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The effect of semi-quantitative T1-perfusion parameters for the differentiation between pediatric medulloblastoma and ependymoma

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Abstract

Background: The differentiation between medulloblastomas and ependymomas plays an important role in treatment planning and prognosis for children. This study aims to investigate the role of T1-perfusion parameters during the differentiation between medulloblastomas and ependymomas in children. The institutional review board approved this prospective study. The brain magnetic resonance imaging (MRI) protocol, including axial T1-perfusion, was assessed in 26 patients, divided into a medulloblastoma group (group 1, $n = 22$) and an ependymoma group (group 2, $n = 4$). The quantified region of interest (ROI) values for tumors and the tumor to parenchyma ratios were collected and compared between the two groups. Receiver operating characteristic (ROC) curve analysis and the Youden index were utilized to identify the best cut-off, sensitivity, specificity, and area under the curve (AUC) values for the independent T1-perfusion parameters.

Results: The relative enhancement, maximum enhancement, maximum relative enhancement, time to peak, and AUC values for medulloblastomas were significantly higher than those for ependymomas ($p < 0.05$). Furthermore, the maximum enhancement and maximum relative enhancement for medulloblastoma to parenchyma ratios were also significantly higher than those for ependymomas. A cut-off maximum enhancement value of 100.25 was identified as sufficient to discriminate between medulloblastoma and ependymoma and resulted in a sensitivity of 90.9%, a specificity of 100%, and an AUC of 94.3%.

Conclusion: A cut-off maximum enhancement value of 100.25 derived from T1-perfusion was able to discriminate between medulloblastoma and ependymoma, with high sensitivity, specificity, and accuracy values.

Keywords: Medulloblastoma, Ependymoma, Magnetic resonance imaging, Semi-quantitative T1-perfusion

Background

Brain tumors are referred to as “intra-axial” when they are rooted in the brain parenchyma and are located above or below the tentorium and as “extra-axial” if the origin of the tumor is outside of the brain. In adults, supratentorial tumors are more common than infratentorial tumors, whereas infratentorial tumors represent the most common type of brain tumor found in children. Medulloblastoma, ependymoma, and pilocytic astrocytoma are the three most common infratentorial tumors found in children. Although the optimal treatment for these tumors is surgery, they require differential treatment planning and prognosis. Thus, the correct differential diagnosis of these tumors prior to surgery is necessary for developing the correct treatment strategies and achieving effective outcomes for patients [1, 2].

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Magnetic resonance imaging (MRI) is globally recognized as the best method for assessing brain tumors in children because it is noninvasive and does not expose the subject to radiation. Among the three most common pediatric posterior fossa brain tumors, medulloblastoma and ependymoma are predominantly solid tumors, whereas pilocytic astrocytoma is a predominantly cystic tumor. Unfortunately, solid medulloblastoma and ependymoma have similar imaging characteristics, despite differences in treatments and prognosis. Therefore, the ability to distinguish between these two types of tumors preoperatively is critical in clinical practice [3–6].

Several studies have utilized MRI to distinguish between medulloblastoma and ependymoma. However, the results of some studies have shown several overlapping imaging characteristics between these two tumor types; therefore, differentiating between medulloblastoma and ependymoma remains an ongoing concern that is currently being studied [7–13].

Perfusion MRI is an advanced method for investigating the perfusion of a region of interest (ROI) in diseases, such as cancers and cerebral infarctions. Information regarding tissue perfusion information is also an important parameter that is considered during differential diagnosis and when developing a treatment strategy and prognosis. Most of the previous studies have used T2*-perfusion to assess and distinguish among different types of brain tumors in children. In contrast, few studies have utilized T1-weighted (T1W) perfusion to distinguish between medulloblastoma and ependymoma [8, 14, 15].

Aim

This study aimed to assess the use of semi-quantitative T1W perfusion parameters during the differentiation between pediatric medulloblastoma and ependymoma.

Methods

The Institutional Review Board of Children's Hospital 02 approved this prospective study. Informed consent was received from all patients' legal representatives before the MRI procedure was performed. Inclusion criteria were (1) between February 2019 and December 2019, (2) age less than 16 years, (3) preoperative MRI with T1-perfusion, (4) operated only at our institution, and (5) histological diagnosis of medulloblastoma and ependymoma. Exclusion criteria included (1) other tumor than medulloblastoma and ependymoma, (2) prior surgical treatment at a different institution, and (3) previous treatment such as biopsy, stereotactic biopsy, and/or radiotherapy.

