

Correlation between MRI characteristics of medulloblastoma with histopathological subtypes and 2-year survival

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Abstract

Objectives: The objective of this study is to describe the imaging features of medulloblastoma (MB) and correlate the MR characteristics with the different histological subtype of MB with 2-year survival. **Materials and Methods:** This is a retrospective descriptive study. A total of 29 patients diagnosed with MB from January 2005 to December 2015 were included in this study. The MRI brain and spine studies of these patients were retrieved and reviewed by a pediatric radiologist and a neuroradiologist independently, both blinded from the histological type of the MB. The HPE slides were also retrieved and reviewed by a pathologist. **Results:** 80% of desmoplastic MB showed the presence of intracranial leptomeningeal seeding and 57.1% of anaplastic MB showed the presence of necrosis. The presence of intracranial leptomeningeal seeding ($P = 0.002$) and necrosis ($P = 0.019$) was predictive of the histological subtypes. There is a significant correlation between the enhancement pattern and the 2-year outcome ($P = 0.03$) with 6 out of 8 patients whose tumors showed minimal enhancement having disease progression within 2 years. A significant correlation was also seen between the presence of necrosis with a poorer outcome ($P = 0.03$) and between the HPE subtype and 2-year outcome ($P = 0.03$) with anaplastic MB having the poorest prognosis. **Conclusion:** MR imaging features of intracranial leptomeningeal seeding and the presence of necrosis were correlated with a specific histologic subtype of MB. The enhancement pattern as well as necrosis correlated with 2-year poorer outcome of the disease.

Key words: Medulloblastoma; MRI; survival

Introduction

Medulloblastoma (MB) is a malignant neuroepithelial tumor and is considered the most common malignant tumor of the posterior fossa in children (30%–40%). They are thought to arise from primitive cells of the external granular layer of

the cerebellum, which persists until the beginning of the second year of life.^[1]

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The World Health Organization (WHO), in the 2016 edition of *WHO Classification of Tumors of the Central Nervous System*, defines MB as a malignant, invasive embryonal neoplasm of the cerebellum with a tendency for CSF dissemination. MB are universally classified as grade IV because of their aggressive nature, with malignant cytologic features, rapid disease evolution, and a fatal outcome if not treated with multimodal therapies. These tumors were classified based on their histological subtypes that have been long-established: desmoplastic, MB with extensive nodularity, and large cell (LC) or anaplastic MB. Updated classification has been made based on genetic (molecular) subgroups of MB, namely, WNT-activated, SHH-activated, group 3 and group 4 MB.^[2]

MR imaging is performed in all patients with brain tumor and remains the primary method for diagnosis, surgical guidance, and surveillance of these tumors. MRI can be used as primary imaging technique in such patients prior to surgery, during the follow-up, and in postoperative phase.^[3]

Prior studies have shown that MBs present with heterogeneous imaging features, including location and enhancement patterns. These phenotypic radiologic features may reflect underlying differences in tumor biology.^[3]

Histopathology is an important prognostic factor, particularly in young children. The impact of histopathology was studied in a cohort of 260 children less than 5 years of age who were treated on national protocols in Europe and the United States. Even after accounting for stage (the presence of metastases, residual disease), patients with desmoplastic/nodular or desmoplastic with extensive nodularity had a significantly better event-free and overall survival compared with the classic form of MB on multivariate analysis. In contrast, those with large cell or anaplastic variants had a significantly poorer prognosis.^[4]

In our institution, MBs are not characterized into their molecular subgroups, but they are classified according to their histological characteristics (i.e., Classic, MB with extensive nodularity, Desmoplastic, and Anaplastic/Large cell). In this study, we hypothesized that distinct MR imaging features can predict the histopathological subtype of pediatric MB and whether these MRI features can predict and prognosticate the disease.^[5]

Materials and Methods

Ethical consideration

Ethical approval was obtained from the institution Research and Ethics Committee in January 2017 (project code: FF-2017-016). This is a retrospective descriptive study and informed consent was waived.

Subject and procedures

The study was conducted in the Radiology Department in a tertiary university hospital. The retrospective analysis was based on patient data collected from the Coding Unit, Health Information Department using a word search of “medulloblastoma.” MRI brain was performed using Siemens 1.5T with multiple sequences included: T1, T2, gradient echo sequence, FLAIR, and postcontrast sequences. Meanwhile, MRI spine included T1 T2, STIR, and postcontrast sequences, which was performed at the same setting or few days later depending on the clinical situation at that time.

Data collection and statistical analysis

The MRI brain and spine studies of these patients were retrieved and reviewed by a pediatric radiologist and a neuroradiologist independently, both blinded from the HPE. The HPE slides were also retrieved and reviewed by a pathologist.

