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ORIGINAL ARTICLE

The reliability and interobserver reproducibility of T2/FLAIR mismatch in the diagnosis of *IDH*-mutant astrocytomas

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PURPOSE
The reliability and reproducibility of T2-weighted imaging/ fluid-attenuated inversion recovery (T2/FLAIR) mismatch were investigated in the diagnosis of *isocitrate dehydrogenase (IDH)* mutant astrocytoma between WHO grade II and III diffuse hemispheric gliomas.

METHODS
WHO grade II and grade III diffuse hemispheric gliomas (n=133) treated in our institute were included in the study. Pathological findings and molecular markers of the cases were reviewed with the criteria of WHO 2016. The finding of mismatch between T2-weighted and FLAIR images in preoperative magnetic resonance imaging (MRI) of the cases was evaluated by two different radiologists. The readers reviewed MRIs independently, blinded to the histopathologic diagnosis or molecular subset of tumors. The cases were classified as *IDH*-mutant astrocytoma, oligodendroglioma and *IDH*-wildtype (*IDH*-wt) astrocytoma according to molecular and genetic features.

RESULTS
T2/FLAIR mismatch positivity was observed in 46 patients (34.6%). T2/FLAIR mismatch positivity was observed in 42 of 75 *IDH*-mutant astrocytomas (56%) and 4 of 43 oligodendrogliomas (9.30%), while it was not seen among *IDH*-wt astrocytomas (0/15, 0%). The T2/FLAIR mismatch ratio was significantly different between *IDH*-mutant astrocytomas (WHO grade II and grade III) and oligodendrogliomas (chi-square, p <0.05). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of T2/FLAIR mismatch in predicting *IDH*-mutant astrocytomas were 58.7%, 90.7%, 91.7%, 61.4%, and 70.3% respectively. Radiologist 1 diagnosed T2/FLAIR mismatch in 48 of 133 cases (36.1%) and Radiologist 2 in 66 of 133 cases (49.6%). The interrater agreement for the T2/FLAIR mismatch sign was 0.61 (p <0.05), 95% CI (0.55, 0.67).

CONCLUSION
T2/FLAIR mismatch appears to be an important MRI finding in distinguishing *IDH*-mutant astrocytomas from other diffuse hemispheric gliomas. However, it should be kept in mind that T2/FLAIR mismatch sign can be seen in a minority of oligodendrogliomas besides *IDH*-mutant astrocytomas.

Preoperative prediction of histopathological diagnosis of tumors is highly relevant during treatment of diffuse hemispheric gliomas (DHG). This preliminary diagnosis strongly influences the treatment plan and the surgical strategy. *Isocitrate dehydrogenase* (*IDH*) mutant gliomas constitute the majority of DHG (WHO grade II and grade III) (1, 2). Among *IDH*-mutant gliomas there are two tumor entities: *IDH*-mutant astrocytoma and *IDH*-mutant 1p/19q co-deleted oligodendroglioma (3). A smaller proportion of DHG carry molecular alterations of glioblastoma and such tumors exhibit a tumor biology comparable to glioblastomas (1, 2, 4). Independent of the WHO grade, DHG with no *IDH* mutation exhibit worse prognosis than their *IDH*-mutant counterparts (5). Each of these three molecular tumor subsets has a very different tumor biology and requires a matching treatment strategy, which underlines the importance of noninvasive preoperative diagnosis.

Conventional magnetic resonance imaging (MRI) and computed tomography (CT) imaging is widely used to differentiate these tumors. Coarse calcifications, which are best visible on unenhanced CT scans are characteristic to oligodendrogliomas and absent in astrocytomas. Other typical features of oligodendrogliomas are a cortical-subcortical location and

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a more heterogeneous appearance of astrocytomas on T2-weighted images (6). Advanced MRI sequences also have a potential to noninvasively identify these DHGs. In perfusion-weighted imaging, higher cerebral perfusion volumes are observed in oligodendrogliomas compared to astrocytomas (7).

