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Early detection of recurrent medulloblastoma: the critical role of diffusion-weighted imaging

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Abstract

Background: Imaging diagnosis of medulloblastoma recurrence relies heavily on identifying new contrast-enhancing lesions on surveillance imaging, with diffusion-weighted imaging (DWI) being used primarily for detection of complications. We propose that DWI is more sensitive in detecting distal and leptomeningeal recurrent medulloblastoma than T1-weighted postgadolinium imaging.

Methods: We identified 53 pediatric patients with medulloblastoma, 21 of whom developed definitive disease recurrence within the brain. MRI at diagnosis of recurrence and 6 months prior was evaluated for new lesions with reduced diffusion on DWI, contrast enhancement, size, and recurrence location.

Results: All recurrent medulloblastoma lesions demonstrated reduced diffusion. Apparent diffusion coefficient (ADC) measurements were statistically significantly lower ($P = .00001$) in recurrent lesions (mean=0.658, SD=0.072) as compared to contralateral normal region of interest (mean=0.923, SD=0.146). Sixteen patients (76.2%) with disease recurrence demonstrated contrast enhancement within the recurrent lesions. All 5 patients with nonenhancing recurrence demonstrated reduced diffusion, with a mean ADC of 0.695 ± 0.101 (normal=0.893 ± 0.100, $P = .0027$). While group 3 and group 4 molecular subtypes demonstrated distal recurrence more frequently, nonenhancing metastatic disease was found in all molecular subtypes.

Conclusion: Recurrent medulloblastoma lesions do not uniformly demonstrate contrast enhancement on MRI, but all demonstrate reduced diffusion. Our findings support that DWI is more sensitive than contrast enhancement for detection of medulloblastoma recurrence, particularly in cases of leptomeningeal nonenhancing disease and distal nonenhancing focal disease. As such, recurrent medulloblastoma can present as a reduced diffusion lesion in a patient with normal postgadolinium contrast MRI.

Key words

diffusion | DWI | leptomeningeal | medulloblastoma | metastasis

Medulloblastoma is the most common malignant pediatric tumor of the central nervous system and accounts for up to 38% of pediatric posterior fossa tumors.[1–3] Advances in multimodal therapy for treatment of medulloblastoma have led to 5-year overall survival rates of up to 85% for average-risk disease and up to 65% for high-risk disease.[4–8] On the other hand, up to 30% of patients with medulloblastoma experience recurrence, which is nearly uniformly fatal.[9,10] Previous studies, which focus on detection of gadolinium contrast-enhancing lesions,[11,12] have

supported that surveillance imaging does not necessarily result in improved overall survival.[9,10] This could be due to late detection of medulloblastoma, as a few studies showed that subependymal metastatic disease within the ventricles does not always show enhancement.[13,14] A role for diffusion-weighted imaging (DWI) was suggested in 1 patient from a case series that demonstrated suprasellar tumor recurrence that had reduced diffusion with no associated contrast enhancement.[15] In our cohort of patients with recurrent medulloblastoma, we show that for distant and leptomeningeal disease, DWI is more sensitive in detecting medulloblastoma recurrence than gadolinium contrast enhancement. We argue that in the current environment of novel therapies and targeted approaches, early detection of recurrence by DWI may allow us to provide earlier treatment for these patients and potentially improve survival for a historically dismal diagnosis.[16]

Medulloblastoma consists of 4 distinct molecular subtypes: WNT-activated, SHH-activated, group 3, and group 4. These subtypes have been reported to carry distinct imaging findings and anatomic locations.[17,18] A recent study investigating recurrence patterns of medulloblastoma found that molecular subtype of recurrent medulloblastoma remains constant from time of original diagnosis.[4] Additionally, local or disseminated recurrence appears to be largely driven by the tumor's molecular subtype.[4] For instance, SHH-activated medulloblastoma recurs mostly within the tumor resection bed, while groups 3 and 4 recur distally with metastatic disease.[4] Meanwhile, WNT-activated medulloblastoma recur very rarely, with only 3 cases of recurrence out of 203 total patients from a multi-institutional cohort analysis.[4] In this report, we analyze imaging features of recurrent medulloblastoma with a focus on detecting distant and leptomeningeal metastatic disease with DWI.

