The T2-FLAIR mismatch sign as an imaging marker for non-enhancing IDH-mutant, 1p/19q-intact lower-grade glioma: a validation study

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Department of Neurology, Maastricht University Medical Center, Maastricht, Netherlands (M.P.G.B., M.H.M.E.A.); Department of Neurology, The Brain Tumor Center at Erasmus MC Cancer Institute, Rotterdam, Netherlands (M.P.G.B., M.M.J.W., M.J.v.d.B.); Department of Radiology and Nuclear Medicine, Erasmus MC, University Medical Center Rotterdam, Rotterdam, Netherlands (M.S.); Department of Pathology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, Netherlands (H.J.D.); Department of Neurosurgery, Maastricht University Medical Center, Maastricht, Netherlands (O.E.M.G.S.); Department of Pathology, GROW-school for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, Netherlands (J.B.); Department of Radiology, Maastricht University Medical Center, Maastricht, Netherlands (A.A.P.)

***Corresponding Author:** Martinus P.G. Broen, M.D., Ph.D., Department of Neurology, Maastricht University Medical Center, P.O. Box 5800 6202 AZ Maastricht, the Netherlands (martijn.broen@mumc.nl).

Abstract

Background. The purpose of this study was to assess the reproducibility of the previously described T2–fluid attenuated inversion recovery (FLAIR) mismatch sign as a specific imaging marker in non-enhancing isocitrate dehydrogenase (*IDH*) mutant, 1p/19q non-codeleted lower-grade glioma (LGG), encompassing both diffuse and anaplastic astrocytoma.

Methods. MR scans (n = 154) from 3 separate databases with genotyped LGG were evaluated by 2 independent reviewers to assess (i) presence/absence of "T2-FLAIR mismatch" sign and (ii) presence/absence of homogeneous signal on T2-weighted images. Interrater agreement with Cohen's kappa (κ) was calculated, as well as diagnostic test performance of the T2-FLAIR mismatch sign to identify *IDH*-mutant astrocytoma.

Results. There was substantial interrater agreement for the T2-FLAIR mismatch sign [κ = 0.75 (0.64–0.87)], but only fair agreement for T2 homogeneity [κ = 0.38 (0.25–0.52)]. The T2-FLAIR mismatch sign was present in 38 cases (25%) and had a positive predictive value of 100%, negative predictive value of 68%, a sensitivity of 51%, and a specificity of 100%.

Conclusions. With a robust interrater agreement, our study confirms that among non-enhancing LGG the T2-FLAIR mismatch sign represents a highly specific imaging marker for *IDH*-mutant astrocytoma. This non-invasive marker may enable a more informed patient counsel and can aid in the treatment decision processes in a significant proportion of patients presenting with non-enhancing, LGG-like lesions.

Keywords

IDH-mutant astrocytoma | imaging marker | lower grade glioma | T2-FLAIR

Diffuse lower-grade glioma (LGG) comprises a heterogeneous group of infiltrative World Health Organization (WHO) grades II and III primary brain tumors.[1] LGGs have a wide range of outcomes (both overall survival [OS] and progression-free survival), even within LGG subgroups with identical morphological phenotype.[2,3] The improved

Importance of the study

Our study confirms with a robust interrater agreement that the previously described T2-FLAIR mismatch sign is a highly specific imaging marker for *IDH*-mutant astrocytoma. A reliable molecular subtyping before neurosurgery would provide useful information in the decision process. As an example, recent studies have shown that in *IDH*-mutant astrocytomas even small postoperative tumor remnants have a negative impact on overall survival, arguing for a second look operation in this subtype to remove minor residues if safely possible. Because of its 100% positive predictive value in non-enhancing glioma, the T2-FLAIR mismatch sign may stimulate surgeons to achieve a gross total resection. Identification of this simple marker on conventional imaging can therefore aid in treatment decisions and enable a more informed patient counsel.

