased. The mortality rate was significant, representing 67.16% of the sample. As for patients in palliative care who were discharged, they represent four of the 22 patients in the "living" group.

When relating the presence or absence of IDH1-R132H mutation in high-grade gliomas and death, it was verified that 90% of the patients were IDH-wild type and only 10% were IDH-mutant, with statistically significant results (p=0.1934), as shown in Graph 1. Regarding the clinical outcome, associating with gliomas classified as

Table 2. Results of immunohistochemical analysis of antibodies IDH1, P53, ATRX, Ki-67 in relation to tumor histological grade (n=62)

Antibodies	Result	AST/OLIG grade 2	AST/OLIG grade 3	AST grade 4	GBM
IDH	Positive	6	3	4	0
	Negative	1	1	0	47
P53	Wild type	6	3	1	42
	Mutated	1	1	3	5
ATRX	Expressed	5	4	1	46
	Not Expressed	2	0	3	1
KI-67	Mean %	3.75%	18.75%	35%	37.7%

Captions: AST = Astrocytoma; OLIG = Oligodendroglioma; GBM = Glioblastoma.

high grade (Graph 1), the patients were categorized into two groups: Living and deceased. The mortality rate was more prevalent in the glioblastomas group, representing 65.45% (36 patients) of the sample. In the group of grade 3 and 4 gliomas and IDH-mutant, the percentage of living (4 patients) and deceased (4 patients) patients was equivalent, each corresponding to 7.27%. In the glioblastomas group, patients in palliative care who were discharged represented three of the 11 patients in the "living" group, corresponding to 5.45%.

DISCUSSION

In 2008, studies of the exome sequence of grade 4 gliomas, classically called glioblastomas, identified mutations in a Krebs cycle gene in the IDH enzyme[6]. Later, new research showed that this genetic alteration was found in about 80% of grade 2 and 3 gliomas, in 73% of glioblastomas deemed as secondary at the time, and in 3.7% of primary[5,6]. IDH1 and IDH2 enzymes catalyze the conversion of isocitrate to alfacetoglutarate, a decarboxylation reaction[6]. In cases of mutations in these genes, frequently occurring in exon 4, in the hotspots R132H of *IDH1* and R140 and R172 of *IDH2*, enzymatic changes are induced in glial cells[6]. Thus, the conversion of isocitrate to 2-HG occurs, considered an oncogenic metabolic that inhibits, then, the functions of alfacetoglutarate-dependent enzymes[6].

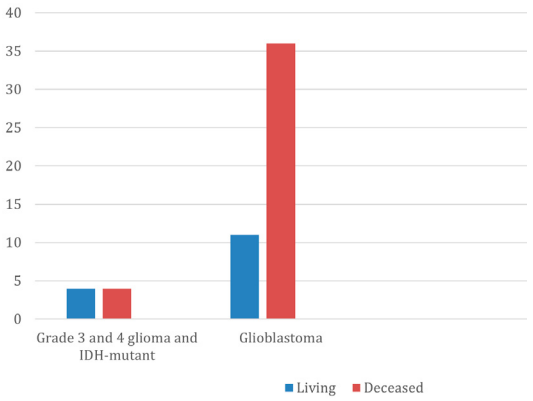
Thus, *IDH* mutations mark the beginning of the pathogenesis of certain glial neoplasms, increasing the functionality of metabolic enzymes IDH1 and IDH2[3]. These enzymes start to produce in greater quantity the 2-HG oncometabolite, whose effects on the cell epigenomic states and gene regulation drastically alter cellular homeostasis, facilitating, for example, functional losses in genes such as ATRX and TP53, which are respectively associated with gene instability and tumor suppression[5].

Regarding the epidemiological profile of patients diagnosed with cerebral gliomas from November 2019 to June 2023 at HUEM, men were more affected than women, representing approximately 60% of the cases. This 1.4 times greater involvement in men can be explained by several factors. For example, testosterone can stimulate the growth of glioblastomas through the androgenic receptor, promoting greater cell proliferation and tumor progression. In contrast, estrogen may offer protection against the development of these tumors, which may explain the lower incidence in women[10,11].