Materials and Methods

We performed a retrospective cohort analysis of patients at our institution with a new diagnosis of medulloblastoma between 2010 and 2016. Twenty-one patients with long-term follow-up developed disease recurrence seen as a progressively growing lesion on available MRI. Two patients with recurrence were excluded due to lack of available imaging for analysis. Two patients had exclusively bony metastatic disease and no intraparenchymal or leptomeningeal metastatic disease and were excluded from the study. This study was performed in compliance with Health Insurance Portability and Accountability Act regulations and approved by our Institutional Review Board.

All patients underwent MRI of the brain on either 1.5T or 3T clinical scanners using subtle variations of the following protocol: 3-plane localizer, axial T2-weighted (TR/TE 2500/80), 3D fluid-attenuated inversion recovery (FLAIR, TR/TE/TI 5500/136/2200), T1-weighted (TR/TE 10/4) with and without intravenous gadolinium contrast, and axial DWI (TR/TE 7000/60) sequences. All available imaging was reviewed, ranging from time of diagnosis to most recently available imaging. All imaging was reviewed by both a neuroradiology attending (S.C.) and neuroradiology fellows (M.S.A and Y.L.). Characteristics of recurrent lesions were recorded, including time to recurrence; location of recurrence (tumor bed, metastatic disease, mixed recurrence); lesion size; qualitative evaluation of lesion enhancement (none, trace, medium, high); signal on DWI and ADC; and quantitative ADC measurement (10^{-3} mm^2/sec). Tumor characteristics at time of diagnosis including tumor size, tumor location, enhancement, mass effect, multifocal appearance, DWI and ADC appearance, and quantitative ADC measurement were also recorded. Statistical analysis was performed using Stata (StataCorp LP, Texas, USA), which included *t* test comparison of means. The extent of resection was determined based on postoperative MRI at the institution that performed the operation. In patients with available preoperative and postoperative MRI, the extent of resection was confirmed based on noncontrast and postcontrast imaging. DWI sequence was not used to determine resection extent due to presence of immediate postsurgical changes. In 8 patients without preoperative imaging, extent of resection was obtained from clinical notes that used radiographic and surgical interpretation of resection cavity. All of the patients in our study had postsurgical surveillance imaging prior to detection of metastatic disease.

Results

We retrospectively reviewed 53 patients with diagnosis of medulloblastoma between 2010 and 2016. Twenty-one patients were identified to have medulloblastoma recurrence on follow-up surveillance imaging. A total of 21 patients were included in our final analysis. Time to recurrence ranged from 0.13 to 10.1 years and on average was 2.4 ± 2.3 years (median 2.15 years). Four of the patients died from their disease within a range of 1.1 to 11.1 years from time of surgery. Salvage therapy was variable and included high-dose chemotherapy, radiation therapy, and surgical resection. The initial tumor was located within the midline posterior fossa in 11 patients and within the cerebellar hemisphere in 2 patients. Eight patients did not have available preoperative imaging and location of the original tumor was not specified. Average volume of the original tumor was 38.1 ± 23.9 cm^3 and gross total resection was achieved in 16 patients. Subtotal resection was seen in 1 patient with metastatic disease at original diagnosis and another patient with a residual lesion. Three patients were found to have spinal metastases at diagnosis. Twelve of the patients had standard-risk medulloblastoma, 5 patients had high-risk medulloblastoma, and 4 patients were below the age of 3 years.

In our cohort, 2 patients had recurrence within the resection bed, 10 patients had distant metastases, and 9 patients demonstrated mixed metastatic disease (Table 1). No patient exhibited recurrence solely within the spine. Among 8 patients with non-WNT/non-SHH molecular subtype, 3 recurred with strictly distal disease, 1 recurred within the resection bed, and 4 patients had mixed disease (Fig. 1). Among 4 patients with SHH-activated tumors, 2 recurred with strictly distal disease, 1 recurred within the resection bed, and 1 patient had mixed disease. There were no

patients with WNT-activated recurrent medulloblastoma in our cohort.

