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DIAGNOSTIC ACCURACY OF THE T2/FLAIR MISMATCH SIGN IN PREDICTING ISOCITRATE DEHYDROGENASE MUTATION IN LOW-GRADE GLIOMAS

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ABSTRACT

BACKGROUND: Gliomas represent a significant global health burden due to their high morbidity, infiltrative nature and often limited therapeutic options. MRI is pivotal in their diagnosis, providing detailed structural and functional assessments that refines tumor characterization. Accurate MRI driven evaluation carries strong prognostic implications, guiding personalized treatment and improving outcome prediction.

OBJECTIVE: To evaluate diagnostic accuracy of T2/FLAIR mismatch sign in predicting IDH mutations in low grade gliomas.

METHODOLOGY: This cross-sectional study analyzed 52 histologically confirmed glioma patients from 2022 to 2024 at AKUH. Preoperative 1.5T (GE) and 3T (Toshiba) MRI were reviewed by two neuroradiologists for T2/FLAIR mismatch and additional imaging features and compared with molecular profiling i.e. IDH1/2 following WHO 2021 criteria. Statistical analysis was done with Fisher's exact test.

RESULTS: : IDH mutant gliomas exhibited frequent T2/FLAIR mismatch i.e. 58.3% vs 10.7% in wildtype, which highlights the utility of conventional MRI techniques as a reliable, non-invasive tool for predicting IDH status.

CONCLUSION: T2/FLAIR mismatch sign along with conventional MRI features, may serve as a useful non-invasive adjunct, particularly where molecular testing is unavailable.

KEYWORDS: : Low-grade glioma, IDH mutation, T2/FLAIR mismatch, Magnetic resonance imaging, Radio genomics

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INTRODUCTION

According to the 2021 WHO criteria, low-grade gliomas (LGGs) are generally WHO Grade I or II tumors, characterized by slow growth, but the classification now heavily integrates molecular features alongside histology, defining specific entities like *IDH*-mutant astrocytomas (Grade II) and paediatric-type LGGs (MAPK pathway altered) (Grade II), with some tumors historically considered low-grade now reclassified based on mutations (e.g., glioblastoma with specific molecular markers). These latest guidelines divide these tumours into three broad categories: Glioblastoma, IDH-wildtype, Astrocytoma IDH Mutant or Oligodendroglioma. Clinically LGGs potential for malignant transformation necessitates attentive diagnostic and therapeutic strategies. Imaging biomarkers, particularly those correlating with genotypic traits are emerging as valuable tools for LGG diagnosis.[1] Molecular profiling with markers such as IDH mutations play a critical role in prognosis and this has revolutionized the diagnosis of LGG as shown in Fig.1.[2]

While histopathology is essential for glioma diagnosis, its invasive nature adds limitations; and whilst lacking genetic specificity, necessitating non-invasive tools for tumour characterization. Similarly standard MRI detects tumor anatomy but lacks specificity to differentiate molecular subtypes gap.[3] In resource limited settings, genetic testing is invasive, costly and not universally available. Radio genomics has emerged with an aim to correlate imaging features with molecular alterations, offering a non invasive, quick and cost effective alternative to genetic testing.

T2/FLAIR mismatch sign is a promising candidate under active investigation.[4] It is a distinctive MRI feature characterized by a lesion that is hyperintense on T2 weighted images and hypo or isointense on FLAIR.[5] This radiologic pattern distinguishes IDH mutant gliomas from other subtypes. Zhang et al reported a sensitivity of 42%, specificity of 100% and PPV of 100% for IDH mutant astrocytoma.[6] Consequently, the need exists to evaluate the diagnostic performance of T2/FLAIR mismatch sign against the molecular gold standard and measure its generalizability and reliability across clinical settings and imaging environments as seen in Fig.2. In addition, T2/FLAIR mismatch is also a reliable predictor in distinguishing astrocytoma's from oligodendrogliomas, with high specificity for IDH mutant astrocytoma's.

The objective of this study is to evaluate the diagnostic accuracy of T2/FLAIR mismatch sign in identifying IDH mutations in Low grade gliomas to determine the diagnostic accuracy via sensitivity, specificity, PPV and NPV using molecular testing as reference standard. Review of literature reveals considerable heterogeneity in reported sensitivity which ranges from 30% to 95% and specificity from 46% to 100%.[7-10] Most existing datasets originate with minimal representation from South Asian and western populations, where genetic, epidemiological and radiological profiles may differ.