glioma classification using molecular parameters has resulted in the 2016 update of the WHO Classification of Tumors of the Central Nervous System in which phenotypic and genotypic parameters are integrated in glioma tumor classification.[1] In particular the presence of mutations in the isocitrate dehydrogenase gene 1 or 2 (*IDH1/2*) and 1p/19q copy number status are now central in the classification of diffuse gliomas.[4]

Apart from the WHO tumor classification, specific imaging features of brain tumors may help to further characterize LGG and may contain prognostic information early in the diagnostic process.[5,6] For example, Law et al[7] demonstrated that LGG with high perfusion on dynamic susceptibility contrast magnetic resonance (MR) imaging had a worse prognosis compared with high-grade tumors with low perfusion. Unraveling correlations between molecular profiles and image phenotypes may yield prognostic information non-invasively, which can help in guiding clinical decisions.

A recent study by Patel et al[8] identified a possible imaging marker of LGG molecular subgroups: the presence of a complete/near-complete hyperintense signal on T2-weighted (T2W) MRI sequences, in combination with a relative hypointense signal on fluid attenuation inversion recovery (FLAIR) MR sequences except for a hyperintense peripheral rim (Fig. 1). This so-called T2-FLAIR mismatch sign on conventional MRI represented in that dataset a highly specific imaging marker (positive predictive value [PPV] of 100%) for *IDH*-mutant, 1p/19q non-codeleted tumors. These tumors encompass both molecularly defined diffuse astrocytoma (grade II) as well as anaplastic astrocytoma (grade III), which together can be denoted as *IDH*-mutant astrocytoma. If indeed the non-invasive T2-FLAIR mismatch sign distinguishes between WHO 2016 glioma subgroups, this might enable a more informed pretreatment management plan and patient counsel early in the diagnostic process.[8]

The aim of this study was to assess the reproducibility of the T2-FLAIR mismatch sign as a highly specific imaging marker of *IDH*-mutant astrocytoma in a large sample of genotyped non-enhancing LGG. In contrast with Patel et al,[8] we focused on non-enhancing lesions, since contrast enhancing tumors will usually be aggressively treated and enhancement is frequently a sign of (focal) dedifferentiation into high-grade glioma.[9] Therefore, we thought that the possible clinical relevance of identifying the T2-FLAIR mismatch sign is most relevant in patients with non-enhancing tumors.

Methods

Patient Selection

A multicenter retrospective study was performed at the Erasmus MC, University Medical Center Rotterdam (Erasmus MC), and Maastricht University Medical Center (MUMC+). We included adult supratentorial molecularly defined LGG cases, which were available from 3 databases. Two were at Erasmus MC: EMC1 and EMC2, the former comprising a project on the extent of resection in LGG with samples since 2003,[10] and the latter covering routine clinical diagnostics since 2013. The third database, at MUMC+, covers clinical diagnostics since 2015. We selected those cases with lower-grade histology, with full information on *IDH* and 1p/19q status available, and with adequate MRI (defined as presence of FLAIR, T2W, and pre- and postcontrast T1W sequence) acquired before surgery. Both Erasmus MC databases also include histopathology-based LGGs, but with glioblastoma (GBM)-like molecular characteristics[11]: *IDH* wildtype, telomerase reverse transcriptase promoter mutation, gain of chromosome 7, loss of chromosome 10q, and/or mutations in the epidermal growth factor receptor gene.[12] This *IDH* wildtype, GBM-like subgroup was included in the analysis. The specifics of the case selection are shown in the flowchart (Fig. 2).

Histopathology diagnosis, WHO grade, patient characteristics(including sex, age at diagnosis, and OS time) were collected. The design of this study was approved by the institutional review board and conducted according to institutional and national ethical guidelines.

Molecular Analysis

The majority of samples were molecularly classified using an in-house dedicated next-generation sequencing (NGS) panel as described elsewhere.[13,14] The primer panel consisted of primers for mutations in genes and loss or gain of chromosomal regions characteristic for gliomas. In the remaining cases, *IDH1/2* mutation status was assessed using Sanger sequencing, and 1p/19q loss with fluorescence in situ hybridization (FISH). Since FISH for 1p using a probe for the 1p36.6 region may only indicate loss of the tip of chromosome 1p,[15,16] in cases with a positive T2-FLAIR mismatch sign and 1p/19q status primarily assessed by FISH, the molecular analysis was repeated with NGS.

