Research Article

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The Role of Molecular Biology in Low-Grade Gliomas

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ABSTRACT

Central Nervous System (CNS) tumors constitute a heterogeneous group of neoplasms characterized by considerable morbidity and mortality.

Objective: This study aimed to utilize the new classification systems based on Molecular Biology, which, in turn, allow for improved diagnostic approaches and better therapeutic planning.

Materials and Methods: The results of biopsies and molecular biology tests of 75 patients with low- grade gliomas were analysed. Patients were selected from the database of Pathology Service B, with 38 diagnosed with astrocytoma and 37 with oligodendroglioma (WHO grade II).

Results: 56.9% astrocytomas and 49,3% oligodendrogliomas were detected, with molecular biology showing good correlation with histology.

Conclusion: Molecular biology data allowed for the delineation of two molecular classes concordant with IDH, 1p/19q, ATRX, and histology. Low-grade gliomas with IDH mutations exhibited 1p/19q co-deletion or ATRX mutation, both clinically relevant markers of these gliomas.

Keywords: Low-Grade Gliomas; Histology; Molecular Biology

Introduction

Tumors of the Central Nervous System (CNS) are a heterogeneous group of neoplasms associated with significant morbidity and mortality. Recent advancements in the oncogenic mechanisms responsible for the development of these tumours have led to the adoption of new classification systems based on Molecular Biology. These new systems enable more precise diagnostic strategies and enhanced therapeutic planning. Diffuse low- and intermediate-grade gliomas, classified as grades II and III by the World Health Organization (WHO), are infiltrative neoplasms that frequently occur in the cerebral hemispheres of adults. These include astrocytomas, oligodendrogliomas, and oligoastrocytomas [1,2]. Most of these tumours occur sporadically, and various risk factors have been associated with their development, such as exposure to ionizing radiation or electromagnetic waves, as well as the presence of conditions like diabetes, hypertension, and Parkinson's disease. A smaller proportion of primary CNS tumors arises due to hereditary syndromes.

It is crucial to employ molecular genetics tools to adapt glioma classification according to the new WHO 2022 guidelines. These tools allow for a more precise prognosis and the determination of the most suitable treatment for each case. Specific molecular classifications enable treatments to be tailored more effectively to patients, offering new options for those who may have found prior treatments ineffective. Mutations in IDH1 and IDH2, collectively known as IDH, characterize most low-grade gliomas in adults and define a subtype associated with a favorable prognosis [3-5]. What is known as the "1p/19q co-deletion" occurs when two sequential nucleotide fragments of DNA from human chromosomes 1p and 19q are essentially deleted.

While the reasons for its positive impact on patient outcomes remain unclear, the absence of these DNA fragments is associated with slower tumor growth and, more importantly, increased sensitivity to radiation and certain categories of chemotherapy. Certain brain tumors exhibit a 1p/19q co-deletion, others show mutations in IDH genes, and some have mutations in the ATRX gene. In some cases, all three alterations coexist, while in others, none are detected, or only one or two are present.

The absence of two or all three alterations is referred to as double-negative or triple-negative, respectively. Therefore, the molecular analysis of these tumors to detect these three alterations enables their classification into molecular groups with prognostic and predictive value. By utilizing just three key genetic mutations, gliomas could be classified into three groups sharing specific characteristics, such as the age of onset. These three molecular groups can predict the patient's prognosis -namely, life expectancy- and at least two of the groups determine the type of treatment the patient will receive. For instance, a glioma classified as triple-positive (i.e., presenting with 1p/19q co-deletion, IDH mutation, and ATRX mutation) is presumed, via molecular algorithms, to have an oligodendroglioma origin and should receive a chemotherapy and radiotherapy regimen specifically designed for that tumor type. If a tumor lacks the 1p/19q co-deletion, likely of astrocytic origin, chemotherapy should unquestionably be administered to the patient, either alongside or following radiation therapy. Radiation alone could double life expectancy from approximately 8 years to around 15 or 16 years, or more. This study aimed to use the new classification systems based on molecular biology to improve diagnostic approaches and therapeutic planning. The molecular algorithm for gliomas is detailed below (Figure 1).