In 2017, Patel et al. (8) presented an analysis of The Cancer Genome Atlas (TCGA) cohort and showed that in lower-grade gliomas, the T2/FLAIR mismatch sign represented a highly specific imaging biomarker for the *IDH*-mutant, 1p/19q non co-deleted molecular subtype. The T2/FLAIR mismatch denotes that the tumor has a high and homogeneous signal intensity on T2-weighted images whereas it has relatively hypointense signal with a hyperintense rim on T2-FLAIR images. Jain et al. (9) have shown that it may have false positives due to interobserver variability in application of the signs imaging criteria, differences in image acquisition and selection of the applied cohort. Therefore we sought to determine the reliability and reproducibility of the T2/FLAIR mismatch in the diagnosis of *IDH*-mutant astrocytoma among WHO grade II and III diffuse gliomas in our own institutional cohort, which is of comparable size to the original study by Patel et al. (8).

Methods

Cohort selection

This is a retrospective cohort analysis. Patient records from the Neurosurgery and Radiology Departments between January 2005 and May 2019 were reviewed for lower-grade (WHO grade II and III) hemispheric diffuse gliomas (oligodendroglioma WHO grade II, anaplastic oligodendroglioma WHO grade III, diffuse astrocytoma WHO grade II; anaplastic astrocytoma WHO grade III, oligoastrocytoma WHO grade II or anaplastic oligoastrocytoma WHO grade III). These histopathological diagnoses on patient files were only used to select for lower-grade glioma patients but not for further analyses.

Only patients with complete preoperative MRI examination (including T2-weighted and T2-FLAIR sequences) were included. Exclusion criteria were pediatric age group, non-hemispheric (cerebellar, brainstem or thalamic) localization and previous tumor resection from the same anatomical site.

The study was approved by our institutional review board (2019/18). Since the study was designed retrospectively, informed consent was not obtained.

Cohort characteristics

The cohort consisted of 133 patients. Sixty-one of the patients were female (45.8%) and 72 were male (54.2%), with a male to female ratio of 1.2. The mean age was 38.5±11.3 years (median age, 36 years; range, 20–68 years). Cohort characteristics are presented in Table 1.

Pathological diagnosis

All pathological diagnoses were re-evaluated by a single dedicated neuropathologist (A.E.D.). The tumors were confirmed to have diffuse/infiltrative pattern. DNA was extracted from the formalin-fixed paraffin embedded tissue using standard methods (Qiamp DNA FFPE tissue kit) and used for sequencing. Histopathological analysis was performed on the excised surgical specimens to determine the tumor type and grade according to the World Health Organization 2016 Central Nervous System Tumor Classification Scheme (10). ATRX expression was determined using immunohistochemistry. *IDH1* or *IDH2* (*IDH1/2*) and *telomerase reverse trnscriptase* (*TERT*) mutations were determined by Sanger sequencing. The presence of a 1p/19q codeletion was determined by fluorescent *in situ* hybridization using Zytolight SPEC 1p36/1q25; 19q13/19p13 dual color probe kit.

Based on the morphomolecular findings, the tumors were diagnosed as oligodendroglioma when the tumors exhibited retained ATRX immunoexpression, *IDH* mutation, *TERT* mutation and 1p/19q codeletion. The tumors were diagnosed as *IDH*-mutant astrocytoma when the tumors exhibited *IDH* mutation, loss of ATRX immunoexpression along with 1p/19q non codeletion. The histological grading was performed based on the findings of mitosis, necrosis and vascular endothelial proliferation according to the World Health Organization 2016 Central Nervous System Tumor Classification Scheme.

MRI interpretation

MRI examinations were evaluated retrospectively by two radiologists experienced in neuroradiology (İ.Ö.Y. and M.E.Y.). The readers reviewed MRIs independently and blinded to the histopathologic diagnosis or molecular subset of tumors. T2/FLAIR mismatch finding was defined as homogeneous hyperintensity in T2-weighted series as well as broad hypointensity in the central region except the peripheral rim in FLAIR (Fig. 1). Evaluation was made as T2/FLAIR mismatch positive or negative. Atypical/controversial

Main points

- Different types of gliomas present with similar radiological findings.
- T2/FLAIR mismatch sign has been reported to be a specific finding for *isocitrate dehydrogenase (IDH)* mutant astrocytomas.
- T2/FLAIR mismatch appears to be an important MRI finding in distinguishing *IDH*-mutant astrocytomas from other diffuse hemispheric gliomas.
- It should be kept in mind that T2/FLAIR mismatch sign can be seen in a minority of oligodendrogliomas besides *IDH*-mutant astrocytomas.

