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APPARENT DIFFUSION COEFFICIENT(ADC) OF PERITUMORAL TISSUE IN DIFFERENTIATION OF BRAIN METASTASES FROM GLIOMAS

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Peritumoral edema of high grade gliomas represents a combination of neoplastic cell infiltration and vasogenic edema, while peritumoral edema of intracranial metastases is purely vasogenic. The aim of this study was to examine whether ADC can be used as a noninvasive parameter to distinguish peritumoral brain tissue in metastases from peritumoral tissue in cerebral gliomas.

A prospective study involved 71 patients, 22 with histologically proven intracranial metastases and 49 with gliomas. All patients underwent conventional MRI and DWI up to 7 days before undergoing surgery. ADC values were obtained in three regions of interest within peritumoral brain tissue and compared with the histopathological findings.

The mean minimum ADC values in the peritumoral regions of low grade gliomas were significantly higher (< 0.001) than those of high grade gliomas. The mean minimum ADC values in the peritumoral regions of metastases were significantly higher than those in high grade gliomas. The ADC values of peritumoral brain tissue of lung carcinoma metastases (0.000947 ± 0.000043 mm^2/s), melanoma (0.000842 ± 0.000018 mm^2/s) and breast metastases (0.000783 ± 0.000048 mm^2/s) were significantly higher than the ADC values of peritumoral brain tissue of astrocytoma grade I (0.000775 ± 0.000013 mm^2/s), grade II (0.000411 ± 0.000005 mm^2/s), grade III (0.000121 ± 0.000004 mm^2/s) and glioblastoma multiforme (0.000076 ± 0.000011 mm^2/s).

The minimum ADC values of the peritumoral edema in brain metastases were significantly higher than those in gliomas. ADC values can provide additional diagnostic information for distinguishing gliomas from metastases.

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Key words: *brain imaging, brain metastases, diffusion-weighted imaging, cerebral gliomas*

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Introduction

Conventional Magnetic Resonance Imaging (MRI) often shows difficulties in the differentiation of glioblastomas from solitary brain metastases, as they both can demonstrate similar imaging characteristics and contrast-enhanced patterns. Preoperative distinction between these tumors is important for their surgical approach and therapeutic procedures, which could be completely different (1). Patients with glioblastomas are almost always treated by surgical resection, while patients with suspected brain metastases without a clinical history of systemic cancer should undergo a complex systemic staging to determine the site of primary carcinoma and evaluate other distant metastases before any surgical intervention or medical therapy (2]) Diffusion-weighted imaging (DWI) provides valuable information beyond just anatomy and structure of the brain tissue (3). Apparent diffusion coefficient (ADC) value is a quantitative parameter of DWI which reflects diffusion movements of water molecules in the brain tissue. The degree of restriction of water diffusion is correlated with tissue cellularity, medium viscosity and integrity of cell membranes (4).

The key for distinguishing gliomas from metastases can lie in detecting the changes within the peritumoral area – which is the area beyond the enhancing margin on postcontrast T1W imaging. Most of these tumors are surrounded by a T2W hyperintensity that has been named vasogenic edema (5). Local disruption of the blood-brain barrier increases capillary permeability and induces a pressure gradient from the vascular to the extracellular compartment that results in the retention of plasma fluid and protein in the extracellular space. In high grade gliomas, the T2W hyperintensity comprises not only

vasogenic edema but also infiltrating tumor cells outside of contrast enhancing lesions, whereas the T2W hyperintensity that surrounds brain metastases is purely vasogenic (6). Therefore, the aim of this study was to examine whether ADC can be used as a noninvasive parameter to distinguish peritumoral brain tissue in metastases from peritumoral tissue in cerebral gliomas.

Material and methods

Patients

This is a single-center retrospective study in which we retrospectively reviewed MR images of patients with cerebral gliomas and metastases. The study was approved by our Institutional Review Board. Written informed consent for this study was waived because of the retrospective nature of our clinically acquired data. All patients were referred for MR imaging by a single academic neurosurgical clinic in a period of five years.

Seventy-one patients (42 male, 29 female, mean age 52.8 ± 3.39) were involved in the study, including a group of 22 patients (12 male, 10 female, mean age 55.20 ± 10.37) with histologically proven intracranial metastases and 49 patients (30 male, 19 female, mean age 50.40 ± 12.53 years) with gliomas (Tables 1 and 2). All patients underwent conventional MRI and DWI up to seven days before surgical intervention at our institution. Histopathologic diagnosis was based on the World Health Organization (WHO) criteria using surgical specimens.