Anesthesia procedure

In this study, all patients were fasted at least 6 h prior to adopting anesthesia. The induction of anesthesia was performed by the injection of midazolam intravenously (5 mg/1 ml), at a dose of 0.1 mg/kg (Hameln Pharm GmbH, Germany), followed by 1% propofol, an intravenous anesthetic (10 mg/1 ml), at a dose of 3 mg/kg (Fresofol, Fresenius Kabi GmbH, Austria).

MRI procedure

Pediatric patients were scanned with a 1.5 Tesla MRI machine (Multiva, Philips, Best, The Netherlands). All patients were studied using T1-perfusion, with the following detailed parameters: repetition time (TR), shortest; echo time (TE), shortest; flip angle, 8°; slice thickness, 5 mm; gap, 0 mm; field of view, 220 mm × 183 mm; matrix, 140 mm × 115 mm; plane, axial; number of acquisition, 1; dynamics, 30 phases, with macrocyclic gadolinium-based contrast enhancement, using 0.1 ml/kg Gadovist (Bayer, Germany) or 0.2 ml/kg Dotarem (Guerbet, France); and duration, 3.09 min. The perfusion map was automatically derived from the T1-perfusion scan by utilizing the MR T1 perfusion analysis tool available in Philips Intellispace Portal, version 11.

Investigative parameters

Quantification of the perfusion map parameters was performed by establishing ROIs on the tumor and the parenchyma region. The software automatically calculates the following indicators: relative enhancement (%), maximum enhancement, maximum relative enhancement (%), time to peak (s), wash-in rate (s^{-1}), wash-out rate (s^{-1}), and area under the curve (AUC). The tumors to parenchyma ratios were calculated as the rations between each tumoral perfusion-weighted imaging (PWI) parameter and the matching parenchymal PWI parameter, based on the index from the perfusion map (Figs. 1 and 2).

The T1-perfusion was analyzed by two radiologists who have worked in the field of diagnostic imaging for over 10 years. All radiologists have a practicing certificate and are trained in the field of magnetic resonance imaging of at least 6 years. For histopathological results, it is read by the chief physician of the Department of Histopathology of Children's Hospital 2 with 12-year experience. Histopathologist also has a practicing certificate and is trained in the field of brain tumor histopathology of at least 6 years.

Statistical analysis

The SPSS software, version 26 (IBM Corp, Armonk, New York, USA), was used to perform statistical analysis. Quantitative variables are presented as the median and interquartile range. We compared quantitative variables in this study using the Mann-Whitney *U* test. Receiver operating characteristic (ROC) curve analysis and the Youden index were used to assess the cut-off point, accuracy, sensitivity, and specificity of independent PWI parameters. Differences were considered to be significant when $p < 0.05$.

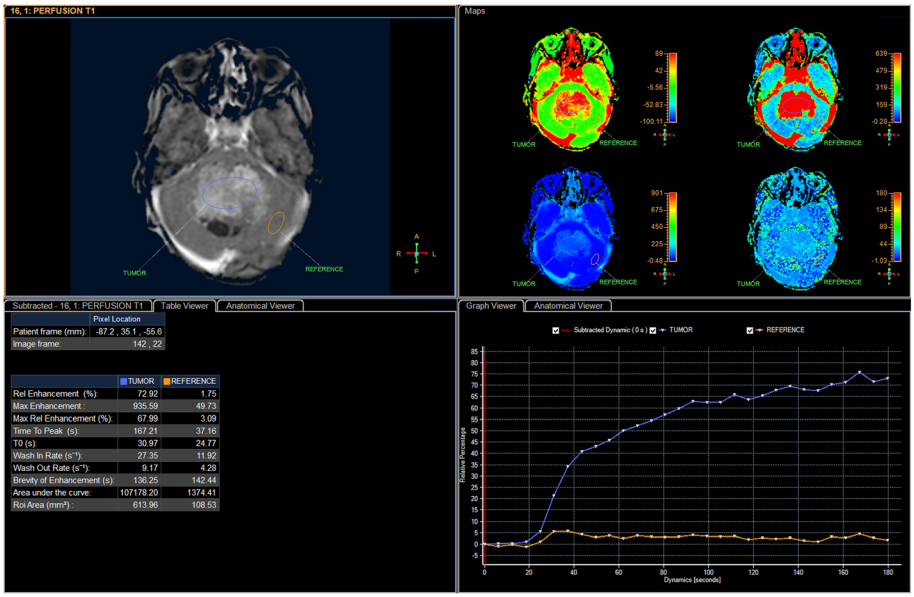

Fig. 1 A 4-year-old male patient with a tumor intra-fourth-ventricle, which was confirmed as medulloblastoma after surgery. A semi-quantitative perfusion MRI was analyzed by drawing ROIs within the area of the tumor and the area of the parenchyma, on one of the perfusion MRIs (upper left). The software automatically generated maps for each perfusion parameter (upper right) and the semi-quantitative perfusion MRI parameters (lower left). The time–signal intensity (SI) curve for the medulloblastoma is higher than that for the parenchyma (lower right)