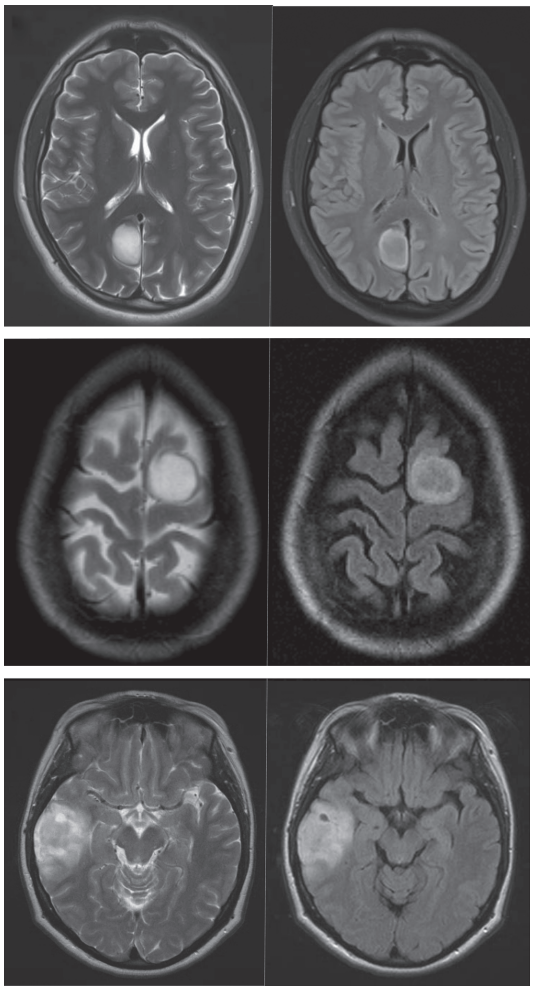

Fig. 1 Examples of the T2-FLAIR mismatch sign. (A, B) T2-FLAIR mismatch sign in 2 cases with *IDH*-mutant astrocytoma. The lesions display relatively hypointense signal throughout the majority of the lesion compared with T2W (left images), with the exception of a peripheral rim of hyperintense signal. (C) Absence of mismatch sign in *IDH*-mutant, 1p/19q codeleted oligodendroglioma.

Tumors were then classified into 5 molecularly defined subgroups according to the WHO 2016 classification: (i) diffuse astrocytoma, *IDH*-mutant, 1p/19q non-codeleted, (ii) diffuse oligodendroglioma, *IDH*-mutant, 1p/19q codeleted, (iii) anaplastic astrocytoma, *IDH*-mutant, 1p/19q non-codeleted, (iv) anaplastic oligodendroglioma, *IDH*-mutant, 1p/19q codeleted, and (v) diffuse astrocytoma, *IDH*-wildtype.

Imaging Analysis

MR scans were acquired at 1.5T or 3.0T and assessed by 2 independent reviewers (M.P.G.B., neurologist, and M.S., neuroradiologist), with 3 and 10 years experience, respectively. Both were blinded to clinical history and diagnosis. Imaging markers were visually scored using a binary scoring system (yes/no): (i) absence or presence of a T2W homogeneous signal intensity and (ii) absence or presence of a complete/near-complete hyperintense signal on T2W and relatively hypointense signal on FLAIR except for a hyperintense peripheral rim, the T2-FLAIR mismatch sign (Fig. 1). If there were discordant scores regarding the T2-FLAIR mismatch sign, both reviewers independently assessed the images for a second time, and if disagreement persisted a third reviewer (M.v.d.B.) was asked to adjudicate.