Of 71 patients, gliomas were diagnosed in 49 patients [30 males (71.4%) and 19 females (64.9%)]. According to the WHO classification, there were 4 (9.5%) patients with astrocytoma grade I, 12 (16.9%) patients with astrocytoma grade II, 13 (18.3%) patients with anaplastic astrocytoma and 20 (28.1%) patients with glioblastoma multiforme. Brain metastases were diagnosed in 22 patients (12 males and 10 females). Metastatic brain tumors included lung carcinoma in 5 (7%) patients, breast metastases in 5 (7%) patients, genital metastases in 3 (4.2%) patients, melanoma metastases in 4 (5.6%) patients, and mastases of unknown origin in 5 patients.

Imaging and data analysis

Whole-brain imaging was conducted on the same 1.5-T MR (Avanto, Siemens, Erlangen, Germany) with the standard protocol: sagital T1W, axial T1W, T2W, FLAIR, coronal T2W and postcontrast T1W. Intravenous gadolinium based contrast agent was administered in a dose of 0.1 mmol/kg of body weight. DWI was performed in the transverse plane with a single-shot gradient-echo echo-planar pulse sequence with next parameters: TR 3600, TE 99, b values of 0 and 1000, section thickness 5mm, intersection gap 10%, FOV 230, averages 3, concatenations 1, base resolution 128 and voxel size 1.8x1.85. The diffusion gradient was encoded in three orthogonal directions.

The ADC maps were calculated from isotropic DWI using software DP Tools. Two radiologists conducted the quantitative analysis by the use of three operator defined region-of-interest (ROI) measurements. Oval ROIs with diameters of 1cm were placed within peritumoral area. ADC values (avoiding calcifications and cystic or necrotic areas) were obtained as the mean of measurements from three ROIs within peritumoral brain tissue. ADC values were compared with the histopathologic findings after surgery, using the World Health Organization (WHO) criteria

None of the patients had begun corticosteroid treatment or radiation therapy, and none had previous brain biopsy at the time of MRI. Tumors with large calcifications, hemorrhages or both were excluded.

Statistical analysis

Data are shown as the arithmetic mean (Xsr), and a standard deviation (SD), the minimum values (min.), the maximum (max.) values and index structure (%). Comparison of the ADC values between patients with different histological diagnoses was performed by ANOVA and Bonferon's post hoc test. P values less than 0.05 were considered to indicate statistically significant differences. Comparison of the ADC values between peritumoral brain tissue with histopathological diagnosis and contralateral healthy brain tissue was performed by (Student t test - P). The statistical analysis of data was performed by using SPSS 10.0 software package.

Results

Demographic characteristics (age and sex) of patients and histopathologic diagnosis of brain gliomas and metastases are shown in Tables 1 and 2. The average age of patients with gliomas was 50.40 ± 12.53 years. The youngest patient was 19 and oldest 77 years old. Patients with glioblastoma multiforme (54.08 ± 2.83) and anaplastic astrocytomas were older than those with the astrocytoma grade I (49.00 ± 2.83) and astrocytoma grade II (39.80 ± 9.63). The average age of patients with metastases was 55.20 ± 10.37 years.

Data of ADC (mm^2/s) value in peritumoral brain tissue in comparison with histopathologic diagnosis are shown in Table 3 and Table 4. The ADC values in peritumoral edema showed statistical difference between different grades of gliomas ($p < 0.001$). There was a decrease in ADC values with increasing of glioma grade. ADC values in peritumoral edema were higher in the most benign astrocytoma Gr I (0.000755).