Table 1. Cohort characteristics between groups are shown

Cohort characteristics		Group 1 n=75	Group 2 n=43	Group 3 n=15
WHO grade, n (%)	Grade II	44 (58.7)	28 (65.1)	12 (80)
	Grade III	31 (41.3)	15 (34.9)	3 (20)
Age (years)	Mean	34.8	41.7	47.93
	Range	20-62	26-68	21-64
Sex, n	Female	38	15	8
	Male	37	28	7
Largest diameter (mm)	Mean	56.31	53.98	40.87
	Range	22–100	22–97	20–70
Smallest diameter (mm)	Mean	40.64	37.26	27.20
	Range	15–91	15–86	12–52

Group 1, *IDH*-mutant astrocytomas; Group 2, *IDH*-mutant 1p/19q codeleted oligodendrogliomas; Group 3, *IDH*-wildtype tumors.

Table 2. Locations in the brain are summarized according to the tumor type

	Frontal n (%)	Temporal n (%)	Parietal n (%)	Insula n (%)	Total
Group 1	35 (46.7)	25 (33.3)	9 (12)	6 (8)	75
Group 2	27 (62.8)	12 (27.9)	1 (2.3)	3 (7)	43
Group 3	4 (26.7)	8 (53.3)	2 (13.3)	1 (6.7)	15
Total	66 (49.6)	45 (33.8)	12 (9)	10 (7.5)	133

Group 1, *IDH*-mutant astrocytomas; Group 2, *IDH*-mutant 1p/19q codeleted oligodendrogliomas; Group 3, *IDH*-wildtype tumors.

Table 3. Comparison of some MRI features in T2/FLAIR mismatch positive and negative cases

	Overall	T2/FLAIR mismatch present n (%)	T2/FLAIR mismatch absent n (%)	Chi-square test *p*
No of patients	133	46	87	48 vs. 85
T1 heterogeneity	50 (37.6)	5 (10.4)	45 (52.9)	0.001
T2 heterogeneity	52 (39.1)	6 (12.5)	46 (54.1)	0.001
Contrast enhancement (12 marked; 9 faint)	22 (16.5)	1 (2.1)	21 (24.4)	0.001
Multifocality	4 (3)	0	4 (4.7)	0.127
Gliomatosis pattern	8 (6)	0	8 (9.4)	0.028
WHO grade II/III ratio	84/49=1.71	32/16=2.00	52/33=1.57	0.528

MRI, magnetic resonance imaging; T2-FLAIR, T2-weighted fluid-attenuated inversion recovery; WHO, World Health Organization.