Statistical Analysis

An interrater agreement analysis using Cohen's kappa statistic (κ) was performed to determine consistency among the 2 raters after the second reading. A κ value of $\leq$0.2 indicates slight agreement, 0.21–0.4 fair agreement, 0.41–0.6 moderate agreement, and >0.6 substantial agreement.[17] To further validate the T2-FLAIR mismatch sign as an imaging marker of *IDH*-mutant astrocytoma, sensitivity, specificity, PPV, and negative predictive value (NPV) were calculated using the final scores after adjudication. In addition, *IDH*-mutant, 1p/19q non-codeleted tumors with and without the presence of the T2-FLAIR mismatch sign were compared using sex distribution, tumor location, age at diagnosis, and tumor grade. All analyses were computed with SPSS 24.

Results

Cohort Characteristics

The final cohort consisted of 154 patients (Table 1, Fig. 2). The majority had either WHO grade II diffuse *IDH*-mutant astrocytoma (45.5%) or diffuse molecularly defined oligodendroglioma (40.9%), with only a few grade III anaplastic *IDH*-mutant astrocytoma (3.2%) and molecularly defined anaplastic oligodendroglioma (2.6%). Ten of the 142 *IDH*-mutant tumors had an *IDH2* mutation. Twelve tumors were *IDH*-wildtype (7.8%). One hundred and forty-seven samples were molecularly classified by NGS, the remaining 7 with Sanger sequencing (*IDH1/2*) and FISH (1p/19q status). In 3 of these 7 cases, molecular analysis was repeated with NGS because a T2-FLAIR mismatch was identified. In 2 of them the *IDH* mutation and 1p/19q status were confirmed by NGS, and in 1 case there was only limited tissue available and NGS results were inconclusive. At the time of the analysis 33 patients (21%) had died. Due to the limited number of survival events, a meaningful correlation analysis of patients with and without the T2-FLAIR mismatch sign with OS was not possible.

Interrater Agreement

Independent MRI assessment revealed a substantial interrater agreement for the T2-FLAIR mismatch sign with a κ of 0.75 ($P < 0.001$; 95% CI: 0.64–0.87). Both reviewers scored the T2-FLAIR mismatch sign as present in 34 cases (22%) and as absent in 105 (68%). Fifteen cases (10%) had a discordant score and were reassessed independently by both reviewers (M.B. and M.S.). After reassessment, 2 additional

tumors with a mismatch sign were identified, bringing the total to 36 (23%) cases. Disagreement remained in 10 cases, and those were reviewed by M.v.d.B. (see Supplementary Figures S1–S10 for description and final characterization of these cases). When looking closer at the discordant cases, no specific pattern could be noticed. Seven cases were scored as a mismatch by M.S. and not by M.B., and 3 cases vice versa. Three out of 10 cases had a very subtle T2W and