METHODOLOGY:

This cross sectional diagnostic accuracy study analysed histologically confirmed glioma patients from 2022 to 2024 at AKUH with review of preoperative MRIs for T2/FLAIR mismatch and molecular profiling including IDH Mutation status. Ethical approval with reference number 2024-10036-29591 was obtained from Ethical review committee Aga Khan University Karachi.

Sample size was calculated to detect a 30% difference in the prevalence of the T2/FLAIR mismatch sign between groups, with a significance level of $\alpha = 0.05$ and a statistical power of 80%, yielding a minimum requirement of 50 patients, thus a sample size of 52 was obtained. This study was conducted at Departments of Radiology and Pathology, Aga Khan University Hospital, Karachi, a tertiary care referral centre for neuro-surgical and neuro-oncology patients to analyse clinical, radiological and histopathological data.[11] Patients were selected using non-probability consecutive sampling. Inclusion criteria required histologically confirmed low grade gliomas (WHO grade I-II) along with convenience of a complete immunohistochemical profile including IDH mutation status and availability of pre-operative MRIs. Exclusion criteria included histologically proven high grade gliomas, missing clinical or radiological data, incomplete imaging sequences or motion artifacts, diagnoses other than gliomas or previously treated tumour cases/prior surgery. Also the nature of lesions, including cystic/necrotic with surrounding edema, where the T2/FLAIR mismatch is not applicable, were excluded. All patients underwent brain MRI. Sequences were acquired with standard imaging parameters.

Mismatch was defined as ≥50% of the tumor volume showing T2 hyperintensity with corresponding FLAIR hypo-intensity for this study. All MRI scans were independently studied by two neuroradiologists, who were blinded to the IDH mutation status and any discrepancies in interpretation were resolved through mutual agreement with substantial interobserver agreement for T2/FLAIR mismatch ($\kappa = 0.75$, 95% CI: 0.60–0.90). Each case underwent detailed molecular profiling using IHC and PCR based techniques for IDH1 mutation status, mutant or wild type. IDH1 R132H mutation was detected via immunohistochemistry (anti-IDH1 R132H antibody, clone H09). Non-R132H mutations were confirmed by Sanger sequencing. SPSS was used for descriptive statistics calculation for all variables. Complete collected data were initially tabulated using Microsoft Excel Workbooks and during cleaning process, incomplete entries e.g. missing information on contrast enhancement, FLAIR mismatch or molecular marker status were marked as "Not Available". Subsequently a 2 x 2 table was generated to evaluate the sensitivity and specificity of the T2/FLAIR mismatch sign with IDH mutation status. (Table 1)