The MR imaging features assessed included tumor location, enhancement pattern, cysts/cavities, hemorrhage/mineralization, tumor margin, necrosis as suggested by ring-enhancement on post-gadolinium images, intracranial or leptomeningeal seeding, and intraspinal drop metastases. Necrosis often has irregular and thicker margin with some heterogeneity within the lesion on T2 WI. Meanwhile, cysts have smoother margin with homogenous high T2 signal within it.

“Tumor location” was defined as midline vermin/fourth ventricle, cerebellar hemisphere, or cerebellar peduncle/cerebellopontine angle cistern (CP/CPA).

“Tumor margin” was characterized as ill-defined if >50% of the margin could not be distinguished from the surrounding cerebellar parenchyma on the basis of all imaging sequences. “Enhancement pattern” was defined as minimal/none if <10% was estimated to enhance, solid if >90% of the tumor volume was estimated to enhance, and heterogeneous if varying degrees of enhancement were seen in 10%–90% of the tumor volume on the basis of radiologists’ visual assessments. Low signal on 2D gradient recalled-echo was used to detect hemorrhage/mineralization.

A pathologist re-reviewed the histopathology slides and classified the histopathological examination (HPE) into four main HPE subtypes of classic MB, desmoplastic MB, MB with extensive nodularity, or large cell (LC) or anaplastic MB. The statistical analysis was performed using SPSS software package IBM version 25.

Results

A total of 29 patients with MRI brain imaging and histopathological results were included in the study.

Nineteen were male and 10 were female patients. The youngest patient was 3 months old and the oldest was 16 years old, with a mean age of 8.97 years. Out of the 29 subjects, twenty-two were Malay (75.9%), four Chinese (13.8%), two Indian (6.9%), and 1 (3.4%) was of Somalian (3.4%) ethnicities.

All these subjects underwent surgery with tissue samples sent for histopathological diagnosis, subsequently had chemotherapy and/or radiotherapy. Seventeen patients (58.6%) were diagnosed with Classic type MB, seven patients (24.1%) diagnosed with Anaplastic/Large Cell MB, and five patients (17.2%) diagnosed with Desmoplastic MB [Figure 1].

On 2-year follow-up, sixteen of the patients were disease/progression free (55.2%) and twelve had disease progression (41.4%) and one died (3.4%).

MR imaging correlation of histopathological subtypes

80% of desmoplastic MBs showed the presence of intracranial leptomeningeal seeding [Figure 2] and 57.1% of anaplastic MBs showed the presence of necrosis. The presence of intracranial leptomeningeal seeding ($P = 0.002$) and necrosis ($P = 0.019$) was predictive of the histological subtypes. A summary of the findings can be found in Table 1.

We also observed that the tumor does extend through the Luschka's foramina in 34.5% of case ($n = 10$) while 13.7% extend through both Luschka's and Magendie's foramen [Figure 2].

MR imaging correlation of 2-year outcome

There is a significant correlation between the enhancement pattern and the 2-year outcome ($P = 0.04$) with 6 out of 8 patients (75%) whose tumors showed minimal enhancement having disease progression within 2 years [Figure 3]. A summary of the findings can be found in Table 2.

There is also a significant correlation between the presence of necrosis with a poorer outcome ($P = 0.03$). Five out of six patients whose tumors had necrotic component had disease progression within the 2-year follow-up period.

We found no significant correlation between the outcome with location ($P = 0.653$), margin of tumor ($P = 0.198$), cysts/cavities ($P = 0.113$), hemorrhage/mineralization ($P = 0.321$), intracranial leptomeningeal seeding ($P = 0.436$), and intraspinal drop metastases ($P = 0.730$).

HPE correlation with 2-year outcome

There is a significant correlation between the HPE subtype and 2-year outcome with anaplastic MB having the poorest prognosis ($P = 0.03$); six out of seven patients (85.7%) had subsequent disease progression, as shown in Table 3.

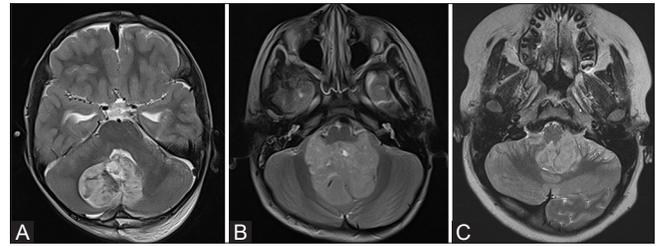


Figure 1 (A-C): Three different medulloblastoma subtypes. (A) Classic subtype (B) Anaplastic subtype (C) Desmoplastic subtype