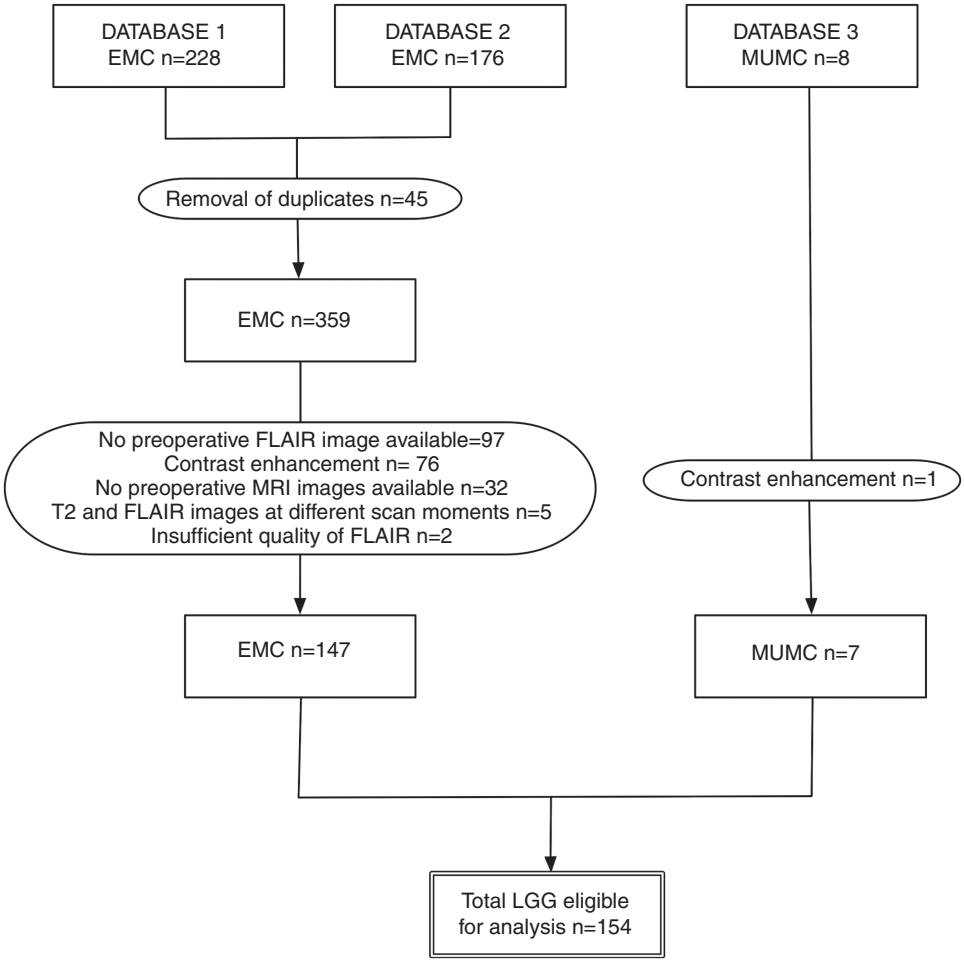

Fig. 2 Flowchart of selection process.

Table 1 Characteristics of the LGG cohort

	EMC1 *N* = 121	EMC2 *N* = 26	MUMC+ *N* = 7	Total *N* = 154	T2-FLAIR mismatch sign (*N*)
Male (*N*)	65	18	3	86 (55.8%)	
Mean age at diagnosis, y (range)	43 (20–82)	46 (27–74)	41 (24–52)	43 (20–82)	
Diffuse astrocytoma, *IDH*-mutant (WHO grade II)	59	5	6	70 (45.5%)	34
Diffuse oligodendroglioma, *IDH*-mutant, 1p/19q codeleted (WHO grade II)	50	12	1	63 (40.9%)	0
Anaplastic astrocytoma, *IDH*-mutant (WHO grade III)	0	5	0	5 (3.2%)	4
Anaplastic oligodendroglioma, *IDH*-mutant, 1p/19q codeleted (WHO grade III)	0	4	0	4 (2.6%)	0
***IDH*-wildtype, GBM-like**	12	0	0	12 (7.8%)	0

FLAIR difference (for example, see Supplementary Fig. S1), 3 tumors had some degree of a cystic component defining a mismatch (for example, see Supplementary Fig. S2), and 4 had only a partial mismatch.

There was only a fair interrater agreement for the T2 homogeneity score with a κ of 0.38 ($P < 0.001$; 95% CI: 0.25–0.52). In line with previous work,[8] consensus review was not undertaken for this imaging metric, and no further analyses were performed due to the low level of interrater agreement. Eight cases were concordant, scored as having a complete/near-complete hyperintense signal on T2W MRI but with an absence of T2-FLAIR mismatch (for example, see Supplementary Fig. S11). All of them were rated as "absent T2-FLAIR mismatch sign." Among those 8 cases, 6 were *IDH*-mutant, 1p/19q non-codeleted; 1 was *IDH*-mutant, 1p/19q codeleted (for example, see Supplementary Fig. S4); and 1 was a GBM-like, *IDH*-wildtype LGG.