Results

As shown in Table 1, the study comprised 26 children (median age = 7.5 years; male/female ratio = 17/9), including 22 with medulloblastoma (median age = 8 years; male/female ratio = 13/9) and four with ependymoma (median age = 3.5 years; all male).

Relative enhancement, maximum enhancement, maximum relative enhancement, time to peak, and AUC values for medulloblastomas were significantly higher than those for ependymomas ($p < 0.05$, Table 2). Furthermore, the tumors to parenchyma ratios for maximum enhancement and maximum relative enhancement

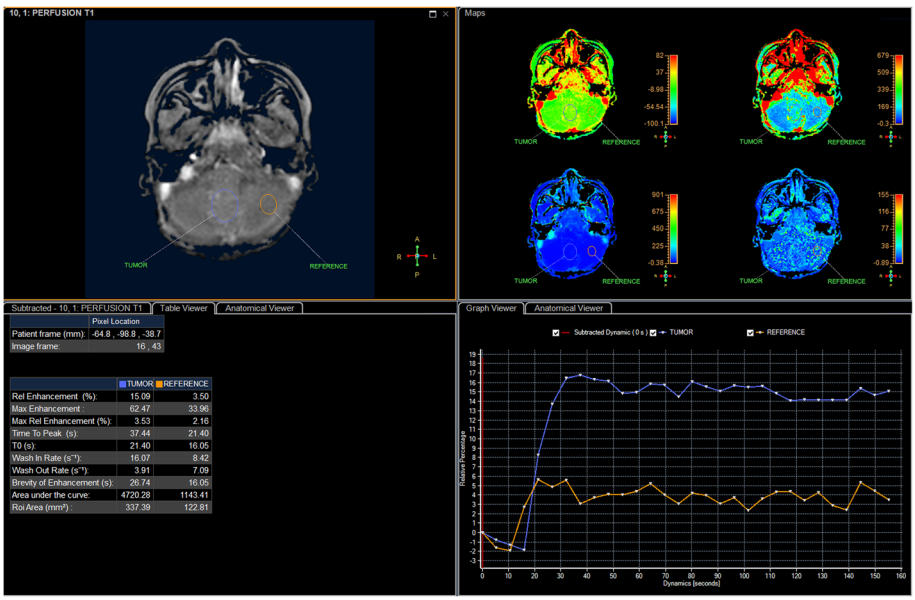

Fig. 2 A 3-year-old male patient had a tumor intra-fourth-ventricle, which was confirmed as ependymoma after surgery. A semi-quantitative perfusion MRI was analyzed by drawing ROIs within the area of the tumor and the parenchyma, on one of the perfusion MRIs (upper left). The software automatically generated maps for each perfusion parameter (upper right) and the semi-quantitative perfusion MRI parameters (lower left). The time–signal intensity (SI) curve for the ependymoma is higher than that for the parenchyma (lower right)

Table 1 Basic characteristics of population

Parameters	***n*** (%)
Gender	
Male	17 (65.4)
Female	9 (34.6)
Histopathology	
Medulloblastoma	22 (84.6)
Ependymoma	4 (15.4)

were significantly higher for medulloblastomas than for ependymomas ($p < 0.05$, Table 2).

A cut-off maximum enhancement value of 100.25 was able to distinguish between medulloblastomas and ependymomas, resulting in a sensitivity of 90.9%, a specificity of 100%, and an AUC of 94.3% (Table 3, Fig. 3).