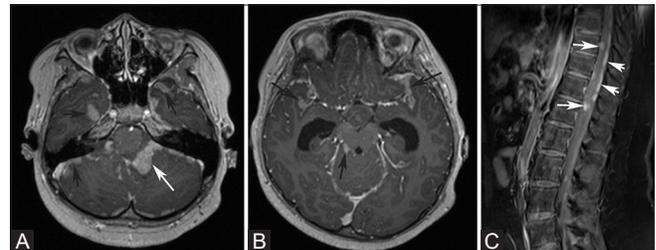


Figure 2 (A-C): 12-year-old boy with desmoplastic medulloblastoma. (A) Axial T1W post-gadolinium shows primary tumor extending into the left foramen of Lushka (white arrow) (B) Axial T1W post-gadolinium image taken at higher level shows multiple intracranial leptomeningeal metastases (black arrows) with intraspinal leptomeningeal metastases (white arrows) in (C) sagittal T1 post-gadolinium fat saturation

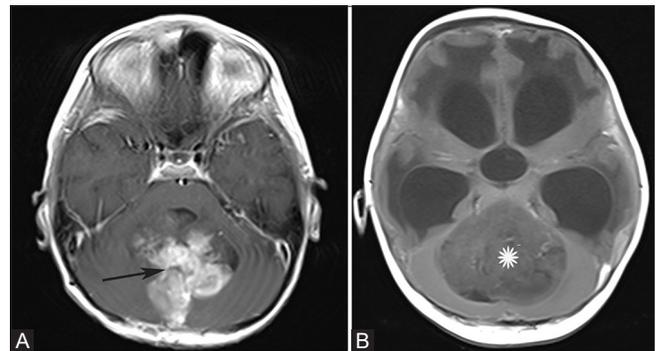


Figure 3 (A and B): Two different cases with variable pattern of enhancement. (A) Axial T1W post-gadolinium of an 8-year old with desmoplastic WHO grade IV medulloblastoma shows heterogenous enhancement of the fourth ventricle mass (black arrow). The child was well 5 years since the diagnosis. (B) Axial T1W post-gadolinium of a 3-month old shows the fourth ventricle mass with minimal enhancement (white asterisk). The child succumbed 2 months later while on chemotherapy after debulking surgery

Discussion

MBs occur in childhood and adolescence with a remarkable decrease in incidence at the second and third decades of life.^[6] In this study, patients age ranges between 3 months old to 16 years old with a mean age of 8.97 years. The incidence is higher in males with a male: female ratio of 1.5-2:1.^[6] In this study, a ratio of 1.9:11.9/1 was observed which is concordant with the previous studies.

Table 1: Summary of histologic subtype of medulloblastoma and the MRI features

	Classic (n=17)	Anaplastic/Large Cell (n=7)	Desmoplastic (n=5)	Total (n=29)	P
Tumor Location					
Midline	16 (94.2%)	6 (85.7%)	4 (80%)	26 (89.7%)	P=0.29
CP/CPA	0	1 (14.3%)	0	1 (3.4%)	
Cerebellar hemisphere	1 (5.8%)	0	1 (20%)	2 (6.9%)	
Margin					
Well-defined	10 (58.8%)	1 (14.3%)	4 (80%)	15 (51.7%)	P=0.053
Ill-defined	7 (41.2%)	6 (85.7%)	1 (20%)	14 (48.3%)	
Enhancements					
Minimal	3 (17.6%)	4 (57.1%)	1 (20%)	8 (27.6%)	P=0.313
Homogenous	4 (23.5%)	1 (14.3%)	2 (40%)	7 (24.1%)	
Heterogenous	10 (58.8%)	2 (28.6%)	2 (40%)	14 (48.3%)	
Characteristics					
Cyst/Cavities	13 (76.5%)	4 (57.1%)	3 (60%)	20 (69%)	P=0.579
Hemorrhage/Mineralization	12 (70.6%)	6 (85.7%)	4 (80%)	22 (75.9%)	P=0.713
Necrosis	1 (5.8%)	4 (57.1%)	1 (20%)	6 (20.7%)	P=0.019*
Intracranial leptomeningeal seeding	1 (5.8%)	4 (57.1%)	4 (80%)	9 (31.3%)	P=0.002*
Intraspinal drop metastases	3 (17.6%)	3 (42.9%)	2 (40%)	8 (27.6%)	P=0.360

*P<0.05

Table 2: Summary of 2-year clinical outcome and the MRI features of medulloblastoma