Furthermore, genetic and molecular variations among the sexes play a crucial role, and mutations in genes such as *TP53* and *EGFR* may be more prevalent in the male population, which may have an impact on treatment

Table 4. Outcome of patients with gliomas (n=67)

Outcome	n=67	%
Living	22	32.84%
Deceased	45	67.16%
Total	67	100%



Graph 1. Relationship between clinical outcome *versus* classification of high-grade gliomas (n=55)

Table 3. Classification of gliomas according to updated 2021 WHO nomenclature (n=62)

2021 WHO Classification	n=62	%
IDH-mutant astrocytoma, grade 2	4	6.44%
IDH-mutant astrocytoma, grade 3	2	3.22%
IDH-mutant astrocytoma, grade 4	4	6.44%
IDH-wild type glioblastoma, grade 4	47	75.8%
IDH-mutant oligodendroglioma, grade 2	3	4.83%
IDH-mutant oligodendroglioma, grade 3	1	1.61%
IDH-wild type oligodendroglioma, grade 3	1	1.61%
Total	62	100%

Caption: WHO = World Health Organization.

and prognosis[12], and contribute to the higher prevalence of gliomas in men[13,14]. Regarding the age distribution of glioma cases, presented in Table 1, it is observed that the main affected age group was 51 to 70 years, and in total 66 cases were recorded, and 73.96% of them occurred in patients aged 50 years or older. According to the most recent American data, the peak incidence of glioblastoma occurs in the 65-74 years age group[12], which is in line with the Brazilian regional sample studied[15].

The incidence of gliomas also shows significant variations between different racial groups around the world. Recent studies indicate that in the United States, the incidence rate of glioblastoma is higher among whites compared to blacks and Asians. According to data from the American Brain Tumor Association (2022)[15] and the study by Ostrom et al.[16], whites have an incidence rate approximately 1.5 to 2 times higher than blacks[15,16].

The analysis of gliomas revealed significant information on the distribution of molecular types and their relationship with the histological grade of tumors, represented in Table 3. The mutation of the *IDH1* gene, an important diagnostic marker and prognosis in gliomas, was highly prevalent in tumors below histological grade 4. These findings corroborate the literature that indicates a predominance of the *IDH1* mutation in low-grade tumors, including astrocytomas and oligodendrogliomas, and its absence in glioblastomas previously designated as primers, which have a distinct and more aggressive molecular profile [17,18].

The analysis of the P53 marker revealed that the wild type was predominant in lower histological grades. Also, cases of over-expression for P53 protein were observed associated with mutated (3 cases) and non-mutated (5 cases of glioblastoma) *IDH1* cases. The predominance of *TP53* mutated in high-grade gliomas is due to the avoidance of cellular control mechanisms and the promotion of a more aggressive tumoral phenotype, characterized by greater cell proliferation, resistance to apoptosis and invasiveness. These molecular alterations are closely related to tumor progression and worsening of clinical outcome in these patients[19]. As for the ATRX marker, the results indicated absence of ATRX expression in IDH1 high-grade mutant cases, after all, the loss of ATRX, a protein involved in the maintenance of genomic stability and regulation of the chromatin structure, has been widely correlated with aggressiveness in brain gliomas. Inactivation of ATRX, often observed in specific gliomas subtypes, results in epigenetic changes that favor telomeric instability and aberrant DNA replication[19].

The immunohistochemical analysis of the 62 cases, referring to Table 3, revealed significant variation in histological types and degrees, with a remarkable predominance of IDH-wild type glioblastomas (75.8%) in this sample. This pattern is consistent with the current literature, which describes glioblastomas as the most frequent and aggressive gliomas associated with the absence of the *IDH1* mutation[19]. In terms of absolute numbers, while wild-type *IDH* glioblastoma is responsible for approximately 60% of diffuse gliomas (including all degrees), mutated *IDH* astrocytomas represent about 20% to 30% of these tumors[19,20].