T2-FLAIR Mismatch Sign as Biomarker

After resolving the discordant cases, the T2-FLAIR mismatch sign was present in 38 cases (25%) and absent in 116 cases (75%). Table 1 shows the presence of the T2-FLAIR mismatch sign, stratified by LGG subgroup. In both diffuse (WHO grade II) and anaplastic (WHO grade III) astrocytoma, the T2-FLAIR mismatch sign was present, in 34/70 and 4/5 cases, respectively. There was no difference in sex, age at diagnosis, WHO grade, or tumor location between *IDH*-mutant, 1p/19q non-codeleted tumors with versus without the T2-FLAIR mismatch sign (Supplementary Table S1). Both *IDH1* as well as *IDH2* mutated tumors displayed a positive T2-FLAIR mismatch sign. None of the *IDH*-mutant, 1p/19q codeleted, or *IDH*-wildtype GBM-like LGG displayed the mismatch sign. The T2-FLAIR mismatch sign thus had a 100% PPV for identifying *IDH*-mutant astrocytoma. The NPV was 68%, with a sensitivity of 51% and a specificity of 100%. In none of the *IDH*-wildtype, GBM-like LGG was the mismatch sign present. It is noteworthy that 2 of the 15 discordant cases were *IDH*-mutant 1p/19q codeleted tumors; all the others were *IDH*-mutant astrocytomas. Both cases (Supplementary Figures S3 and S4) had only a partial mismatch with some cystic components and there was absence of a hyperintense rim on FLAIR. The third reviewer rated both as having no mismatch sign.

Discussion

Our results confirm that among non-enhancing LGG the T2-FLAIR mismatch sign represents a highly specific imaging marker for *IDH*-mutant astrocytoma. The mismatch sign was present on conventional MR in 38 of 154 cases (25%), with a robust interrater agreement.

Patel et al[8] investigated the mismatch sign in 2 datasets of genotyped LGG with a test set of 125 cases and a validation set of 60 cases. In the first set 12% had a T2-FLAIR mismatch, and in the validation set 17%. In both sets the sign was a marker of *IDH*-mutant, 1p/19q non-codeleted glioma, with a PPV of 100%. Our study confirms these findings, with identical interrater agreement (κ 0.75). The T2-FLAIR mismatch sign seems to be specific (100% PPV) for *IDH*-mutant astrocytoma, and the robust interrater agreement is due to the striking imaging appearance. Especially the relatively hyperintense rim on FLAIR sequence seems to be important to correctly diagnose this feature, since both *IDH*-mutant, 1p/19q codeleted tumors with a discordant score showed no clear or only partial hyperintense rims. In addition, the high specificity requires strict adherence to considering only these cases with a clearly homogeneous T2W signal hyperintensity, thereby excluding tumors with cystic components. Our observation that 2 out of 8 cases with a homogeneous T2W signal, but no T2-FLAIR mismatch, were *not* IDH-mutant astrocytoma underlines the importance of combining both the hyperintense rim on FLAIR sequence and the homogeneous T2 signal hyperintensity to achieve high specificity. However, interrater agreement on T2W signal homogeneity is unsatisfactory. This is probably due to the used binary scoring system, whereas subtle changes may result in different interpretations across readers. We advise to only consider the presence of the T2-FLAIR mismatch sign if a clear-cut homogeneous T2W signal is present. Although by doing so more cases will be discarded, we believe that the high specificity is what makes this imaging sign clinically relevant.

More advanced MRI techniques such as perfusion-weighted imaging,[18] MR-spectroscopy for 2-hydroxyglutarate detection,[19] or ^{18}F–fluoro-ethyl-tyrosine (FET)-PET[20] have been previously reported to allow distinction between certain molecular glioma subtypes. However, some of these more advanced MR techniques such as MR-spectroscopy and ^{18}F-FET-PET are not widely available in daily practice, and the fact that T2W and FLAIR sequences are part of standard, conventional MRI routinely used in every hospital is an important strength of the T2-FLAIR mismatch sign. The rapid development of radiogenomics[21,22] may allow the incorporation of quantitative measures alongside relatively simple imaging features such as the T2-FLAIR mismatch sign to further distinguish between molecular subgroups.