Discussion

Tumoral neoangiogenesis is a crucial step during disease pathogenesis and refers to the formation of new vascular channels required to meet the increasing demands of tumoral growth. Tumors have increased vascular demands, due to rapidly growing cells and persistent cell division. The new vessels supplement preexisting vessels to carry nutrients and oxygen to the tumors. High-grade malignant tumors are more likely to exhibit increased angiogenesis compared with low-grade tumors. Based on the current literature, medulloblastoma that could be rectangular, round, or wedge-shaped, primarily consists of small cells, with minimal cytoplasm and homogeneous, dark nuclei. Medulloblastoma is a malignant tumor, characterized histologically by high cell density and rapid cell division, and is considered to be a grade-IV tumor, based on the World Health Organization (WHO) classification, which is the highest malignancy grade used to describe central nervous system tumors. Ependymomas, in contrast, are less cellular and well-circumscribed than medulloblastomas. The characteristic histology of ependymoma includes perivascular pseudorosettes and, occasionally, ependymal rosettes. Thus, the reduced cellular density, and the subsequent reduced demand for nutrients and oxygen, of ependymomas is reflected by a reduced level of tumor perfusion compared with medulloblastomas [4, 6, 14–23].

According to the ROC analysis performed on our subjects, the relative enhancement, maximum enhancement, maximum relative enhancement, time to peak, and AUC values and the tumor to parenchyma maximum enhancement ratio and maximum relative enhancement ratio represent very effective parameters for the differentiation between medulloblastoma and ependymoma, with AUCs greater than 80%. Among these parameters, a cut-off value of 100.25 for maximum enhancement returned the sensitivity value of 90.9%, with a specificity of 100%, and an AUC of 94.3%. The values for all of the parameters mentioned above were lower in the ependymoma group than in the medulloblastoma group. This finding is promising and suggests that the use of these parameters may become an excellent reference when attempting to distinguish between medulloblastoma and ependymoma in the future.

Table 2 Comparison of PWI parameters between medulloblastoma and ependymoma

	Medulloblastoma; ***n*** = 22	Ependymoma; ***n*** = 4	***p*** value
PWI			
Relative enhancement (%)	39.42 (44.79)	15.74 (20.02)	0.019[a]
Maximum enhancement	329.66 (704.32)	66.83 (50.69)	0.006[a]
Maximum relative enhancement (%)	11.13 (57.51)	4.43 (2.23)	0.013[a]
Time to peak (s)	164.87 (32.14)	84.57 (105.26)	0.016[a]
Wash-in rate (s^{-1})	18.10 (21.00)	19.20 (19.30)	0.776
Wash-out rate (s^{-1})	2.74 (6.24)	7.74 (6.95)	0.053
Area under the curve	10,577.78 (102,680.84)	1,421.12 (3,316.47)	0.023[a]
PWI ratios			
Relative enhancement ratio	13.62 (16.81)	6.90 (9.03)	0.065
Maximum enhancement ratio	9.00 (16.79)	1.65 (2.48)	0.016[a]
Maximum relative enhancement ratio	5.95 (20.71)	1.69 (1.77)	0.019[a]
Time to peak ratio	2.65 (2.98)	1.71 (2.08)	0.177
Wash-in rate ratio	1.71 (4.61)	2.36 (7.85)	0.722
Wash-out rate ratio	0.57 (1.03)	1.01 (0.96)	0.151
Area under the curve ratio	39.12 (151.34)	3.68 (19.14)	0.088

[a]Statistically significant

Table 3 ROC analysis of PWI parameters for the differential diagnosis between medulloblastoma and ependymoma

	Cut-off point	AUC	Sensitivity	Specificity	95% CI
PWI parameters					
Relative enhancement (%)	27.35	0.875	0.727	1.000	0.730–1.000
Maximum enhancement	100.25	0.943	0.909	1.000	0.853–1.000
Maximum relative enhancement (%)	7.26	0.898	0.773	1.000	0.770–1.000
Time to peak (s)	106.14	0.886	0.909	0.750	0.718–1.000
Area under the curve	1591.18	0.864	0.909	0.750	0.694–1.000
PWI ratios					
Maximum enhancement ratio	4.04	0.886	0.682	1.000	0.734–1.000
Maximum relative enhancement ratio (%)	3.37	0.875	0.727	1.000	0.726–1.000