Peritumoral edema of the most malignant glioblastoma multiforme showed the lowest ADC values (0.000076). Peritumoral edema of brain metastases had significantly higher ADC values than that of gliomas (0.000750 vs. 0.000340) ($p < 0.05$). The ADC values of peritumoral brain tissue of lung meta-

stases (0.000947 ± 0.000043 mm^2/s), melanoma (0.000842 ± 0.000018 mm^2/s), metastases of unknown origin (0.000626 ± 0.000011) and breast metastases (0.000783 ± 0.000048 mm^2/s) were significantly higher than the ADC values of peritumoral brain tissue of astrocytoma grade I (0.000775 ± 0.000013 mm^2/s), grade II (0.000411 ± 0.000005 mm^2/s), grade III (0.000121 ± 0.000004 mm^2/s) and glioblastoma multiforme (0.000076 ± 0.000011 mm^2/s). There was no significant difference between peritumoral ADC values of Astocytoma Gr I and malilignant melanoma metastases.

Table 1. Histopathologic diagnosis and sex of examined patients

Histopathological diagnosis	Sex		Total
	Male	Female	
Astrocytomas grade I	4 (9.5 %)	-	4 (5.6%)
Astrocytomas grade II	6 (14.2%)	6 (31.5%)	12 (16.9%)
Anaplastic astrocytomas	8 (19%)	5 (26.3%)	13 (18.3%)
Glioblastoma multiforme	12 (28.5%)	8 (42.1%)	20 (28.1%)
Gliomas total	30 (71.4%)	19 (64.9%)	49 (69.1%)
Lung metastases	5 (11.9%)	-	5 (7%)
Breast metastases		5 (17.8%)	5 (7%)
Melanoma metastases	2 (4.7%)	2 (7.1%)	4 (5.6%)
Genital metastases	2 (4.7%)	1 (3.5%)	3 (4.2%)
Metastases of unknown origin	3 (7.1%)	2 (7.1%)	5 (7%)
Metastases total	12 (28.6%)	10 (35.2%)	22 (30.9%)

% - index of structure

Table 2. Histopathologic diagnosis and age of examined patients

Histopathologic diagnosis	Parameter				
	Xsr	SD	Med.	Min.	Max.
Astrocytomas grade I	49.00	2.83	49.00	47.00	51.00
Astrocytomas grade II	39.80	9.63	43.00	29.00	52.00
Anaplastic astrocytomas	52.00	19.56	61.00	24.00	72.00
Glioblastoma multiforme	54.08	9.59	55.00	38.00	77.00
Gliomas total	50.40	12.53	51.00	24.00	77.00
Lung metastases	52.50	6.36	52.50	48.00	57.00
Breast metastases	52.50	19.09	52.50	39.00	66.00
Melanoma metastases	51.00	0.00	51.00	51.00	51.00
Genital metastases	64.50	17.68	64.50	52.00	77.00
Metastases of unknown origin	55.50	3.54	55.50	53.00	58.00
Metastases total	55.20	10.37	52.50	39.00	77.00

Xsr – arithmetic mean; S – standard deviation: Min. – minimum value;
Max. – maximum value; M – mediana

Table 3. The value of ADC (mm2/s) in peritumoral brain tissue in comparison with histopathologic diagnosis

Histopathologic diagnosis	Parameter				
	Xsr	SD	Med.	Min.	Max.
Astrocytomas grade I	0.000755	0.000013	0.000761	0.000701	0.000789
Astrocytomas grade II	0.000411	0.000005	0.000640	0.000000	0.000992
Anaplastic astrocytomas	0.000121	0.000004	0.000000	0.000000	0.000604
Glioblastoma multiforme	0.000076	0.000011	0.000075	0.000071	0.000081
Gliomas total	0.000340	0.000009	0.000598	0.000000	0.000992
Lung metastases	0.000947	0.000043	0.000958	0.000892	0.000990
Breast metastases	0,000783	0.000048	0.000800	0.000694	0.000831
Melanoma metastases	0.000842	0.000018	0.000848	0.000815	0.000859
Genital metastases	0.000556	0.000011	0.000812	0.000000	0.000862
Metastases of unknown origin	0.000626	0.000019	0.000000	0.000000	0.000000
Metastases total	0.000750	0.000027	0.000815	0.000000	0.000990

Table 4. Comparison of the value of ADC (mm2/s) in peritumoral brain tissue between different histopathologica diagnoses (ANOVA and Bonferon's post hoc test - P)

Histopathologic diagnosis	Astrocytomas grade II	Astrocytomas grade II	Glioblastoma multiforme	Lung metastases	Brest metastases	Malignantmelanoma	Genital metastases	Unknown origin metastases
Astrocytomas grade I	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.9999	< 0.001	< 0.001
Astrocytomas grade II		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Anaplastic astrocytomas			< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Glioblastoma multiforme				< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Discussion

Our study revealed significant difference in ADC values between peritumoral edema of brain metastases and gliomas. The minimum ADC values of the peritumoral edema in brain metastases were significantly higher than those in gliomas. The present findings can provide additional diagnostic information for distinguishing gliomas from metastases.