Average tumor volume of metastatic lesions at time of recurrence was 897 mm^3 (range, 4 – 6188 mm^3). Recurrent tumor enhancement was found in 16 (76.2%) patients (Table 3). Classic pattern of medulloblastoma recurrence is shown in Fig. 1, with multiple nodular lesions located within the tumor resection bed demonstrating avid gadolinium contrast enhancement and reduced diffusion. The lesions are usually surrounded by edema with prominent associated FLAIR hyperintensity (Fig. 1).

Table 1 Characteristics of Patients With Medulloblastoma Recurrence

Patient Characteristics	
Number of patients with recurrence	21
Age at resection, years (range)	8.4 ± 5.7 (1.2 – 20.2)
Location of original tumor	
Midline	11
Cerebellar hemisphere	2
Unknown	8
Type of Resection	
Gross total resection	16
Subtotal resection	5
Time to recurrence, years (range)	2.4 ± 2.3 (0.13 – 10.1)
Location of recurrence	2 resection bed, 10 distant, 9 mixed

In all patients, medulloblastoma at initial diagnosis exhibited different degrees of contrast enhancement (Table 2). Among the midline tumors (n = 11), 5 had only mild enhancement, 5 had medium enhancement, and 1 had intense enhancement. Among the hemispheric tumors (n = 2), 1 patient had medium contrast enhancement and another had high intensity enhancement. All medulloblastomas at original diagnosis exhibited reduced diffusion with $ADC_{average}$ measuring 0.706 ± 0.106 (Table 3).

The majority of patients with nonenhancing disease at recurrence (5 patients, 23.8%) had distant lesions, including leptomeningeal recurrence (1 patient), subependymal nodular recurrence within a distal calcarine sulcus (1 patient), sylvian fissure nodule with concurrent resection bed recurrence (1 patient), and new subependymal nodule within the lateral ventricles (2 patients). In the patient with diffuse leptomeningeal recurrence within the folia of cerebellar hemispheres and vermis, the lesions were clearly visible on DWI and seen as hyperintense foci on FLAIR sequence. Interestingly, none of these lesions were seen on postcontrast T1-weighted imaging (Fig. 2). Nonenhancing leptomeningeal disease was also found in a patient with enhancing recurrent disease, while the leptomeningeal extent was not seen on contrast-enhanced images.

Nonenhancing metastatic medulloblastoma is also commonly found within either the sulci or within the subependymal portion of the ventricles. In 2 patients with distant recurrence within the calcarine sulcus and sylvian fissure, nodular recurrence was only seen on DWI and was not seen on postgadolinium T1-weighted imaging or FLAIR (Fig. 3). One of these patients had a lesion with reduced diffusion within the sylvian fissure and this lesion was