	Progression free (n=16)	Disease progression (n=13)	P
Location			
Midline	14 (87.4%)	12 (92.3%)	P=0.653
CP/CPA	1 (6.3%)	0	
Cerebellar Hemisphere	1 (6.3%)	1 (7.7%)	
Margin			
Well-defined	10 (62.5%)	5 (38.5%)	P=0.198
Ill-defined	6 (37.5%)	8 (61.5%)	
Enhancement			
Minimal	2 (12.5%)	6 (46.2%)	P=0.039*
Homogenous	3 (18.8%)	4 (30.8%)	
Heterogenous	11 (68.7%)	3 (23%)	
Characteristics			
Cyst/Cavities	13 (81.3%)	7 (53.8%)	P=0.113
Hemorrhage/Mineralization	11 (68.8%)	11 (84.6%)	P=0.321
Necrosis	1 (6.3%)	5 (38.5%)	P=0.033*
Intracranial leptomeningeal seeding	4 (25%)	5 (38.5%)	P=0.436
Intraspinal drop metastases	4 (25%)	4 (30.8%)	P=0.730

*P<0.05

Table 3: 2-year outcome of each histologic subtype of MB

	Outcome		Total
	Disease Free	Progression/Death	
HPE			
Classic	11	6	17
Anaplastic	1	6	7
Desmoplastic	4	1	5
Total	16	13	29

P<0.05 (0.03)

As noted by Robinson, while no single tumor feature should be used alone to determine tumor subtype or tailor treatment, MR imaging can offer additional

opportunities.^[7] Several studies have investigated the use of magnetic resonance imaging (MRI) as a means to differentiate histological subtypes.^[7]

The preferential site of this tumor is midline in the posterior fossa in 26 patients (89.7%). A more lateral involvement of the cerebellar peduncle/CP angle was found in 1 subject (3.4%) from the anaplastic MB group and 2 subjects (6.9%) with tumors centered in the cerebellar vermis.

Tumor extension through the fourth ventricle drainage foramina has been associated with ependymoma. However, MBs generally grow into and fill the fourth

ventricle and may extend through the Magendie's and Luschka's foraminae.^[6,8] This was also observed in our study in which 34.5% tumors extend through the Luschka's foramina [Figure 2] and 13.7% extend through both Luschka's and Magendie's foramen. These findings emphasize the necessity of including MB in the differential diagnosis of tumors affecting these foramina.

According to the previous literatures, MBs present heterogenous signal associated with the presence of cysts, necrosis, small blood vessels, and/or calcifications.^[1,2,7] We postulated this is because poor enhancement related to less neovascularization within the tumor, causing less concentration of chemotherapy that can reach the tumour. In view of the less effective chemotherapy target to the tumour, thus it causes poorer prognosis. Pattern of our results was very much concordance with the above-mentioned findings, where minimal enhancement of the tumor was observed in 27.6% cases, and homogenous enhancement in 24.1% cases, while the remaining 48.3% cases, there was heterogenous enhancement [Figure 3]. We have also observed that almost half of the MB cases that presented with minimal enhancement were associated with poorer outcome (46.2%) ($P = 0.039$).

In the present study, the presence of intracranial leptomeningeal seeding was found in 57.1% of cases in the anaplastic histological type, 80% of cases in the desmoplastic type, and 5% of cases in the classic type [Figure 3]. This is discordant with the previous literatures that concluded the presence of leptomeningeal spread was positively correlated with the anaplastic or large cell subtype and inversely correlated with the classic and desmoplastic subtype.^[2,7-9] This may be due to the small sample size and unequal distributions between the number of each histologic types in this study.

On the other hand, we found that the presence of intraspinal leptomeningeal seeding does not correlate with poorer outcome ($P = 0.730$), which may be attributed to similar reason.

Necrosis was observed in 20.1% of cases and it correlates with the anaplastic type, which also correlates with poorer outcome in which 83.3% of cases progressed. This is consistent with the previous literatures, whereby anaplastic/large cell MB has been associated with poorer outcome.^[10-12] We did not find a correlation between other MRI features with the histologic subtype of MB.

This study was limited by its retrospective nature. We were unable to retrieve some imaging studies specifically those done in other centers. In addition, some heterogeneity in imaging protocols reduced the sample size for some components of our analysis, excluding some of the patients who did not have imaging of the spine done in our center.

A larger sample size is needed for better evaluation of the correlation between MR features and histopathologic subtype of MB, as well as the 2-year outcome in order to obtain more concrete and statistically significant association.

Conclusion

MR imaging features of intracranial leptomeningeal seeding and the presence of necrosis were correlated with specific histologic subtype of MB. The enhancement pattern as well as necrosis correlated with the poorer 2-year outcome of the disease. This study supports an important step in using MR imaging as a surrogate to predict histologic subtype of MB. A study in larger group of sample size is needed to evaluate the risk of assessments of MRI characters in the future.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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