T2-FLAIR Mismatch Sign and Response to Radiotherapy in Diffuse Intrinsic Pontine Glioma

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Keywords

T2-FLAIR mismatch · Diffuse intrinsic pontine glioma · Diffuse midline glioma · Imaging marker · Pediatric brain tumors

Abstract

Purpose: The T2-fluid-attenuated inversion recovery (FLAIR) mismatch sign was previously reported as a diagnostic indicator of diffuse astrocytoma, isocitrate dehydrogenase-mutant, and 1p/19q noncodeletion. Subsequently, it was reported that the same findings were observed in diffuse intrinsic pontine glioma (DIPG). We investigated the clinical significance of T2-FLAIR mismatch sign in DIPG. **Methods:** Twenty-one patients with DIPG (Male: Female = 12:9) were treated at our institute between 2004 and 2019. All patients were treated with local radiotherapy of 54 Gy/30 fractions. The positive T2-FLAIR mismatch sign was defined if it fulfilled the following criteria: (1) T2-FLAIR mismatch volume was >50% of T2 high volume at nonenhanced area, (2) the FLAIR low lesion is not associated with gadolinium enhancement

(inside of enhancement or just outside of enhancement defined as edema), and (3) signal-intensity of FLAIR lowest lesion at tumor is lower than the normal cerebellar cortex. **Results:** In our patient series, T2-FLAIR mismatch sign was found in 5 out of 21 patients. Objective response rate of radiotherapy was 100% in patients positive for T2-FLAIR mismatch, while it was 25.0% in patients negative for T2-FLAIR mismatch, and this difference was statistically significant ($p < 0.01$, Fisher's exact test). In patients under the age of 18-years, T2-FLAIR mismatch positive had a slightly better prognosis ($p < 0.05$, Wilcoxon test). **Conclusion:** T2-FLAIR mismatch sign in DIPG may be an indicator for better response to radiotherapy and a better prognostic factor.

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Introduction

Diffuse intrinsic pontine glioma (DIPG) accounts for 10–15% of childhood brain tumors and up to 80% of pediatric brain-stem tumors [1]. Despite treatment efforts

using chemotherapy and radiotherapy, the median overall survival (OS) remains around 1 year from diagnosis and remains as one of the most difficult tumors to treat successfully. The management strategies other than local irradiation are ineffective, with the benefit of irradiation being transient at best [2]. The anatomic location and infiltrative nature of DIPG severely limit any opportunity for fruitful surgical resection to impact prognosis, and no effective chemotherapy has been reported to improve progression or OS [3, 4]. A previous study reported the long-term survivors of DIPG were aged <3 or >10 years and had long symptom duration, while the short-term survivors presented with symptoms of cranial nerve palsy and had ring enhancement, necrosis, and extrapontine extension on imaging [5]. However, these data do not help in decision-making for the initial treatment for DIPG.

The “T2-FLAIR (fluid-attenuated inversion recovery) mismatch sign” was recently reported as an imaging biomarker for diagnosis of diffuse glioma, isocitrate dehydrogenase (IDH)-mutant, and 1p/19q noncodeleted. Several studies demonstrated that the specificity of T2-FLAIR mismatch sign is high for diagnosis of diffuse astrocytoma with IDH-mutant genomic alteration [6]. However, the previous studies for T2-FLAIR mismatch were confirmed only among lower grade glioma, in other words, “diffuse astrocytic and oligodendroglial tumors” [7–10]. Subsequent studies demonstrated that this sign could be observed in other gliomas including diffuse midline glioma, H3 K27M mutant of the thalamus [11]. However, there has been no report about T2-FLAIR mismatch sign in DIPG. In this study, we focused on the clinical implication of T2-FLAIR mismatch sign observed in a subset of DIPG. We found that T2-FLAIR mismatch sign in DIPG is an indicator for better response to radiotherapy.