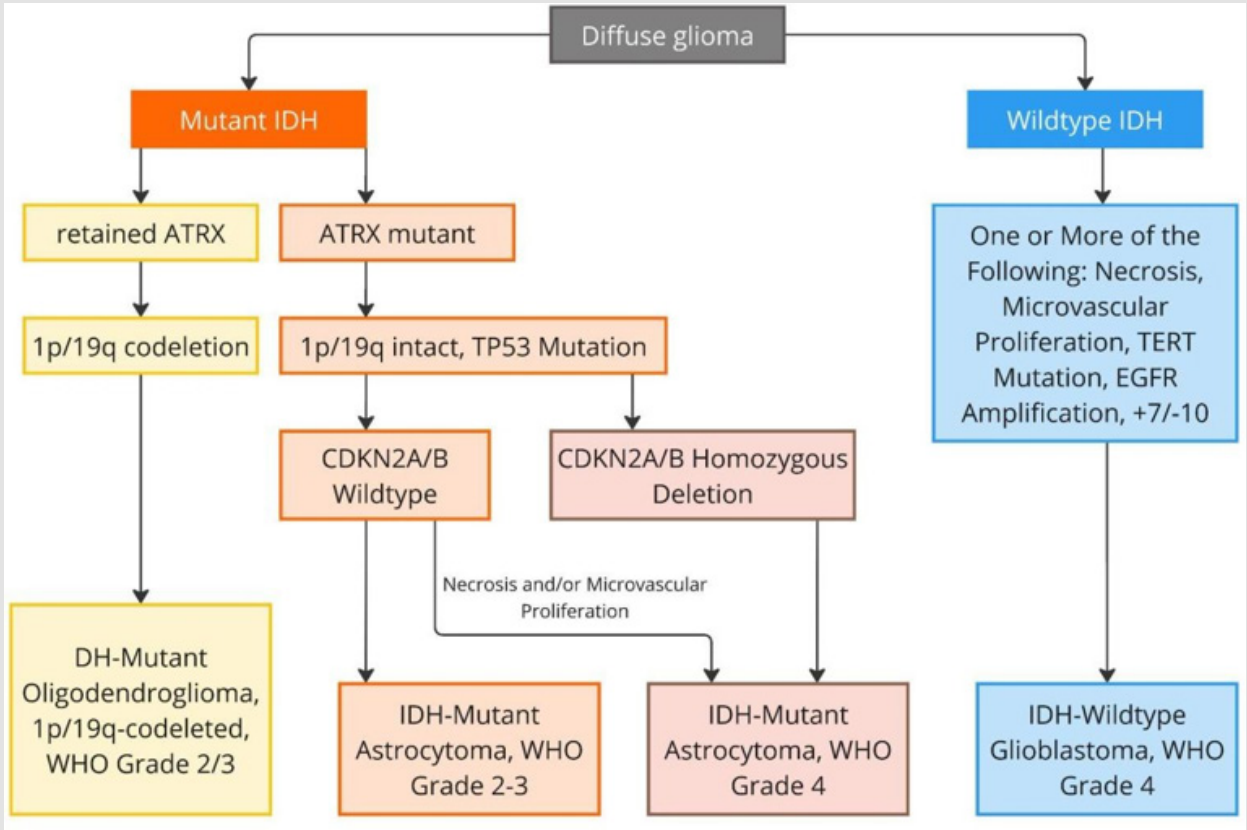

Figure 1: Molecular algorithm for gliomas.