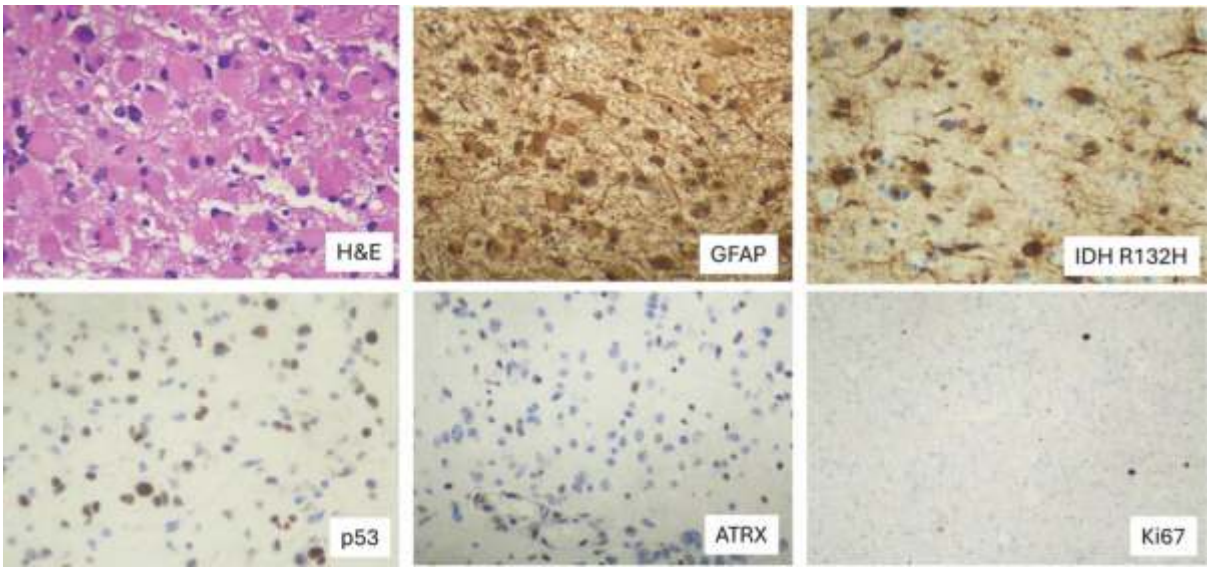

Fig.1: Histopathology image (High power H&E) shows astrocytic tumor with cells showing gemistocytic differentiation with glassy eosinophilic cytoplasm and fibrillar glial processes. GFAP is diffuse positive in tumor cells, IDH1 R132H immunostain is positive (mutant) in tumor cells, p53 immunostain is positive (mutant), ATRX nuclear expression is lost, Ki67 proliferative index is low.

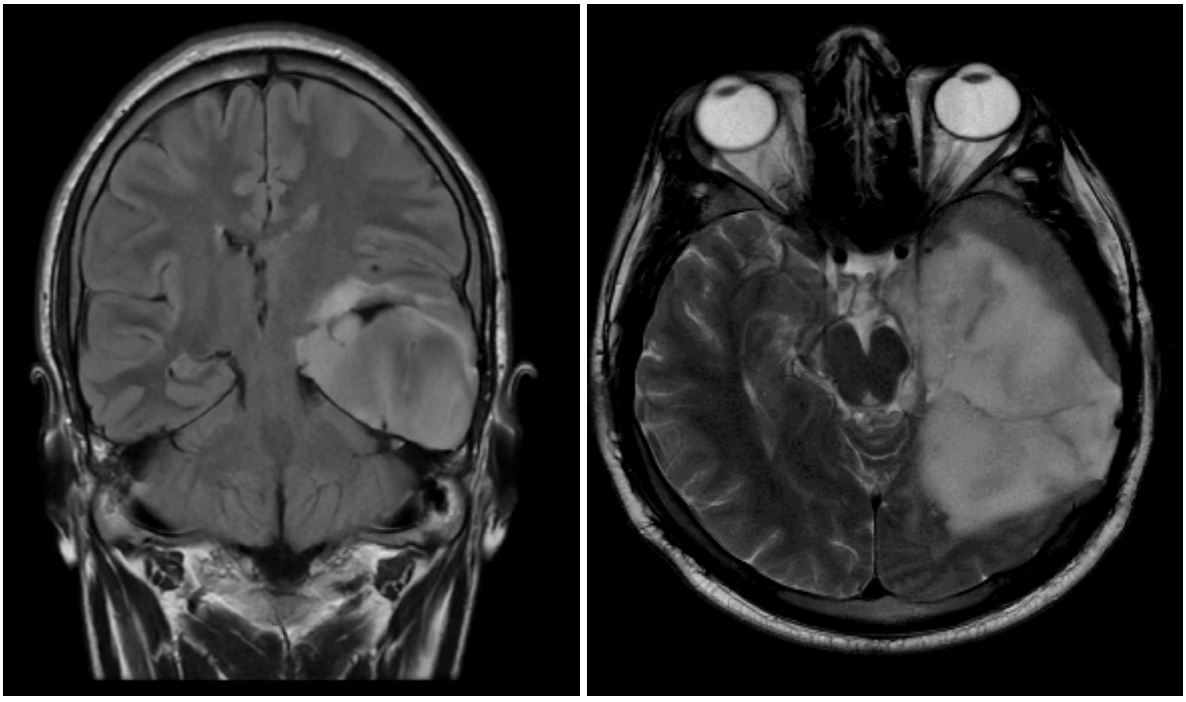

Fig.2: Radiology Images showing T2/FLAIR Mismatch, Coronal FLAIR and axial T2 weighted image.

RESULTS

Sensitivity and specificity were calculated to evaluate MRI based diagnostic accuracy (T2/FLAIR mismatch Sign) for IDH mutation status (Mutant or Wild), with genetic testing as the reference as shown in Table 2. Standard error of proportion and Confidence intervals were also calculated.