Materials and Methods

Patients Selection

Our institutional review board approved this retrospective study (IRB No. 2922/E-1650). To protect patient privacy, we removed all identifiers from our records upon completion of the analyses. Between 2004 and 2019, 21 patients with DIPG (12 male and 9 females) were treated at our institute. We excluded the patients with diffuse midline glioma, H3 K27M-mutant at thalamus, because age, clinical characteristics, surgical intervention and prognosis of diffuse midline glioma at thalamus are much different from DIPG, even though the genetic pathway reportedly resembles the histone 3 mutation.

The patients' age of DIPG ranged from 3 to 36 (median 6) years. The number of patients <18 years was 18 (age range 3–17,

median 6 years). All patients underwent MRI study which included nonenhanced T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), FLAIR, diffusion-weighted imaging, and gadolinium-enhanced T1WI with slice thickness 7 mm or less, at least every 2 months until recurrence. Recurrence was defined as imaging progression with or without symptomatic progression. All patients were treated with local radiotherapy of 54 Gy/30 fractions after the imaging diagnosis of DIPG. The details about day of onset, confirmation of diagnosis (MR examination date for diagnosis), and death were obtained from medical records. The progression-free survival and the OS were calculated by using the date of diagnosis.

MR Acquisition and Evaluation

MR scans were acquired at 1.5 or 3.0 T scanners and assessed by 2 independent authors (S.O. and F.Y.). Investigators evaluated the T1WI, T2WI, FLAIR, and post-contrast T1WI sequencing of each patient. In this study, the positive T2-FLAIR mismatch sign was defined if it fulfilled the following criteria: (1) T2-FLAIR mismatch volume was >50% of T2 high volume at nonenhanced area, (2) the lesion of FLAIR low is not associated with gadolinium enhancement (inside of enhancement or just outside of enhancement defined as edema), and (3) signal-intensity of FLAIR lowest lesion at tumor is lower than the normal cerebellar cortex and not the white matter. The cutoff point of 50% about T2-FLAIR mismatch volume was defined based on the previous report [8]. On visual inspection, the FLAIR low is highly affected by the surrounding tissue intensity, and therefore, we strictly calculated the intensity of the tumor lesions. Both investigators independently assessed (i) presence or absence of the T2-FLAIR mismatch sign and (ii) presence or absence of gadolinium contrast enhancement. We also defined the areas of visually lower intensity of tumor and intensity of normal-appearing cerebellar cortex on FLAIR image by consensus and calculated the ratio.

Single-voxel proton MR spectroscopy (1H-MRS) was performed as described previously [12]. In brief, 1H-MRS was performed with the point-resolved spectroscopic method (PRESS; repetition time, 2,000 ms [3.0 T]; TE = 144 and 30 ms; data points, 2,048; signals acquired, 64 [3.0 T]; double-spin-echo sequence) on a 3.0 T superconducting system, versions 12 and 15 (Signa Excite HD 3.0 T or Ingenia CX 3.0 T R5.1.2); a circularly polarized head coil or Ds Head 32ch coil was used as described previously. Single-voxel spectroscopic examinations were guided using enhanced T1-weighted images. Under 3D control, the rectangular 1H-MRS voxel was placed on the gadolinium-enhanced tumor area if present. The relative SIs of choline, Cr, and N-acetyl aspartate were obtained by numeric integration of fitted signals.

The effect of radiotherapy on tumor was determined according to Response Assessment in Neuro-Oncology criteria as follows: complete response (complete disappearance), partial response (reduction by ≥50%), stable disease (size change <25%), and progressive disease (increase by ≥25%).

Statistical Analysis

Statistical analyses were performed with SPSS pro ver. 21.0. The relationship between response to irradiation and T2-FLAIR mismatch sign was evaluated by Fisher's exact test. The Kaplan-Meier analysis was used, and statistical significance was assessed using a log-rank test and Gehan-Breslow-Wilcoxon test; $p < 0.05$ was considered statistically significant.