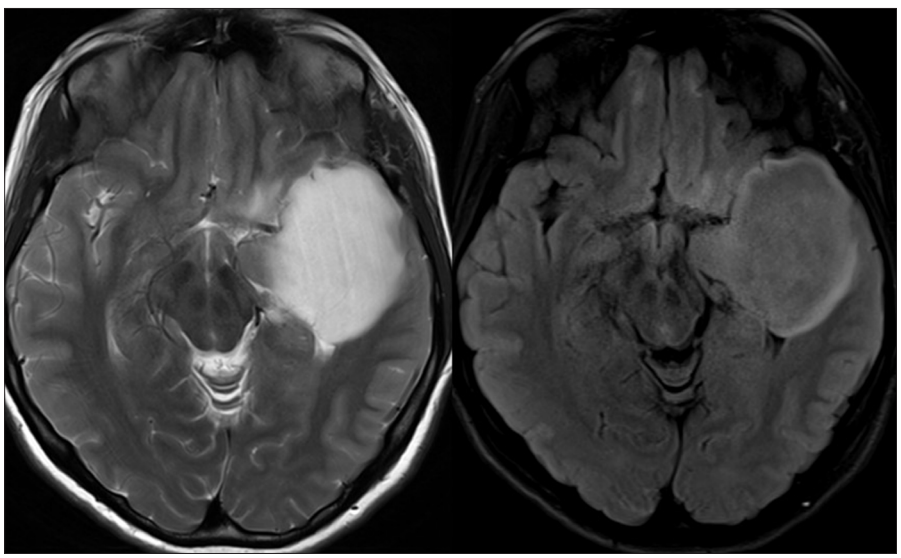

Figure 1. Left temporal mass in a 23-year-old woman with typical T2/FLAIR mismatch. Pathological diagnosis is *IDH*-mutant grade III astrocytoma.

cases were considered negative. When two readers could not agree on T2/FLAIR mismatch, a third neuroradiologist was consulted for the decision (A.D.). In addition to T2/FLAIR mismatch status, characteristics of the cases such as conventional T2-weighted and T1-weighted sequence features and enhancement properties were also recorded.

Statistical analysis

Descriptive analyses were performed. In terms of T2/FLAIR mismatch, chi-square test was performed to analyze whether the *IDH*-mutant DHCs were significantly different from the other two groups. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated. Group means were compared using t-test. ANOVA test was performed to compare the mean values of more than two groups. Cohen's kappa value (κ coefficient) was calculated for interobserver agreement: $\kappa<0.40$ indicated poor agreement, $0.41<\kappa<0.60$ indicated moderate agreement, $0.61<\kappa<0.80$ indicated good agreement and $\kappa>0.81$ indicated substantial agreement. The Kaplan-Meier method was used to estimate overall survival and progression-free survival. All statistical analyses were done using SPSS software (IBM SPSS Statistics 20).

Results

The mean age of patients with *IDH*-mutant diffuse astrocytomas (WHO grade II) was 35.80±10.31 years and that of patients with *IDH*-mutant anaplastic astrocytomas (WHO grade III) was 33.52±7.11 years, with no statistically significant difference between them ($p = 0.29$). The mean age of patients with oligodendroglioma (WHO grade II) was 38.75±8.29 years and that of patients with anaplastic oligodendroglioma (WHO grade III) was 47.13±13.12 years, with statistically significant difference between them ($p < 0.05$). The mean age of patients with *IDH*-wt diffuse astrocytomas (WHO grade II) was 45.25±15.88 years and that of patients with *IDH*-wt anaplastic astrocytomas (WHO grade III) was 58.67±5.86 years, with no statistically significant difference between them ($p = 0.23$).

The largest diameters of the tumors on MRI were measured on axial plane. The median length of the tumors was 53.65 mm (range, 20–100 mm) and the median width was 38.02 mm (range 12–91 mm). Seventy-five tumors (56.4%) were localized on the right and 58 (43.6%) on the left. The mean largest size was 56.05±15.74 mm in *IDH*-mutant astrocytomas, 53.98±16.88 mm in oligodendrogliomas and 40.87±13.60 mm in *IDH*-wt astrocytomas. ANOVA test was used to compare group averages. The size difference between *IDH*-mutant astrocytoma and oligodendroglioma was not significant ($p = 0.77$). However, both *IDH*-mutant astrocytomas and oligodendrogliomas were significantly larger than *IDH*-wt astrocytomas ($p < 0.05$).

The primary anatomical location of the tumors (center of the involved volume where the lobe was most severely expanded) were as follows: 66 (49.6%) frontal, 45 (33.8%) temporal, 12 (9%) parietal and 10 (7.5%) insula. Location differences according to tumor subtypes are summarized in Table 2.