Table 1: **Distribution of Cases**

	IDH Mutant (+)	IDH Wild (–)	Total
T2/FLAIR Mismatch (+)	14	3	17
No Mismatch (–)	10	25	35
Total	24	28	52

Table 2: Sensitivity and Specificity Calculation (Values represent counts (n) unless specified otherwise

Sensitivity	58.3% (95% CI 38.8 – 75.5%), SE 10.1%
Specificity	89.3% (95% CI 72.8 – 96.3%), SE 5.8%
Positive Predictive Value (PPV)	82.4% (95% CI 59.0 – 93.8%), SE 9.2%
Negative Predictive Value (NPV)	71.4% (95% CI 54.9 – 83.7%), SE 7.6%

The evaluation of the T2/FLAIR mismatch sign as an imaging biomarker for IDH mutation in gliomas revealed a sensitivity of 58.3% and a specificity of 89.3%. Among the 24 IDH-mutant cases, 14 exhibited the mismatch sign, while only 3 out of 28 IDH wild-type cases showed this feature. The positive predictive value (PPV) was 82.4%, indicating that the presence of a T2/FLAIR mismatch strongly suggests IDH mutation. In contrast, the negative predictive value (NPV) was 71.4% (aligns with prior study by Zhang et al.: 68%) that the absence of the mismatch corresponds to an IDH wild-type tumor. High specificity (89.3%, 95% CI: 72.8–96.3%) of this sign suggests utility, but relatively low sensitivity (58.3% with 95% CI: 38.8–75.5%) warrants caution in ruling out genetic mutations.

DISCUSSION

Association between the T2/FLAIR mismatch sign and IDH mutation status was reflected by our findings. This verified the findings of prior studies emphasizing its diagnostic utility, hence, reducing the need for invasive tissue sampling, which carries procedural risks and may be limited by tumor heterogeneity.[11] Biologically, T2/FLAIR mismatch reflects distinct microstructural and biochemical tumor characteristics associated with IDH mutation e.g. altered cellular density and myxoid changes that result in the characteristic hyperintense T2 signal with corresponding FLAIR suppression.[12] Where margin smoothness and necrosis appear to complement the T2/FLAIR mismatch by reflecting distinct aspects of tumor biology, multivariable predictive model integrating the T2/FLAIR mismatch sign, margin smoothness and absence of significant necrosis demonstrated superior diagnostic accuracy for IDH mutation status compared to any single imaging feature alone. Necrosis is more prevalent in aggressive wildtype tumors, while smooth margins often indicate less infiltrative growth typical of IDH mutant gliomas, and multivariate approach acknowledges the complex interplay of imaging phenotypes, improving sensitivity and specificity beyond univariate assessments. These are summarised in table 3.

Table 3: Comparative Analysis of Findings

Study	Imaging/ Modality	Key Features	Prediction Accuracy	Key Findings
Present Study	Conventional MRI (T2/FLAIR mismatch margin)	T2/FLAIR mismatch, Smooth margins, Absence of necrosis	Sensitivity of 58.3%, Specificity of 89.3% with a PPV of 82.4% and NPV of 71.4%	Useful biomarker
Yang et al.[10]	cMRI, DWI, SWI, DSC-PWI	rADC, ITSSs, rCBVmax, T2/FLAIR mismatch	AUC: 0.88 Sensitivity. 80.3% Specificity. 78.5%	Multimodal MRI shows strong predictive value
Su et al.[11]	DWI, PWI, MRS	ADC_15th, CBV_80th, MRS, Histogram & spectroscopy	AUC: 0.857 (IDH) 0.733 (1p/19q)	Combines multiple quantitative markers for IDH/1p19q
Song et al.[12]	18F-FET PET + DSC-PWI	TBRmax, nCBVmean	AUC: 0.903	PET/MR-based, less accessible

This study has limitations that warrant consideration. A relatively small sample size, being a single centre study analysing pre-existing datasets from consecutive patients may limit generalizability. Selection bias introduces histological heterogeneity, with our cohort including 70 % grade II gliomas, potentially affecting the consistency of the performance of mismatch sign. Field strength differences may affect T2/FLAIR contrast reproducibility. Being a cross sectional validation study with retrospective data ana

Due to differences in reader's experience and threshold for defining the mismatch, the susceptibility of the T2/FLAIR mismatch sign to variability amongst observers is a recognized limitation.

CONCLUSION

It was demonstrated that a strong and statistically significant association between the T2/FLAIR mismatch sign and IDH mutant tumors is present, confirming its acceptable predictive value. The association between the T2/FLAIR mismatch sign and IDH mutation status verifies findings of prior studies emphasizing its diagnostic utility with this non invasive imaging biomarker offering a complementary surrogate for molecular diagnosis. The T2/FLAIR mismatch sign's high specificity (89.3%) supports its role as a screening tool in resource-limited settings, though negative results require molecular confirmation. Future research should aim to validate these findings in larger, multi-centre prospective studies, with standardized imaging protocols and inclusion of interobserver agreement assessments because such efforts will be essential for translating these imaging biomarkers into widespread clinical application.

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