Fig. 1. Kaplan-Meier survival curve of DIPG patients treated with local radiotherapy. **a** Under age of 18 years, T2-FLAIR mismatch positive patients showed better survival than T2-FLAIR mismatch negative patients ($p = 0.0352$, Gehan-Breslow-Wilcoxon test). **b** Lactate detection was significantly associated with poor prognosis in patients under 18 years ($p = 0.0002$ at log-rank test and $p = 0.0012$ at Gehan-Breslow-Wilcoxon test). DIPG, diffuse intrinsic pontine glioma; FLAIR, fluid-attenuated inversion recovery.

Results

Clinical course and imaging characteristics of patients with T2-FLAIR match and mismatch are summarized in Table 1. Five patients had the characteristics T2-FLAIR mismatch and the ratio was 23.8% (5/21) among all patients, and 27.8% (5/18) among patients under the age of 18 years. In pediatric patients, the age at onset of T2-FLAIR mismatch positive patients (mean 5.8 and median 5) was younger than those without T2-FLAIR mismatch (mean 8 and median 6). No adolescent and young adult (AYA) patients showed the characteristics of T2-FLAIR mismatch.

Table 1. Summary of patients with DIPG

Case No.	Age	Sex	T2WI/FLAIR mismatch	Tumor/cerebellar cortex ratio at FLAIR	Gadolinium enhancement	1H-MRS (TE = 144 ms)			1H-MRS (TE = 30 ms)			Lactate detection at 1H-MRS	Irradiation dose	Response to irradiation	Initial recurrence site	OS	Dead/alive
						NAA/Cr ratio	Cho/Cr ratio	Cho/NAA ratio	NAA/Cr ratio	Cho/Cr ratio	Cho/NAA ratio						
1	3	M	Positive	0.84	None	0.56	0.94	1.68	0.43	0.82	1.91	(-)	54 Gy	PR	Local	22.5	Dead
2	4	M	Positive	0.94	None	1.60	1.60	1.00	1.19	1.24	1.06	(-)	54 Gy	PR	Local	19.0	Dead
3	5	F	Positive	0.93	None	0.38	1.25	3.33	1.06	1.50	1.41	(-)	54 Gy	PR	Local	20.5	Dead
4	6	F	Positive	0.93	None	0.82	1.61	1.96	0.86	1.39	1.44	(+)	54 Gy	PR	Local	12.8	Dead
5	11	M	Positive	0.94	Faint	0.50	2.86	5.71	0.43	1.91	4.47	(-)	54 Gy	PR	Local	19.4	Dead
6	4	F	Negative	1.07	Positive	1.13	2.00	1.78	0.81	2.13	1.71	(+)	54 Gy	PR	Dissemination	6.0	Dead
7	4	M	Negative	1.13	Positive	0.54	1.99	3.71	2.35	2.77	1.18	(+)	54 Gy	PR	Dissemination	10.0	Dead
8	5	F	Negative	1.19	Positive	1.36	1.40	1.03	1.41	1.26	0.88	(+)	54 Gy	SD	Local	6.4	Dead
9	5	M	Negative	1.17	Positive	na	na	na	na	na	na	na	54 Gy	SD	Dissemination	25.1	Dead
10	6	M	Negative	1.42	Positive	1.08	5.39	4.92	na	na	na	(+)	54 Gy	SD	Dissemination	7.9	Dead
11	6	F	Negative	1.16	Positive	na	na	na	1.28	3.00	2.35	(+)	54 Gy	SD	Local	7.1	Dead
12	6	F	Negative	1.20	Faint	0.77	2.77	3.60	0.88	1.59	2.43	(+)	54 Gy	PD	Local	10.6	Dead
13	6	M	Negative	1.34	None	0.78	1.39	1.77	0.95	1.17	1.23	(+)	54 Gy	SD	Local	12.7	Dead
14	8	F	Negative	1.36	Positive	0.78	1.68	2.08	0.99	1.39	1.42	(+)	54 Gy	SD	Local	9.5	Dead
93	10	M	Negative	1.10	None	0.45	3.86	8.65	1.02	3.26	3.20	(+)	54 Gy	PR	Local	9.9	Dead
16	10	M	Negative	1.11	None	0.36	1.56	4.34	0.61	1.11	1.82	(+)	54 Gy	SD	Local	11.5	Dead
17	17	M	Negative	1.45	None	1.25	1.75	1.40	1.29	1.90	1.47	(-)	54 Gy	SD	Local	12.9	Dead
18	17	F	Negative	1.14	Faint	0.80	2.44	3.12	1.12	1.99	1.61	(-)	54 Gy	SD	Local	19.4	Dead
19	32	M	Negative	1.09	None	1.33	2.56	3.42	0.43	1.65	3.81	(+)	54 Gy	PR	Local	15.8	Dead
20	33	F	Negative	1.22	None	1.18	1.77	1.50	0.96	1.45	1.51	(-)	54 Gy	SD	Local	23.0	Dead
21	36	M	Negative	1.08	None	1.12	2.06	1.84	0.97	1.40	1.64	(-)	54 Gy	SD	Local	21.0	Dead