Table 4. T2/FLAIR mismatch positivity between grade II and grade III tumors by tumor type

	Grade II	Grade III	
	T2FMM positivity n (%)	T2FMM positivity n (%)	*p*
Group 1 (n=75)	26/44 (56.5)	16/31 (51.6)	0.30
Group 2 (n=43)	4/28 (14.3)	0/15 (0)	0.12
Group 3 (n=15)	0/12 (0)	0/3 (0)	

n, number of patients; T2FMM, T2/FLAIR mismatch. Group 1, *IDH*-mutant astrocytomas; Group 2, *IDH*-mutant 1p/19q codeleted oligodendrogliomas; Group 3, *IDH*-wildtype tumors.

Table 5. The localizations of the tumors according to the T2/FLAIR mismatch status

	Tumor localization, n (%)				
T2/FLAIR mismatch	Frontal	Temporal	Parietal	Insular	Total, n (%)
Positive	22 (47.8)	16 (34.8)	5 (10.9)	3 (6.5)	46 (100)
Negative	44 (50.6)	29 (33.3)	7 (8)	7 (8)	87 (100)

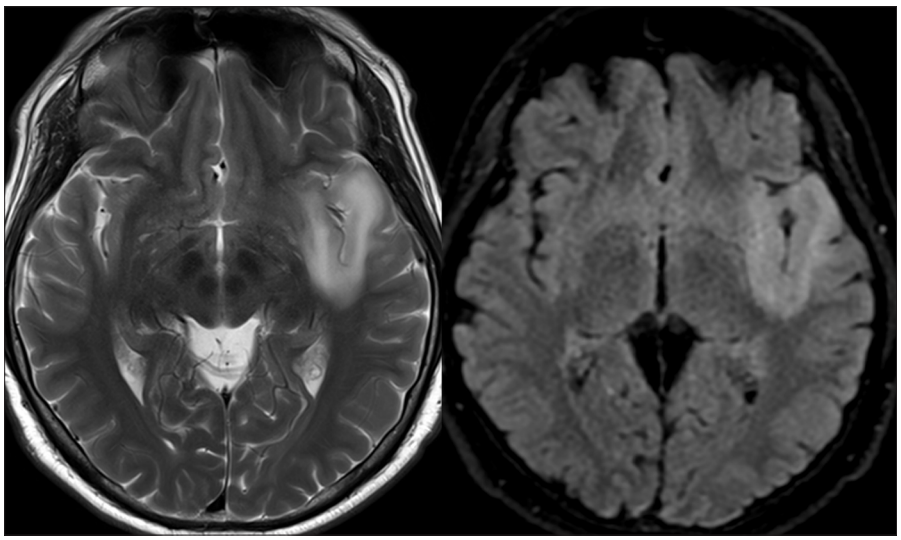

Figure 2. Left insular mass in a 43-year-old man with considered positive T2/FLAIR mismatch. Pathological diagnosis is grade II oligodendroglioma.

One of the most important differences between the T2/FLAIR mismatch positive and negative groups was heterogeneity. T2/FLAIR mismatch negative tumors were significantly heterogeneous ($p = 0.001$). Similarly, contrast enhancement was 24.4% in T2/FLAIR mismatch negative tumors and only 2.1% in positive cases, and the difference was statistically significant ($p = 0.001$). Other radiological findings of tumors are summarized in Table 3.

T2/FLAIR mismatch positivity was observed in 46 patients (34.6%). T2/FLAIR mismatch-positivity was observed in 42 of 75 *IDH*-mutant astrocytomas (56%), 4 of 43 oligodendrogliomas (9.30%), but was not seen in any of 15 *IDH*-wt astrocytomas (10.53%). The T2/FLAIR mismatch ratio of *IDH*-mutant astrocytomas (WHO grade II and grade III) were significantly different than that of oligodendrogliomas (chi-square, $p < 0.05$). The sensitivity, specificity, PPV, NPV, and accuracy of T2/FLAIR mismatch in predicting *IDH*-mutant astrocytomas were 58.7%, 90.7%, 91.7%, 61.4%, and 70.3%, respectively.