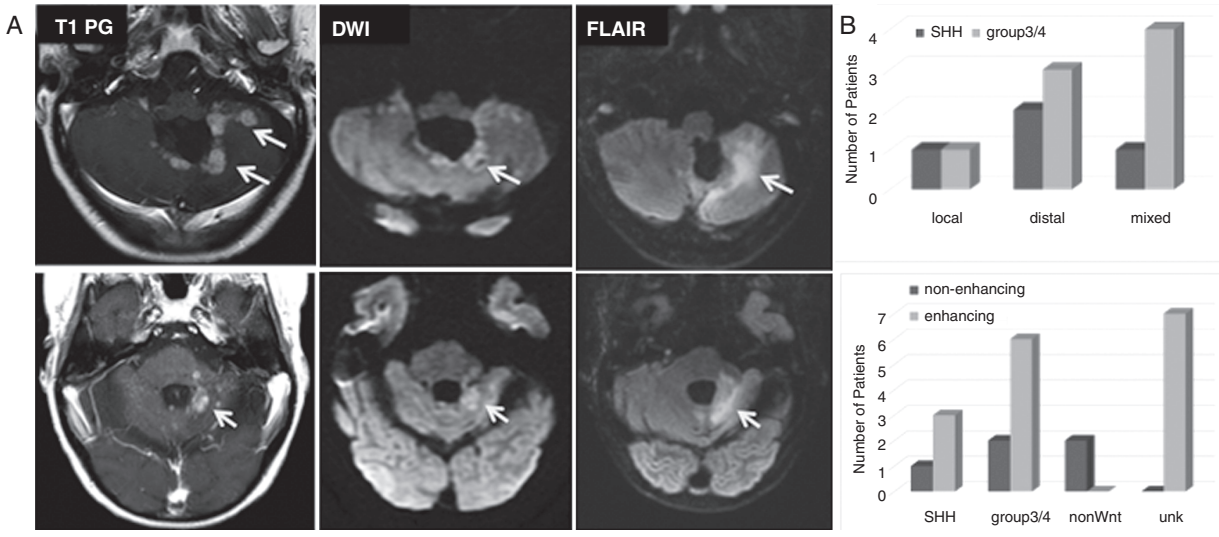

Fig. 1 21-year-old male with recurrent medulloblastoma demonstrates classic imaging pattern of recurrent medulloblastoma with nodular contrast enhancing lesions within tumor resection bed that demonstrate FLAIR hyperintensity and reduced diffusion (A). Characterization of recurrence patterns in SHH and non-WNT/non-SHH molecular subtype medulloblastoma, which were classified as 'local' recurrence located within the resection bed, 'distal' recurrence located distal to resection bed, and 'mixed' recurrence (combination of local and distal) (B). Abbreviations: T1 PG, T1-weighted postgadolinium; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery.

Table 2 Characteristics of the Original Tumor in Patients With Medulloblastoma Recurrence

Original tumor volume (mm^3)*	38 155 ± 23 988 (range, 18 076 – 98 280)
Enhancement	13/13
ADC (10^{-3} mm^2/s)**	0.706 ± 0.106 (range, 0.548–0.900)
Multifocal at presentation	1/21
Molecular subtype	8 non-WNT/non-SHH 4 SHH 2 non-WNT 7 not determined
Pathology	4 anaplastic 6 classic 4 nodular/desmoplastic 7 nonspecified***

*MRI of the initial lesion was available for 13 of the patients.
**10 of the original tumors had appropriate ADC maps for quantitative analysis.
*** Listed in pathology report as medulloblastoma without specification of molecular subtype.

Table 3 Characteristics of Metastatic Disease in Patients With Medulloblastoma Recurrence

	Metastatic Lesion
Metastatic lesion volume (mm^3)	897 ± 1458 (range, 4 – 6188)
Metastatic lesion enhancement	16/21 (76.2%)
Metastatic lesion reduced diffusion	21/21 (100%)
Metastatic lesion $ADC_{average}$	0.677 ± 0.092*
Contralateral ROI $ADC_{average}$	0.909 ± 0.154*

*ADC is measured in 10^{-3} mm^2/s units.
ADC, apparent diffusion coefficient; ROI, region of interest.

not seen on either FLAIR or postgadolinium T1-weighted imaging. In another patient, the disease recurred within the sylvian fissure with prominent reduced diffusion but no evidence of enhancement. Repeat imaging performed 2 months later demonstrated interval development of FLAIR hyperintensity within the metastatic lesion and interval increase in size of the lesion with the reduced diffusion. This lesion never demonstrated contrast enhancement (Fig. 3), but the patient was treated appropriately for recurrent disease based on the DWI results. There were 2 cases of nonenhancing disease recurrence within the subependymal surface of the left lateral ventricle (Fig. 4). This lesion was reduced on diffusion and had associated FLAIR hyperintensity on postgadolinium FLAIR imaging, but was not enhancing on postgadolinium T1-weighted imaging. Overall, nonenhancing medulloblastoma recurrences were identified within the subependymal surface of the lateral ventricles, distal nodularity within the sulci, and leptomeningeal disease.

Qualitative analysis of DWI and ADC maps showed reduced diffusion within all recurrent lesions (Fig. 1 and Table 3). ADC mean values were calculated using an isolated region of interest (ROI) within the recurrent lesion compared to a control ROI immediately anatomically contralateral to the lesion ROI. The $ADC_{average}$ measured within lesion ROIs was 0.677 ± 0.093 (Table 3). This was statistically significantly lower than the $ADC_{average}$ of 0.909 ± 0.154 for contralateral ROIs ($P = .00001$).