Materials and Methods

Seventy-five patients were selected from the database of Pathology Service B, with 38 diagnosed with astrocytoma and 37 with oligodendroglioma (WHO grade II). The average age of the patients was 57 years [SD = 6.5), ranging from 54 to 75 years. Among the astrocytoma patients, 79% (30/38) were female, and 21% (8/38) were male. Conversely, in oligodendroglioma cases, 62% (23/37) were male, and 38% (14/37) were female. An analysis was conducted on the results of biopsies and molecular biology assays from patients diagnosed with low-grade gliomas. The diagnostic assays were performed at the Pathology B and Molecular Biology departments of Clínica Universitaria Reina Fabiola (CURF), as well as at the Molecular Biology Laboratory of Universidad Maimónides. Patient tissue samples were formalin- fixed and paraffin-embedded. Immunohistochemistry (IHC) staining for IDH identification was carried out at the Pathology B laboratory, while IDH mutations were detected using Sanger sequencing at the Molecular Biology Laboratory of Universidad Maimónides. The variables considered in the study included age at diagnosis, patient sex, morphological diagnosis based onhematoxylin-eosin staining, and the status of IDH1, IDH2, 1p/19q, and ATRX genes. To assess IDH gene status, immunohistochemistry staining was performed using the H09 clone to detect the R132H mutation in the IDH1 gene. Additionally, Sanger sequencing was conducted for both, the IDH1 and IDH2 genes. To determine the positivity of IHC staining, cytoplasmic staining in more than 10% of tumor cells was used as the cutoff point [6,7]. Genetic analysis was performed through PCR amplification using specific primers for the coding regions and flanking areas of exon 4 of the IDH1 and IDH2 genes. Bidirectional Sanger sequencing of the amplified products was carried out, and the resulting electropherogram was analyzed against the reference sequences for the IDH1 gene [Ref. Sequence: NG_023319.2) and the IDH2 gene [Ref. Sequence: NG_023302.1). The analysis of the 1p/19q co- deletion was conducted at the Molecular Biology Laboratory of CURF using the FISH [Fluorescence In-Situ Hybridization) technique with the ZytoLight SPEC 1p36/1q25 and 19q13/19p13 Dual Color Probe. The analysis of ATRX was performed using IHC techniques on the automated Venting Benchmark system.

Results

The histopathological analysis revealed that astrocytoma was the most prevalent tumor type among the two types of tumor analysed (Astrocytoma II and Oligodendroglioma). It accounted for 50,6of cases (Table 1). The genetic analysis identified a total of 72 IDH1 mutations and 7 IDH2 mutations among 75 patients with diffuse astrocytomas and WHO grade II oligodendrogliomas. Mutations were exclusively found at codon 132 of IDH1 and codon 172 of IDH2. The most prevalent amino acid sequence alterations were R132H and R132G in IDH1, while R172W and R172K were the most common mutations in IDH2 (see Table 2). The first is related to astrocytomas, and the second to oligodendrogliomas. It is suggested that IDH1 mutations occur at an early stage of tumor formation, as most grade II astrocytomas (A II) and grade II oligodendrogliomas (O II) exhibit this alteration. Regarding IDH2 mutations, their timing of occurrence cannot be clearly established. However, it is important to consider their potential relationship with tumor progression and their association with the development of IDH1 mutations. ATRX mutations were observed in 40 out of 75 brain tumors, with a higher frequency in grade II astrocytomas (35/38 cases). Furthermore, 1p/19q co-deletion (Figure 2) were identified in 37 patients with oligodendrogliomas (Table 3).

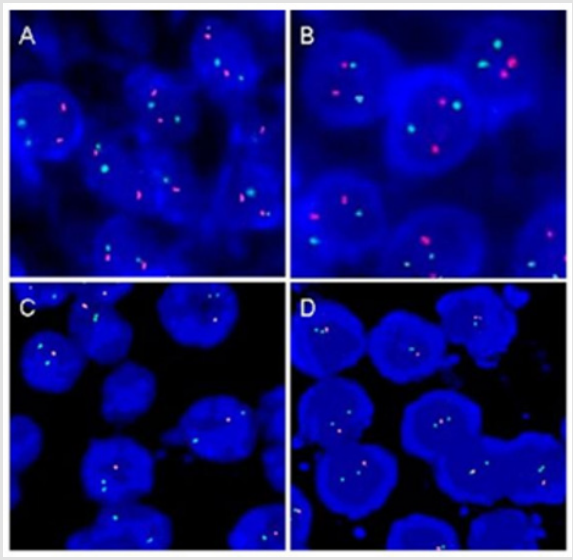

Figure 2:
FISH of 1p/19q
A. No deletion of 1p
B. No deletion 19 q and
C y D Deletion of ip and 19q

Table 1: Histopathological Diagnosis.

Type of Glioma and Histological Grade	Number of Patients	Percentage
Astrocytoma II	42	50,6
Oligodendroglioma	33	49,3

Table 2: Types of Mutations in IDH1 and IDH2.

IDH 1 (72 positive cases)	IDH 2 (7 positive cases)	
R132H35 (48.6)	R162W	6 (85,7)
R132G 37 (51.4)	R172K	1 (14,3)

Table 3: Frequency of mutations in tumor types.