Immunohistochemistry for the detection of IDH1-R132H mutations in gliomas has several limitations[20]. It can result in false-negative results, especially in sections examined from perioperative material, due to the quality of the tissue and/or antibody used[20]. In addition, immunohistochemistry does not detect rare IDH1 mutations beyond R132H, which can generate discrepancies in relation to DNA sequencing methods[20,21]. The heterogeneity of staining in tumor cells can also impair the interpretation of results[20]. Despite being a fast and accessible technique, the need for confirmation by genetic analysis is evident, especially in cases with suspected non-R132H mutations, but the obstacle to access and availability of these examinations in Brazilian public institutions may limit confirmation[20].

The results also highlight the importance of the *IDH1* mutation in the classification of gliomas according to the WHO. The WHO classification now considers the *IDH1* mutation as one of the main criteria for the definition of gliomas, differentiating the IDH-mutant astrocytomas and oligodendrogliomas from IDH-wild types[21]. Patients with gliomas with IDH1 mutations present significantly better overall survival and progression-free survival compared to those with wild IDH1 tumors[21]. A meta-analysis revealed that the IDH1 mutation is associated with a significant reduction in the risk of mortality in patients with glioblastoma, with a relative risk of 0.43, indicating a 57% decrease in the risk of death compared to patients without the mutation[22]. Another study showed that the presence of IDH1/2 mutations in gliomas is associated with a better prognosis, with a combined risk ratio for overall survival of 0.33, suggesting a 67% reduction in the risk of death[23].

Mean survival for patients with *IDH*-mutant gliomas of grades 2 and 3 varies between seven and ten years, depending on the tumor subtype and the treatments applied[4]. For *IDH*-wild type cases (glioblastomas) it is usually between 12 and 15 months, even with intensive treatment including surgery, radiotherapy and chemotherapy[4]. These data highlight the importance of *IDH* status not only in diagnosis, but as a critical factor in prognostic stratification and therapeutic decision-making for patients with brain gliomas.

Knowing the presence of the *IDH* mutation is significant for the therapeutic approach of the patient, since drugs that act in the biochemistry of the IDH enzyme are being developed. Vorasidenib, an IDH1/2 inhibitor, recently approved in August 2024 by the Food and Drug Administration (FDA), has shown to increase progression-free survival for patients older than 12 years, with grade 2 astrocytomas or oligodendrogliomas susceptible to the *IDH1* or *IDH2* mutation, after partial or complete neurosurgical tumor resection[24].

In addition to IDH inhibitors, other therapeutic approaches are being explored with different pharmacological mechanisms, including peptide vaccines specific to the IDH1-R132H mutation, which have shown to induce specific and promising immunological responses in early clinical trials[6,25]. The combination of IDH inhibitors with other therapies, such as immune checkpoint-blocking, is also being investigated, with pre-clinical data suggesting potential to improve immune response and survival[25,26]. Given the knowledge that the *IDH* mutation induces phenotypic hypermethylation, causing different changes in tumor cells, there is therapeutic potential for correcting this dysregulation[6,27]. Another example of the target drug is decitabine, a DNA methyltransferase inhibitor, capable of suppressing the proliferation of glioma cells with mutated *IDH in vitro* and *in vivo*[28]. These strategies reflect a significant advance in the treatment of gliomas with IDH mutation, offering new therapeutic options that can improve the prognosis of these patients[6].

CONCLUSION

The findings reinforce the importance of histological and molecular evaluation in the classification and management of gliomas. The presence of *IDH1* mutations, the relationship between mutated *TP53* and tumor aggressiveness, together with the loss of ATRX, are critical aspects that influence the prognosis and treatment strategy of patients. Understanding these correlations is fundamental for the personalized clinical approach and for the prediction of tumor behavior.

CONTRIBUTIONS

Vitor Bonk Rizzo, Michelle Arrata Ramos and Samya Hamad Mehanna contributed to the study design, planning, data acquisition, analysis and interpretation, wording, and critical review. Eduardo Morais de Castro and Pedro Helo dos Santos Neto have contributed to data analysis and interpretation, wording, and critical review. All the authors approved the final version for publication.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interest to declare.

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