Discussion

Multimodal therapy with surgical resection, radiation therapy, and chemotherapy has significantly improved the treatment of medulloblastoma. Once therapy is complete, surveillance imaging typically occurs every 3 months during the first year after therapy and is slowly spaced out over time. Surveillance is most frequently done with MRI, including gadolinium contrast-enhanced images. In our study, we demonstrated that DWI was more sensitive at diagnosing recurrence than contrast enhancement. We also show that for optimal detection of distant or leptomeningeal spread of disease, DWI screening for metastatic disease should be the primary mode of diagnosis. Notably, our investigation identified that only 76.2% of patients with definitive medulloblastoma recurrence demonstrated gadolinium contrast enhancement on T1-weighted imaging within the recurrent lesion. On the other hand, 100% of recurrent lesions demonstrated reduced diffusion. In patients with nonenhancing recurrent medulloblastoma, a variety of metastatic spread patterns were noted, including local recurrence within the resection bed, distant metastatic spread, and distant leptomeningeal involvement. Leptomeningeal involvement was distinctly best seen on DWI as compared to other imaging sequences (Fig. 2).

Imaging diagnosis of recurrent medulloblastoma, local or distant, has traditionally relied on detection of new or growing contrast-enhancing lesion on MRI. DWI has primarily been used for detection of complications such as ischemia and confirmation of the lesion detected on contrast-enhanced imaging. In our current study, we recommend that DWI be used as a primary sequence for detection of medulloblastoma recurrence. DWI is an important sequence to aid diagnosis of pediatric tumors in the posterior fossa, by identifying highly cellular tumors such as medulloblastoma and differentiating them from less cellular tumors such as pilocytic astrocytoma.[19–21] Differentiation of medulloblastoma from ependymoma is not always simple on DWI as the ADC values do overlap in these tumors and they can both be located within the fourth ventricle.[20]

Our work agrees with preliminary reports in the literature that medulloblastoma recurrence can present as nonenhancing disease, most prominently within the subependymal surface of the ventricles. Although there are a few small studies on nonenhancing medulloblastoma recurrence, none of the studies demonstrated the essential role DWI plays in detecting these nonenhancing recurrences. One of the studies, performed using