					IDH 1	IDH 2	1p/19q	ATRX
Tumor Classification	**n**	**Mean Age**	**Male[%)**	**Female[%)**	**Mut %**	**Mut %**	**Mut %**	**Mut %**
Astrocytoma	38	57	21	79	36+2-	35-3+	38-	35+3-
Oligodendroglioma	37	57	62	38	36+1-	33-4+	37+	32-5+

Note: (+) indicates mutated; (-) indicates notmutated

Discussion

Over the past two decades, the systematic examination of genomic alterations in adults and children with primary brain tumors has provided profound new insights into the pathogenesis of these tumors, leading to a more precise classification and prognosis. It has also identified several recurrent genomic alterations that now define specific subtypes of brain tumors and have opened new opportunities for molecularly targeted therapeutic interventions. A major breakthrough in glioma research was the identification of heterozygous point mutations in the metabolic genes isocitrate dehydrogenase 1 and 2 (IDH1/IDH2) in 70%-80% of adults with WHO-classified grade 2 and grade 3 diffuse adult-type glioma. The most common IDH1 / IDH2 alteration in glioma is the IDH1 R132H mutation, where arginine is replaced by histidine at amino acid 132. This particular mutation can be easily detected through an immunohistochemical test using a mutant-specific antibody. Less common IDH1 and IDH2 mutations require targeted sequencing for detection.

A recent noteworthy finding is that mutations in NADP+ dependent isocitrate dehydrogenases encoded by IDH1 and IDH2 occur in most grade II gliomas (all subtypes) and grade III gliomas, as well as in secondary GBM, but only in a minority of primary GBM cases. These data suggest that IDH mutations represent an early step in the development of LGG (low-grade gliomas). Gliomas with IDH gene mutations demonstrate better survival rates than IDH wild-type gliomas. The survival rate of anaplastic gliomas (grade III) is comparable to that of glioblastoma (grade IV) due to the higher percentage of IDH wild-type anaplastic gliomas. Grade II wild-type astrocytomas exhibit significantly lower survival rates compared to IDH-mutated ones (50% vs. 100%, respectively, in this study). There is a significant correlation between the histological classification of gliomas and their radiological manifestation on RM, which can be used as a prognostic indicator. Low-grade gliomas with IDH mutations typically have a more favourable prognosis and may respond better to treatment compared to gliomas lacking this mutation. The presence of the 1p/19q co-deletion has been associated with improved response to certain treatments. Chromosomal mutations and alterations define three subtypes of lower-grade gliomas with distinct clinical outcomes:

- IDH mutant and 1p/19q co-deletion: The 1p/19q anomaly consists of the deletion of the short arm of chromosome 1 and the long arm of chromosome 19. Mutations in IDH1 and IDH2, which encode isocitrate dehydrogenases, lead to abnormal enzymatic activity, hypermethylation, and dysregulated gene expression. This subtype is associated with the most favourable prognosis.
- IDH mutant without 1p/19q co-deletion, associated with an intermediate prognosis.
- IDH wild-type, associated with the worst outcomes.

The IDH wild-type subtype shares genomic markers and clinical outcomes similar to glioblastomas, suggesting that this lower-grade glioma subtype may be a precursor to its more aggressive counterpart. Molecular signatures and subtypes can guide the classification, diagnosis, and treatment of lower-grade gliomas. Lower-grade gliomas without IDH mutations may benefit from treatment protocols adapted from current glioblastoma therapies.

Conclusions

Recently developed therapies may target the aberrant activity of IDH1/2 proteins in lower-grade gliomas. Advances made in the past five years have transformed the understanding of gliomas. International standards do not consider their diagnosis without molecular biology. Given the lack of access to this resource in many public institutions and considering the relative burden of these central nervous system diseases on public health, we recognize a critical issue that must be addressed. It is unacceptable that, after seven years since its introduction and five years since its inclusion in the WHO classification, diagnosis is still being made solely based on histological standards. The proposed algorithm could be a viable and reliable alternative.

Authors Contribution

It is hereby acknowledged that all authors have accepted responsibility for the manuscript´s content and consented to its submission. They have meticulously reviewed all results.

Ethics Approval and Consent to Participate

This study was approved by the ethical committee of the Clinica Universitaria Reina Fabiola.

Human and Animal Rights

All clinical investigations were conducted according to the Declaration of Helsinki principles.

Consent for Publication

Each volunteer signed a consent form.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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