1H-MRS, single-voxel proton MR spectroscopy; NAA, N-acetyl aspartate; Cho, choline; PR, partial response; SD, stable disease; na, not applicable; Rec, recurrence; DIPG, diffuse intrinsic pontine glioma; OS, overall survival; FLAIR, fluid-attenuated inversion recovery; PD, progressive disease.

Fig. 2. Representative case of 5-year-old girl with T2-FLAIR mismatch sign in DIPG (case No. 3). Pre- (a–c) and post-RT (d–f) images. Axial T2WI (a, d), FLAIR images (b, e), and gadolinium-enhanced image (c, f) of a patient with DIPG. **a** T2WI demonstrates homogeneous high-intensity tumor throughout the lesion. **b** FLAIR image demonstrates lower intensity at majority of tumor

compared to cerebellar cortex. **c** Gadolinium enhanced T1WI demonstrates homogenous low-intensity tumor with no enhancement. **d–f** Tumor showed PR after irradiation. DIPG, diffuse intrinsic pontine glioma; FLAIR, fluid-attenuated inversion recovery; PR, partial response.

All patients underwent local radiotherapy of 54 Gy/30 fractions. Objective response rate of radiotherapy was 100% in patients positive for T2-FLAIR mismatch, while it was 25.0% in patients negative for T2-FLAIR mismatch, and this difference was statistically significant ($p = 0.0062$, Fisher's exact test). In patients under the age of 18 years, the statistical difference of objective response among T2-FLAIR mismatch positive patients was also statistically significant ($p = 0.0065$, Fisher's exact test). Other imaging characteristics including the cyst formation, gadolinium enhancement, and parameters of 1H-MRS were not associated with response to irradiation.

In patients under the age of 18 years, T2-FLAIR mismatch positive had a slightly better prognosis ($p = 0.0352$, Gehan-Breslow-Wilcoxon test, Fig. 1a), while, in the analysis of all patients, T2-FLAIR mismatch sign did not reach statistical significance as the AYA patients showed the tendency of better prognosis. All 5 T2-FLAIR mismatch positive tumors recurred at the original tumor site. We also evaluated the prognostic value of other parameters. Lactate detection was significantly associated with poor prognosis in both pediatric and AYA patients ($p < 0.0001$ at log-rank test and $p = 0.0002$ at Gehan-Breslow-Wilcoxon test) and under age of 18-year patients ($p = 0.0002$ at log-rank test

Fig. 3. Representative case of 6-year-old girl with T2-FLAIR mismatch sign in DIPG (case No. 4). Pre- (**a–c**) and post-RT (**d–f**) images. Axial T2WI (**a, d**), FLAIR images (**b, e**), and gadolinium-enhanced image (**c, f**) of a patient with DIPG. **a** T2WI demonstrates homogeneous high-intensity tumor throughout the lesion. **b** FLAIR image demon-

strates lower intensity at majority of tumor compared to cerebellar cortex. **c** Gadolinium enhanced T1WI demonstrates homogenous low-intensity tumor with partial faint enhancement. **d–f** Tumor showed PR after irradiation. DIPG, diffuse intrinsic pontine glioma; FLAIR, fluid-attenuated inversion recovery; PR, partial response.

and $p = 0.0012$ at Gehan-Breslow-Wilcoxon test, Fig. 1b).