The incidence of T2/FLAIR mismatch-positivity was higher in WHO grade II *IDH*-mutant astrocytomas when compared to WHO grade III *IDH*-mutant anaplastic astrocytomas, although the difference was not statistically significant (chi-square, $p = 0.30$). The incidence of T2/FLAIR mismatch-positivity was higher in WHO grade II oligodendrogliomas when compared to WHO grade III anaplastic oligodendrogliomas and this difference was not statistically significant (chi-square, $p = 0.12$). Other than histologic grade, there were no significant histologic differences among the *IDH*-mutant astrocytomas or oligodendrogliomas with or without T2/FLAIR mismatch-positivity. Histologically there were no neoplastic astrocytic cells within any oligodendroglioma or any neoplastic oligodendroglial cells within any astrocytoma. T2/FLAIR mismatch positivity was not seen in *IDH*-wt astrocytomas. All data are given in Table 4.

The mean age of the T2/FLAIR mismatch-positive group was 32.6±7.8 years, and T2/FLAIR mismatch-negative group 41.7±11.7 years, with statistically significant difference between them (student t-test, $p < 0.05$). The mean age of T2/FLAIR mismatch-positive *IDH*-mutant astrocytomas was 32.4±7.9 years, and T2/FLAIR mismatch-negative *IDH*-mutant astrocytomas was 38±9.8 years, with statistically significant difference between them (student t-test, $p < 0.05$). While T2/FLAIR mismatch was seen in 19 of 28 cases in the 20–29 age group, it was not seen in any of the 9 cases aged over 60 years. The difference between T2/FLAIR mismatch incidence rates among age groups was statistically significant (chi-square test, $p < 0.05$).

Among *IDH*-mutant astrocytomas (WHO grade II or III), T2/FLAIR mismatch positivity was detected in 28 of 38 women (73.7%) and 14 of 37 men (37.8%), with statistically significant difference between sexes (chi-square, $p < 0.05$).

The average size of the tumors was measured approximately 53 mm. For this reason, the size cutoff was determined as 53 mm. T2/FLAIR mismatch positivity was observed in 20 of 61 tumors ≤53 mm (32.8%) and 28 of 72 tumors >53 mm (38.9%). The difference was not statistically significant (chi-square, $p = 0.46$).

There were no diffuse hemispheric gliomas located in the occipital lobe in this series. T2/FLAIR mismatch positivity among all gliomas was observed in 22 of 66 tumors in the frontal lobe (33.3%), 17 of 45 tumors in the temporal lobe (37.8%), 4 of 12 tumors in the parietal lobe (33.3%) and 3 of 10 tumors in the insular lobe (30%). The difference was not statistically significant (chi-square, $p = 0.84$). Similarly, *IDH*-mutant astrocytomas that are T2/FLAIR mismatch-positive were observed in 20 of 35 frontal (57.1%), 15 of 25 temporal (60%), 4 of 9 parietal (44.4%) and 3 of 6 insular (50%) tumors. The difference was not statistically significant (chi-square, $p = 0.86$).

Twenty-two of the T2/FLAIR mismatch-positive tumors were in the frontal lobe, while 44 of the T2/FLAIR mismatch-negative tu-

mors were in the frontal lobe. The difference was not statistically significant (chi-square, $p = 0.93$). The locations of the tumors according to the T2/FLAIR mismatch status are summarized in Table 5.

Radiologist 1 diagnosed T2/FLAIR mismatch in 48 of 133 cases (36.1%) and Radiologist 2 in 66 of 133 cases (49.6%). The interrater agreement for the T2/FLAIR mismatch was 0.61 ($p < 0.05$; 95% CI, 0.55, 0.67). Radiologist 1 diagnosed T2/FLAIR mismatch in 44 of 75 *IDH*-mutant astrocytomas (58.7%) and Radiologist 2 in 49 of 75 (65.3%). The interrater agreement for the T2/FLAIR mismatch-positivity in *IDH*-mutant astrocytomas was 0.63 ($p < 0.05$; 95% CI, 0.54–0.72).