Gliomas and intracranial metastases are the most common mass lesions in the brain and 6 % of patients with newly diagnosed invasive cancer are expected to develop subsequent brain metastases as a progression of their original cancer diagnosis (5). Primary tumors which tend to produce brain metastases are most often localized in the lungs, breast, skin (melanoma), genitourinary tract, colon, rectum and paranasal cavities (4).

On conventional MRI, high grade glioma and solitary metastatic brain tumor often display similar signal intensity characteristics and contrast enhancement patterns (5). DWI has important advantages as it does not require contrast medium, it is a very quick technique and it provides qualitative and quantitative information that can be not only helpful but also essential in the evaluation of tumors (4). In many cases, a biopsy is performed for histologic confirmation even if there is a history of a known primary malignancy (5). If it is possible to obtain these data with MRI examination, this non-invasive modality will become more important both in the determination of the biopsy-sampling area within

the tumor and in the planning of the future therapies (7).

Alongside with tumor detection and characterization, DWI is a potential means of valuating the response of tumors and adjacent areas of vasogenic edema to drugs treatment (7, 8). Additionaly, preoperative DWI distinction between glioma and metastases is important for their surgical approach and therapeutic procedures, which could be completely different [1].

As intratumoral heterogeneity may further complicate the selection of a voxel of interest, the peritumoral region may provide more reliable and reproducible results due to its relative homogeneity (1). Because of their infiltrative nature, peritumoral edema of high grade gliomas represents a combination of neoplastic cell infiltration and vasogenic edema (1, 5). Peritumoral edema of intracranial metastases is purely vasogenic (5), originating from increased extracellular water from the leakage of plasma fluid from altered tumor capillaries, but no tumor cells are present (1). Therefore, the key to distinguishing between these two entities appears to lie in detecting the changes within the peritumoral area, that is, the area beyond the enhancing margin on the imaging (5). It is believed that ADC can be an important diagnostic and prognostic biomarker which shows good negative correlation with cellularity and grade of tumor malignancy. The nest of aberrant tumours` cells, which shows the most aggressive biological behaviour, within heterogeneous tumors, correspond to the lower ADC values (9).

Published data on intracranial tumors indicate that high ADC values were attributable to low cellularity, necrosis or cysts, and lower values to dense, highly cellular tumor (10). ADC is a direct reflection of tumor cell density (11). The results of previous research suggest that ADC values correlate with tumor cellularity for gliomas (12). Some authors (13) have proposed the use of ADC maps in malignant gliomas to demonstrate the boundaries between areas of tumor tissue (with decreased ADC due to elevated cellularity) and peritumoral areas (with increased ADC due to the presence of vasogenic edema).

Miquelini et al. found differences in the ADC values of apparently normal peritumor white matter between glioblastomas and cerebral metastases. The minimum ADC value measured in the apparently normal peritumor white matter was higher for the glioblastomas than for the metastases (14).

Sinha et al. (15) found that in high grade tumors, ADC values in the enhancing tumor region were larger than those in the peritumoral edema region. The lower ADC in tumor tissue may reflect a decreased volume of extracellular space due to higher cell density and increased intracellular viscosity, with a subsequent restriction of water motion (13). Mean diffusivity values in T2W hyperintense regions of presumably noninfiltrating neoplasms (specifically, metastases) were significantly higher (198% of the normal value) than mean diffusivity values in hyperintense regions touching gliomas (158% of the normal value) (8). Previous studies have shown that tumoral ADC is not useful for distinguishing between glioblastomas and metastatic tumors (6). However, Krabbe et al. (16) and Chiang et al. (17) found that the ADC values of cerebral metastasis are significantly higher than those of high grade astrocytoma. On the other hand, several studies have shown that peritumoral ADC is useful for distinguishing between glioblastomas and metastatic tumors (18). Our findings are in accordance with the previously reported ones. The areas of peritumoral neoplastic cell infiltration could be distinguished from predominantly peritumoral edema only if abnormalities were located in the white matter aligned in the direction of the diffusion-weighted gradient, published by Tien et al. (19). Kono et al. (20) do not support the hypothesis that peritumoral neoplastic cell infiltration can be depicted by ADCs or ADC maps. We found that the minimum ADC value of peritumoral edema in glioblastomas was significantly lower than the one in metastases. This finding may be helpful for preoperative differentiation between glioblastomas and metastases. A higher minimum ADC value in the peritumoral regions of metastases suggests that there are higher intracellular and extracellular water fractions than in glioblastomas (5). We also found that the mean minimum ADC values in the peritumoral regions of low grade gliomas were significantly higher than those in high grade gliomas.