We finally evaluated the relationship between T2-FLAIR mismatch sign and 1H-MRS parameters. The T2-FLAIR mismatch tumor showed the tendency of lower choline/Cr ratio. However, we could not find any statistical difference of 1H-MRS parameters between T2-FLAIR mismatch positive and negative patients. Representative cases with T2-FLAIR mismatch sign are shown in Figures 2 and 3. And representative cases without T2-FLAIR mismatch sign are shown in Figures 4 and 5.

Discussion

The typical imaging feature of DIPG is high intensity on T2WI and low to iso-intensity on T1WI, with nonde-limited tumor margins and engulfment of the basilar artery [13]. On FLAIR images, DIPGs usually appear homogeneously hyperintense [14]. However, there have been no reports that focused on FLAIR images. In this study, our results indicate that T2-FLAIR mismatch sign in DIPG could be a possible indicator for better response to radiotherapy. To our knowledge, this is the first report

Fig. 4. Representative case of 6-year-old boy without T2-FLAIR mismatch sign in DIPG (case No. 13). Pre- (a–c) and post-RT (d–f) images. Axial T2WI (a, d), FLAIR images (b, e), and gadolinium-enhanced image (c, f) of a patient with DIPG. **a** T2WI of pre-radiotherapy demonstrates homogeneous high-intensity tumor throughout the lesion. **b** FLAIR image of pre-radiotherapy demonstrates iso- to high intensity at tumor and the signal intensity is higher compared to cerebellar cortex. The ratio of visually lower

intensity inside the tumor and visually higher intensity at cerebellar cortex was 1.43 and confirmed that FLAIR intensity of tumor is higher than cerebellar cortex. **c** Gadolinium enhanced T1WI demonstrates homogenous low-intensity tumor with no enhancement. **d–f** Tumor showed no response after irradiation. DIPG, diffuse intrinsic pontine glioma; FLAIR, fluid-attenuated inversion recovery.

which showed that a subgroup of DIPG potentially has the merit with increased dose intensity of radiotherapy. Our data would be useful for the development of treatment strategy with radiotherapy for DIPG.

Radiotherapy is the only treatment that has shown benefit in the treatment of DIPG both for newly diagnosed and recurrence/refractory cases although it is essentially considered as palliative therapy [15]. Many clinical trials have been conducted over several decades for DIPG [1]. It included hyper-fractionated radiotherapy, hypo-fractionated radiotherapy, with or without, concur-

rent, concomitant chemotherapy, or chemotherapy immediately after radiotherapy. However, there are no reports that showed improved results in patients with DIPG and outcomes remained largely unchanged. The benefit of palliative re-irradiation for recurrent progressive DIPG was reported in both retrospective and recurrent settings [15–21]. However, re-irradiation further requires assessing the optimal dose, fractionation, the interval between upfront RT and re-irradiation, and the persistent period of symptom improvement. Moreover, the failure of the clinical trials with upfront irradiation dose-dense setting

Fig. 5. Representative case of 6-year-old boy without T2-FLAIR mismatch sign in DIPG (case No. 13). Pre- (**a–c**) and post-RT (**d–f**) images. Axial T2WI (**a, d**), FLAIR images (**b, e**), and gadolinium-enhanced image (**c, f**) of a patient with DIPG. **a** T2WI of pre-radiotherapy demonstrates homogeneous high-intensity tumor throughout the lesion. **b** FLAIR image of pre-radiotherapy demonstrates iso- to high intensity at tumor and the signal intensity is higher compared to cerebellar cortex. The ratio of visually lower

intensity inside the tumor and visually higher intensity at cerebellar cortex was 1.06 and confirmed that FLAIR intensity of tumor is higher than cerebellar cortex. **c** Gadolinium enhanced T1WI demonstrates homogenous low-intensity tumor with no enhancement. **d–f** Tumor showed no response after irradiation. DIPG, diffuse intrinsic pontine glioma; FLAIR, fluid-attenuated inversion recovery.

urges defining the real patients' subgroup that can benefit from increased irradiation dose.