Radiologist 1 diagnosed T2/FLAIR mismatch in 28 of 44 (63.6%) WHO grade II gliomas and Radiologist 2 in 29 of 44 (65.9%). The interrater agreement for the T2/FLAIR mismatch-positivity in WHO grade II gliomas was 0.65 ($p < 0.05$; 95% CI, 0.53–0.77). Radiologist 1 diagnosed T2/FLAIR mismatch in 16 of 31 (43.8%) WHO grade III gliomas and Radiologist 2 in 20 of 31 (64.5%). The interrater agreement for the T2/FLAIR mismatch-positivity in WHO grade III gliomas was 0.61 ($p < 0.05$; 95% CI, 0.47–0.75).

Survival data was present for all 133 patients. Median follow-up was 35 months (range, 3–180 months). *IDH*-wt astrocytomas are considered to be glioblastoma multiforme, and progression-free survival analysis was performed only for *IDH*-mutant tumors, as uneven distribution between the two groups would affect the comparison of survival. Log rank analysis indicated that there was neither a statistical overall survival difference ($p = 0.302$) nor a statistically significant progression-free survival difference ($p = 0.922$) between patients that exhibited a T2/FLAIR mismatch and those that did not. The priori power was low both for overall survival (0.1688) and for progression-free survival (0.3654).

Discussion

The T2/FLAIR mismatch finding in DHGs was first reported by Patel et al. (8) in 2017. They reported that T2/FLAIR mismatch was a highly specific finding for *IDH*-mutant DHGs, with 100% PPV and 54% NPV. Broen et al. (11) studied 154 DHG and found 52% sensitivity, 100% specificity, 100% PPV, and 68% NPV for positive T2/FLAIR mismatch sign. We found that the sensitivity of the T2/FLAIR mismatch sign was moderate, and only 42 of 75 *IDH*-mutant grade II and grade III astrocytomas had positive T2/FLAIR mismatch sign. The specificity of T2/FLAIR mismatch sign was high. PPV has been reported as 100% in studies of both Broen et al. (11) and Patel et al. (8). However, in our study, PPV was found to be 91.7%. T2/FLAIR mismatch sign was positive in 4 of 43 oligodendroglioma cases (9.3%), which were all grade II cases. When these cases were re-evaluated histologically, there were no astrocytic cellular component or astrocytic morphologic pattern within these oligodendroglial tumors. In the study of Juratlı et al. (12), T2/FLAIR mismatch sign were found positive in 12 of 42 oligodendroglioma cases (28.5%). However, they combined two other factors with T2/FLAIR mismatch sign, namely, under 40 years at first diagnosis and a tumor size larger than 6 cm, and found these diagnostic criteria to be highly specific for *IDH*-mutant astrocytomas. Johnson et al. (13) also reported that T2/FLAIR mismatch sign may be present apart from *IDH*-mutant astrocytomas. They found T2/FLAIR mismatch positivity in an adult oligodendroglioma case in their series. Furthermore, it has been reported that peripheral hyperintense rim sign may be present in FLAIR series in cystic glioneuronal tumors (14).

Although T2/FLAIR mismatch is practical to use, previous studies indicated considerable interobserver variability. Interrater agreement was reported as 0.747 by Patel et al. (8) and 0.75 by Broen et al. (11). We found the interrater agreement to be lower than the rates in their studies. Lower agreement may be due to differences in raters' experience. In this study, besides typical T2/FLAIR mismatch positive cases, we saw atypical cases similar to T2/FLAIR mismatch sign. Intratumoral cysts and necrosis are confusing elements and should not be considered as mismatches. The criteria for determining T2/FLAIR mismatch should be more precisely defined. Jain et al. (9) emphasized the necessity of abiding by two rules: 1) complete or almost completely homogeneous T2 hyperintensity of the tumor and 2) hypointense signal on T2-weighted FLAIR outside the hyperintense peripheral rim. Lee et al. (15) suggested grading for T2/FLAIR mismatch as follows: positive T2/FLAIR mismatch sign, equivocal and negative T2/FLAIR mismatch sign. This grading may increase the interrater agreement of the T2/FLAIR mismatch.