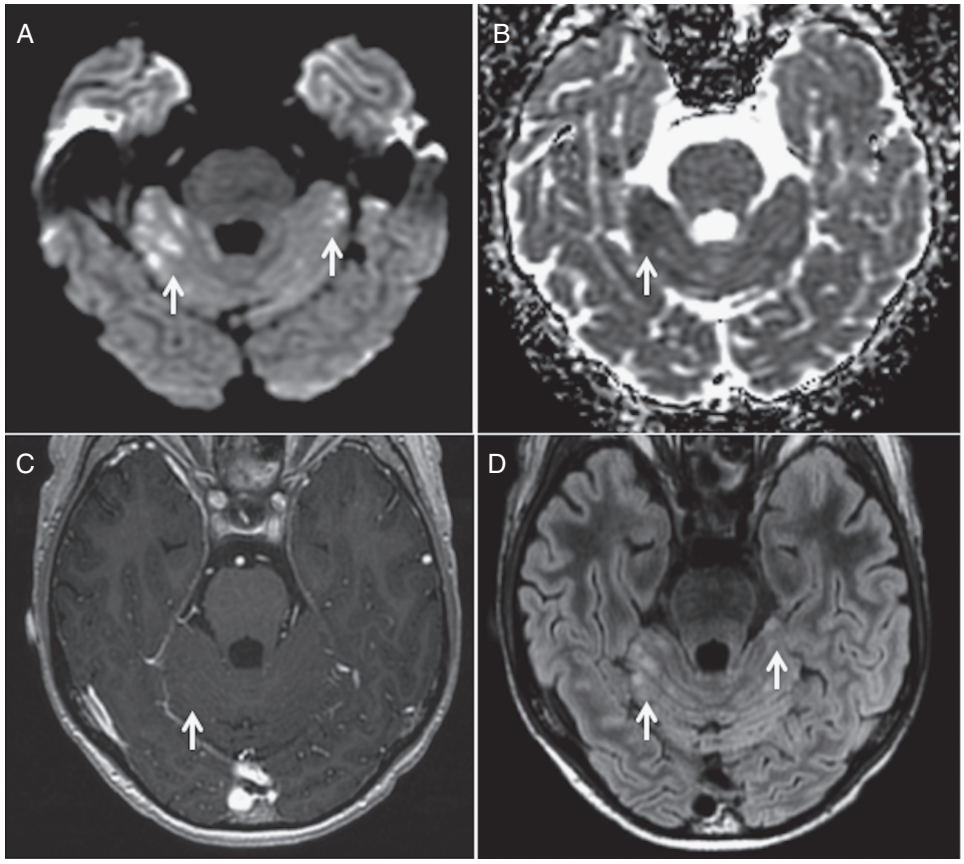

Fig. 2 A 21-year-old man with leptomeningeal recurrence of medulloblastoma visualized as reduced diffusion lesions on DWI (A) with corresponding decrease in ADC values (B). The leptomeningeal spread of disease was not enhancing after contrast administration (C), but did demonstrate FLAIR hyperintensity (D). Abbreviations: ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery.

0.35T MRI and Gad-DTPA contrast, showed that of 9 patients with recurrence, 3 patients did not demonstrate enhancement within intraventricular nodular metastases.[14,22] An additional study on 1.0T and 1.5T MRI demonstrated that among 19 patients with medulloblastoma recurrence, 2 patients had recurrence that did not demonstrate enhancement.[13] A study of 12 patients showed 100% sensitivity on DWI and only 55% sensitivity on contrast-enhanced imaging in detecting recurrent medulloblastoma.[23] One case series of 3 children suggested a role for DWI in detecting nonenhancing recurrent medulloblastoma in one of their patients and recommended further investigation into the role of DWI on detection of medulloblastoma recurrence.[15] Another study suggested the role of DWI in screening for metastatic disease in pediatric patients with CNS embryonal tumors.[24] This study included 16 patients with medulloblastoma, although subclassification based on molecular subtypes was not included. To the best of our knowledge, ours is the largest study to date that characterizes medulloblastoma recurrence on 3.0T and 1.5T MRI and is the first to demonstrate the role of DWI in detection of leptomeningeal disease that is not readily visible on contrast-enhanced images. Our study suggests that earlier detection of nonenhancing distant disease with DWI could potentially lead to earlier treatment intervention and better overall outcomes.

One of the limitations of our study is that we did not evaluate the role of DWI in detecting metastatic disease within the spine. Many patients with recurrent medulloblastoma present with metastatic disease to the spine, but DWI is not a standard sequence for spine imaging in majority of institutions because of the technical difficulty of implementation (Supplemental Fig. 1). Field inhomogeneity around the spinal cord affects the quality of images and DWI is usually added as a troubleshooting sequence to specific cases. It will be important to investigate the role of DWI in detecting metastatic disease to the spine as part of surveillance screening. Another limitation of our study is that 8 of our patients did not have preoperative imaging available for analysis. In these patients, 6 had recurrent disease that was enhancing and 2 had nonenhancing recurrent disease. As these patients could have had a nonenhancing primary tumor, this would suggest to the neuroradiologist to search carefully for nonenhancing recurrent disease.