Recent development in molecular analysis revealed that histone H3 (H3F3A and HIST1H3B/C) K27M mutations are frequent in DIPGs, which arise in the brainstem almost exclusively in children, and in pediatric high-grade gliomas of midline structures such as thalamus and cerebellum, while G34R/V histone H3 mutations occur in pediatric high-grade gliomas of the cerebral cortex [22, 23]. Another analysis showed that patients with H3.1 (HIST1H3B/C) K27M mutation were associated with a

better response to radiotherapy and had better OS compared to patients with H3.3 (H3F3A) K27M mutation [24]. These results are consistent with the reports that younger age at onset had a better outcome for children with diffuse pontine glioma [25]. These reports may be associated with our results that T2-FLAIR mismatch in DIPG developed at younger age than T2-FLAIR match.

T2-FLAIR mismatch sign has been described as good imaging biomarker for predicting diffuse astrocytoma, IDH-mutant in 2017 [6–10]. However, recent reports showed that this sign is not specific for diffuse astrocy-

toma, IDH-mutant, but observed in many other gliomas including pilomyxoid astrocytoma, oligodendroglioma with IDH mutant and 1p/19q codeleted, and low-grade astrocytoma harboring MYB rearrangement [11]. Diffuse midline glioma, H3 K27M-mutant at thalamus, was reported as one of the exceptions for this sign. Diffuse astrocytoma is of 2 subtypes: IDH-mutant subtype corresponding to T2-FLAIR mismatch and IDH-wild-type subtype corresponding to T2-FLAIR match. The T2-FLAIR mismatch tumor, IDH-mutant diffuse astrocytoma, obviously has good prognosis compared to T2-FLAIR match tumors. These facts may be consistent with our results in DIPG.

Our study has some limitations. First, we did not confirm the histological subtype in our patient series. Surgical intervention for DIPG should be avoided as much as possible in nonclinical trial setting and even in clinical trial setting because the prognosis of DIPG is extremely poor. Second, we did not consider the effect of chemotherapy. Third, our patient population is too small for definitive conclusion. Future larger prospective studies are necessary to confirm the clinical value of T2-FLAIR mismatch in DIPG.

Conclusion

T2-FLAIR mismatch sign in DIPG may be an indicator for better response to radiotherapy, and these patients may be a potential candidate to be treated with increased effective biological dose of radiotherapy.

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Statement of Ethics

This retrospective study was approved by our institutional review board approved this retrospective study (IRB No. 2922/E-1650). Patients' written informed consent was waived.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

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Author Contributions

Fumiyuki Yamasaki: the conception and design of the study and writing-original draft preparation. Ikuno Nishibuchi: investigation, writing-reviewing, and editing. Shuhei Karakawa: data curation. Yoko Kaichi: data curation, writing-reviewing, and editing. Manish Kolakshyapati: writing-reviewing and editing. Motoki Takano: data curation. Ushio Yonezawa: data curation. Nobuki Imano: data curation, writing-reviewing, and editing. Akira Taguchi: data curation. Maiko Shimomura: data curation. Maki Taniguchi: data curation. Shumpei Onishi: conceptualization and methodology. Satoshi Okada: supervision, writing-reviewing, and editing. Kaoru Kurisu: supervision. Kazuo Awai: supervision, writing-reviewing, and editing. Kazuhiko Sugiyama: supervision, writing-reviewing, and editing. Yasushi Nagata: supervision, writing-reviewing, and editing.

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