Our study is in concordance with the results reported by previous studies that have examined neoangiogenesis. Yeom et al. [14] reported that in pediatric brain tumors, the relative cerebral blood flow was significantly increased in grades 3 and 4 tumors (1.78–2.14) compared with grades 1 and 2 tumors (0.29–0.60) ($p < 0.05$). They also reported that the relative cerebral blood flow index for medulloblastoma was significantly higher than that for pilocytic astrocytoma ($p < 0.05$). In addition, de Fatima et al. [15] reported that the relative cerebral blood volume for the low-grade tumor group was 1.4 ± 0.9, compared with the high-grade tumor group value of 3.3 ± 1.4 ($p < 0.05$). A relative cerebral blood volume value threshold of at least 1.33 generated a sensitivity of 100%, a specificity of 67%, a positive predictive value of 87%, and a negative predictive value of 100%. Koob and colleagues used T2*-perfusion values to differentiate among pediatric brain tumors and then used these values to classify the tumors into different grades. The results showed that the T2*-perfusion parameters had an accuracy of 38.51% for the classification of tumor type and an accuracy of 50.88% for the classification of tumor grade [8]. Thus, our findings are in agreement with these studies, with notable improvements in percentages.

The small sample size and the single-center study involvement of our study could be regarded as limitations. In addition, the number of recruited patients with ependymoma was relatively low. However, ependymoma has been shown to have a lower prevalence than medulloblastoma, in the literature. We recommend that further studies, using larger sample sizes and multicenter involvement, should be performed to validate our findings. Studies should also consider combining basic MRI tests with an advance T1-perfusion protocol to improve the

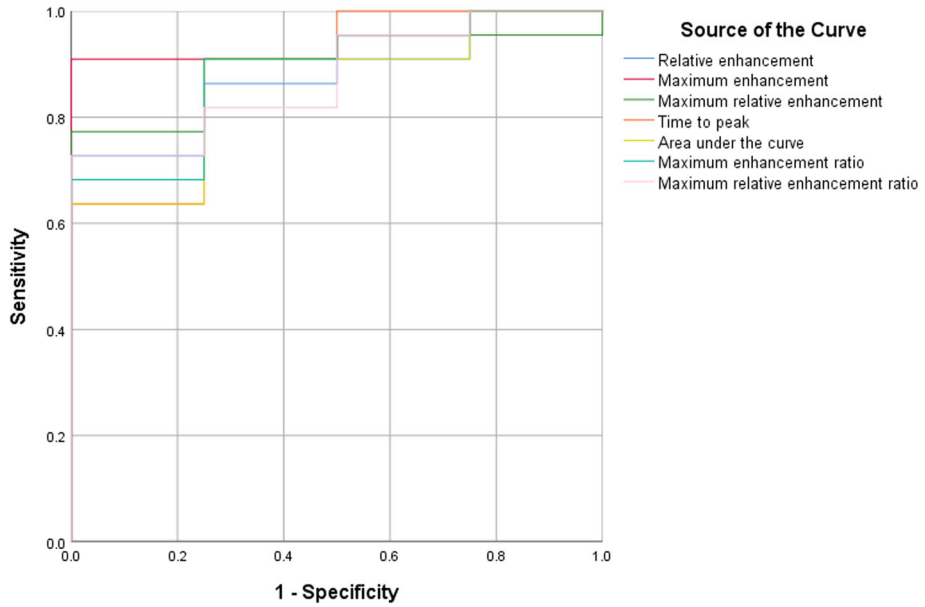

Fig. 3 The receiver operating characteristic (ROC) curves for relative enhancement, maximum enhancement, maximum relative enhancement, maximum relative enhancement, time to peak, area under the curve, maximum enhancement ratio, and maximum relative enhancement ratio

differentiation accuracy between pediatric medulloblastoma and ependymoma.

Conclusion

Our study suggests that the relative enhancement, maximum enhancement, maximum relative enhancement, time to peak, and AUC values for medulloblastomas, derived from T1-perfusion, could be used as important differentiating factors between pediatric medulloblastomas and ependymomas. Among these parameters, a cut-off value of 100.25 for maximum enhancement was able to predict the diagnosis of medulloblastoma with the highest sensitivity, specificity, and accuracy values. Future studies with larger sample sizes should be performed to validate these findings.

Abbreviations

ROC: Receiver operating characteristic; AUC: Area under the curve; MRI: Magnetic resonance imaging; T1W: T1-weighted; WHO: World Health Organization

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Author's contributions

NMD carried out the conception and design of the study, acquisition of data, and analysis and interpretation of data. NMD prepared, drafted, and revised manuscript critically for important intellectual content. NMD gave final approval of the version to be published and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Ethics approval and consent to participate

The institutional review board of Children's Hospital 2 approved this prospective study (Ref: 352/NĐ2-CĐT). Written informed consent of patients was obtained.

Consent for publication

All patients included in this research gave written informed consent to publish the data contained within this study.

Competing interests

There are no conflicts of interest to declare.

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