Well differentiated adenocarcinoma showed hypointensity similar to gray matter which is attributed to inherently low T2 and high water diffusion in tissues and, as a result, both structures exhibited reduction of signal intensity on DWI. Well differentiated adenocarcinomas showed significantly lower SI than poorly differentiated adenocarcinomas and other histologic types of tumors. Therefore, this research suggests that the degree of differentiation may be relevant in their SI on T2-weighted images. The well differentiated adenocarcinomas can be derived from the lung, ovary and uterus, while metastatic brain lesions originate from the colon, lung or breast (21).

Our study had one limitation. The number of patients with brain metastases included in the study was relatively small. Further research with a larger number of patients with different kinds of brain metastasis is needed to confirm our results.

Conclusion

DWI with calculation of ADC maps can be regarded as a reliable useful diagnostic tool, which can provide additional diagnostic information for distinguishing gliomas from metastases. The values of ADC are significantly higher within the peritumoral edema surrounding brain metastases than in gliomas. Further research with a larger number of patients with different kind of brain metastasis is needed to confirm our results.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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"APPARENT DIFFUSION COEFFICIENT-(ADC)" PERITUMORSKOG TKIVA KAO DIFERENCIJALNO DIJAGNOSTIČKI MARKER MOŽDANIH METASTAZA U ODNOSU NA GLIOME

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Peritumorski edem kod visokogradusnih glioma predstavlja kombinaciju tumorske infiltracije i vazogenog edema, dok je peritumorski edem kod intrakranijalnih metastaza čisto vazogenog porekla.

Cilj ove studije bio je da ispita da li ADC može biti korišćen kao neinvazivni parametar u diferencijaciji peritumorskog edema moždanog tkiva kod metastatskih promena i kod cerebralnih glioma.

U ovoj prospektivnoj studiji analiziran je 71 bolesnik, 22 sa histoloski potvrđenim intrakranijalnim metastazama i 49 sa gliomima. Svi bolesnici su podvrgnuti konvencionalnom MRI i DWI sedam dana pre neurohirurške intervencije. ADC vrednosti su dobijene u tri regiona od interesa u okviru peritumorskog moždanog tkiva i upoređivane sa histopatoloskim nalazima.

Prosečne minimalne vrednosti ADC u peritumorskom tkivu niskogradusnih glioma su bile značajno veće (< 0,001) u odnosu na vrednosti nađenih kod visokogradusnih glioma. Prosečne minimalne vrednosti ADC u peritumorskom tkivu kod cerebralnih metastaza su bile značajno više nego one nađene kod visokogradusnih glioma. ADC vrednosti peritumorskog moždanog tkiva kod metastaza karcinoma pluća (0,000947 ± 0,000043 mm^2/s), melanoma (0,000842 ± 0,000018 mm^2/s) i karcinoma dojke (0,000783 ± 0,000048 mm^2/s) bile su značajno veće nego ADC vrednosti peritumorkog moždanog tkiva kod astrocitoma gradus I (0,000775 ± 0,000013 mm^2/s), gradus II (0,000411 ± 0,000005 mm^2/s), gradus III (0,000121 ± 0,000004 mm^2/s) i glioblastoma multiforme (0,000076 ± 0,000011 mm^2/s).

Minimalne vrednosti ADC peritumorskog edema kod moždanih metastaza bile su značajno veće u odnosu na vrednosti kod glioma. ADC vrednosti mogu imati dodatnu dijagnostičku vrednost u razlikovanju glioma u odnosu na moždane metastaze.

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Ključne reči: *MRI, moždane metastaze, DWI, moždani gliomi*