The underlying mechanism for the T2/FLAIR mismatch is not known. Patel et al. (8) referred to a previous study by Tay et al. (16) on protoplasmic astrocytomas and suggested that tumors exhibiting the T2/FLAIR mismatch may be a novel undefined molecular subgroup of astrocytomas. Since the studies in the literature are generally retrospective, detailed molecular analyses are not present. In the retrospective histopathological evaluation of the cases, we did not find any evidence of why T2/FLAIR mismatch occurred. Also, we only screened the cases for *IDH* mutation, *TERT* mutation and 1p/19q co-deletion molecularly. Since there is no unusual histopathologic finding among the oligodendroglioma cases with positive T2/FLAIR mismatch sign and the *IDH*-mutant astrocytomas with no T2/FLAIR mismatch sign, more detailed molecular analysis including whole exome sequencing studies would more accurately guide the questioning of how T2/FLAIR mismatch sign appears.

The T2/FLAIR mismatch sign was consistently seen in younger patients in our series. The reason for this may be that *IDH*-mutant grade II astrocytomas are more common in younger ages and T2/FLAIR mismatch sign is common in this tumor. In our series, T2/FLAIR mismatch positive cases were diagnosed 7 years before those who did not show T2/FLAIR mismatch. Besides, although the finding was found in over two-thirds of those younger than 30 years of age, T2/FLAIR mismatch was not observed in patients older than 60 years. In the studies of Juratlı et al. (12), the median age was 37 years for *IDH*-mutant astrocytomas, while it was 43 years for oligodendrogliomas and 54 years for *IDH*-wt astrocytomas. These findings were very similar to our results.

The gender difference is significant. T2/FLAIR mismatch sign is significantly more common in women than in men. T2/FLAIR mismatch was approximately 2 times more frequent in women than in men. This observation has not been reported in studies of either Patel et al. (8) or Broen et al. (11).

The majority of *IDH*-mutant astrocytomas and oligodendrogliomas were located in the frontal and temporal lobes (17, 18). Location of *IDH*-wt astrocytomas was different. These tumors tend to be localized to the temporal lobe. Fellah et al. (19) found that tumors with 1p/19q codeletion were predominantly located in the frontal lobe. They observed that other glial tumors with-

out this deletion were predominantly located in the temporal and insular regions. In our study, the results were similar.

Conventional MRI is used to detect cranial tumors. Most MRI protocols include T1-weighted, T2-weighted, FLAIR, and T1 sequences after gadolinium administration (20). Like these parameters, the T2/FLAIR mismatch sign is a morphological equivalent of tumor biology. Regardless of tumor grade (grade II/grade III), we found some differences in conventional MRI features between cases with and without T2/FLAIR mismatch. First, T2/FLAIR mismatch positive tumors were more homogeneous. Second, the enhancement of these tumors was significantly lower than T2/FLAIR mismatch negative ones. Contrast enhancement is historically thought to serve as a strong negative prognostic factor (21). Therefore, T2/FLAIR mismatch positive tumors can be expected to have a better prognosis. Juratlı et al. (12) reported that the contrast enhancement was significantly lower in the *IDH*-mutant group than in the *IDH*-wt group. However, the relationship between the T2/FLAIR mismatch finding and conventional MRI features is not well documented in the literature.

This study has some limitations. It is a retrospective study. Although the study has a large cohort from a single institution, the number of *IDH*-wt type tumors was relatively small. Atypical T2/FLAIR mismatch cases were considered negative. In fact, there were indeterminate cases that could not be assigned as T2/FLAIR mismatch positive or negative (Fig. 2). This may have caused the interrater agreement to be slightly lower than the other series. Moreover, 1.5T and 3T scanners and pulse sequences with different parameters were used in the study. However, scanner variability was also present in other studies in the literature.

In conclusion, T2/FLAIR mismatch appears to be an important MRI finding in distinguishing *IDH*-mutant astrocytomas from other DHGs. However, it should be kept in mind that T2/FLAIR mismatch findings can be seen in a minority of oligodendrogliomas besides *IDH*-mutant astrocytomas. T2/FLAIR mismatch sign can serve as a differentiating feature for machine learning studies of gliomas.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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