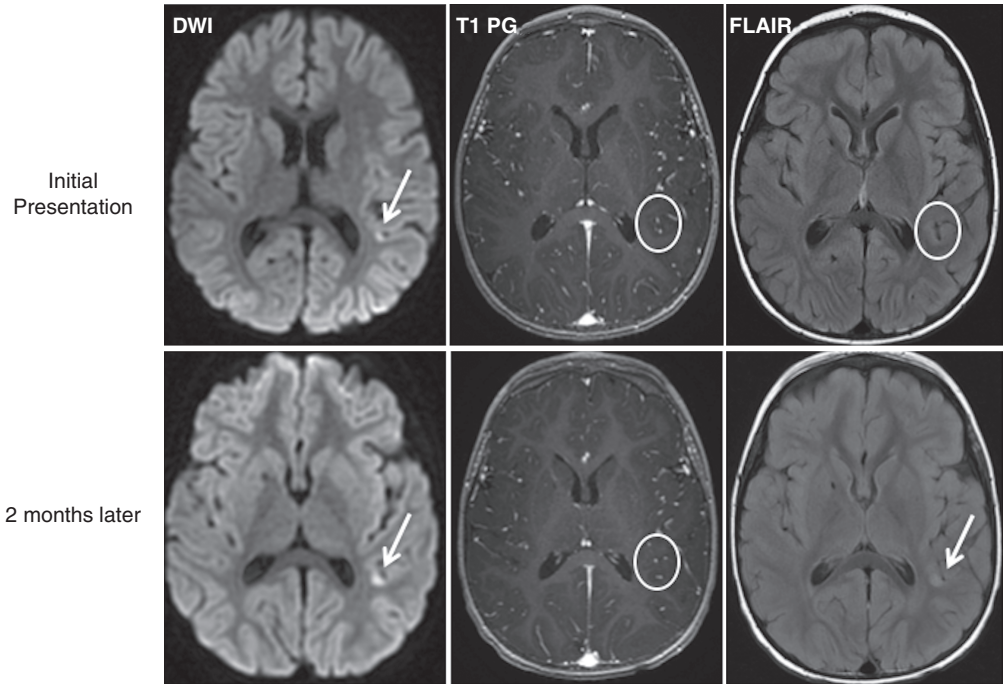

Fig. 3 A 4-year-old boy with nonenhancing medulloblastoma recurrence demonstrating reduced diffusion within the lesion. At initial presentation, the focus of reduced diffusion was not associated with contrast enhancement or FLAIR signal. On 2-month follow-up imaging, the lesion increased in size and demonstrated new FLAIR hyperintense signal. Enhancement of the lesion was not visualized on follow-up imaging. DWI, diffusion-weighted imaging; T1 PG, T1-weighted imaging postgadolinium; FLAIR, fluid-attenuated inversion recovery.

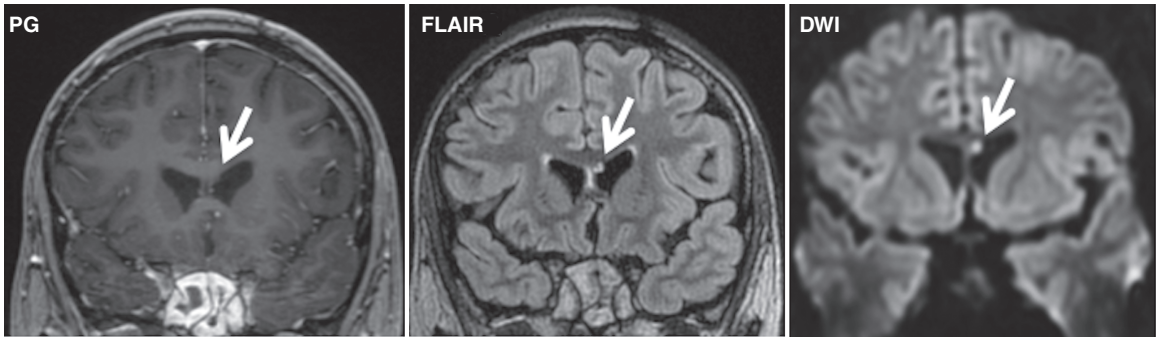

Fig. 4 A 15-year-old boy with nonenhancing medulloblastoma recurrence shows prominent reduced diffusion within the subependymal nodule that also has increased signal on FLAIR. Abbreviations: PG, T1-weighted postgadolinum; FLAIR, fluid-attenuated inversion recovery; DWI, diffusion-weighted imaging.

Considering the dismal outcomes in patients with recurrent medulloblastoma, we recommend using DWI for diagnosis of early medulloblastoma recurrence and having high suspicion for lesions that demonstrate reduced diffusion without evidence of contrast enhancement.

Supplementary Material

Supplementary material are available at *Neuro-Oncology Practice* online.

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Conflict of interest statement

Mariam S Aboian – no conflict of interest
Cassie N Kline – no conflict of interest
Yi Li – no conflict of interest
David A Solomon – no conflict of interest
Erin Felton - no conflict of interest
Anu Banerjee – no conflict of interest
Steve Braunstein – no conflict of interest
Sabine Mueller – no conflict of interest
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Soonmee Cha – no conflict of interest

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