The T2-FLAIR mismatch sign may aid in diagnostic and treatment decisions. Typically, an LGG patient presents with seizures or the lesion is accidentally discovered during MRI for other indications, such as headache. Clinicians then have to decide on a treatment strategy for a *presumed* LGG, based on clinical and imaging parameters: a wait-and-scan policy, biopsy for histopathological verification, or immediate resection.[23] Early resection, when safely possible, is currently the standard of care, although controlled trials exploring the role and timing of surgery are lacking and are largely based on retrospective studies.[23–25] A reliable molecular subtyping before neurosurgery would provide useful information in this decision process. Recent studies have shown that in *IDH*-mutant astrocytomas even small postoperative tumor remnants have a negative impact on OS, arguing for a second-look operation in this subtype to remove minor residues if safely possible.[9,26,27] Because of its 100% PPV in non-enhancing glioma, the T2-FLAIR mismatch sign may stimulate surgeons to achieve a gross total resection.

The pathophysiology of the T2-FLAIR mismatch sign is unclear, and therefore the reason remains unelucidated why only half of the *IDH*-mutant, 1p/19q non-codeleted astrocytomas in our sample manifest the sign. We could not identify an association with sex, age at diagnosis,

tumor grade, and tumor location. Patel et al[8] assumed that the presence of the imaging marker might be related to increased levels of protein in the mammalian target of rapamycin pathway among positive T2-FLAIR mismatch cases, but a validation of their findings is lacking. There is one other study mentioning the T2-FLAIR mismatch sign in gliomas. Tay et al[28] studied 8 protoplasmic astrocytomas and demonstrated portions of signal suppression on FLAIR imaging in all of them, with in 6/8 a partial or complete hyperintense rim on the apparent diffusion coefficient. The study was performed in the pre-molecular classification era, and information about *IDH* or 1p/19q status was not available. Both Patel et al[8] and Tay et al[28] described microcysts in most of the mismatch cases, although this was not a uniform finding. To the best of our knowledge, only one study described a hyperintense ring sign in cerebral nonglioma tumors. Parmar et al[29] investigated the "hyperintense ring sign" on FLAIR images as a marker of dysembryoplastic neuroepithelial tumors (DNETs) in 11 patients ranging in age from 4 to 18 years. They found a complete or incomplete well-defined ring in 9/11 DNETs. There were also 2/21 positive cases in the control group, 1 with an LGG and 1 with a ganglioglioma. Pathological evaluation suggested that the hyperintense ring might correspond to the presence of peripheral loose neuroglial elements; no molecular analysis was available.[29]

There are limitations of this study that may affect its clinical utility. We included only supratentorial, non–contrast enhanced tumors to rule out tumors with possible focal high-grade areas. This inevitably led to a selection bias, while in up to 16% of WHO grade II gliomas some contrast enhancement may be present and probably some grade III and *IDH*-wildtype LGG will be excluded too.[30] We think that the clinical relevance is the highest in the non-enhancing tumor group, since enhancing tumors undergo treatment without delay anyway. In addition, MR scans were acquired at both 1.5T as well as 3.0T, which could have negatively influenced the T2W homogeneity interrated agreement (eg, gliomas could look less homogeneous on 3.0T compared with 1.5T MR scans). However, since only 7 cases were scanned at 3.0T, it is unlikely that this has influenced our results. Last, we were unable to investigate and clarify the pathophysiology of the T2-FLAIR mismatch sign. It therefore remains unclear why only half of *IDH*-mutant, 1p/19q non-codeleted astrocytomas manifest this sign. A recommendation for future studies would be to acquire targeted biopsies from the hyperintense rim and the core of the tumor for molecular and histomorphological analyses. Unraveling its pathophysiology may hopefully further increase its clinical utility.

Conclusion

Our study confirms that among adult non-enhancing LGG the T2-FLAIR mismatch sign represents a highly specific imaging marker for *IDH*-mutant astrocytoma with a robust interrater agreement. Although further studies with extensive genomic and histopathology analyses are needed to clarify the underlying pathophysiology, this simple, noninvasive marker enables a more informed patient counsel and can aid in treatment decision processes in a significant proportion of patients presenting with non-enhancing LGG-like lesions.

Supplementary Material

Supplementary material is available at *Neuro-Oncology* online.

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Conflict of interest statement. No relevant disclosures.

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