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Original Research Article

DWI And ADC Measurements Value in Benign and Malignant Pediatric Primary Brain Tumors Differentiation

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ABSTRACT

The aim of this study was to determine the diagnostic value of MR diffusion techniques in differential diagnosis of benign and malignant central nervous system (CNS) tumors in children.
A retrospective analysis involved 49 brain MR diffusion studies of children (under 16 years of age) with a histologically confirmed tumor. The analyzed group included 31 primary benign and 18 primary malignant CNS tumors. MR exams were conducted in 2009-2012 at the Magnetic Resonance Laboratory, Voxel Medical Diagnostics Centre at the Children's University Hospital in Cracow. MRI was performed using the 1,5T (GE) magnetic field induction MR system. DWI MR was performed at b 0 and 1500. ADC maps were made using GE, Functool software.
The values of the DWI signal and the ADC ratio from the tumor area and peritumoral edema were analyzed. The value of the DWI signal and the ADC factor from those locations was calculated for each patient. A statistical comparison of medians between primary benign and primary malignant brain tumors was made. Statistical analysis was performed using the Wilcoxon and Mann-Whitney test. The results were considered statistically significant for $p < 0.05$. It was found that,

1. The ADC value was statistically significantly higher in the primary benign compared to the primary malignant CNS tumors.
2. No statistically significant differences in the value of the DWI signals were found.
3. The value of the DWI signal from the tumor area and the peritumoral edema decreases with increase of the grade of malignancy of the tumor.
4. The value of ADC in the tumor area decreases and from peritumoral edema increases with the degree of malignancy of the brain tumor.

The conducted studies confirmed the usefulness of assessing the value of the DWI signal and the ADC factor in differentiating cerebral tumors.

Key words: MRI, DWI, primary brain tumor, children.

INTRODUCTION

Brain neoplasms are a heterogeneous group, both in histopathological types and the primary location. The variety of brain tumors the cause great difficulties in the diagnosis; it requires specialized and specific multidisciplinary approaches. [1]

Brain tumors are classified according to the type of tissue they are made of, as opposed to mature tumors. [10] According to the International Classification

of Childhood Cancer (ICCC), childhood neoplasms are divided into 12 groups; group 3 includes central nervous system tumors. [11] The characteristic feature of childhood CNS tumors is that they coexist in many neurodegenerative diseases of the developmental age and in the course of syndromes of the type of congenital developmental disorders.

Neoplasms occurring in the CNS are derived from various primary germplasms and, consequently, from different tissues. [8] Histopathological examination is the basis of tumor diagnoses. [7]

Based on the histopathological classification according to the World Health Organization (WHO) in 2007, brain tumors are divided into 7 main categories and 100 subcategories. From a clinical point of view, the most important for the patient's prognosis is the degree of the malignancy of the lesion. According to the 2007 WHO classification, 4 degrees of neoplasia of brain tumors are distinguished:

- Grade I and II (WHO I, WHO II) are benign tumors (benign, non-benign).
- Grade III (WHO III) are malignant and,
- Grade IV (WHO IV) are highly malignant tumors. [7,8]

However, in the beginning of 2016, a new WHO classification of CNS tumors based on molecular techniques was published. [12] In our study (retrospective, covering the period 2009-2012) the types and extent of brain tumors were determined in accordance with the, then applicable, 2007 WHO classification.

Basic methods in brain tumors diagnostics are computed tomography (CT) and MR imaging techniques. MR imaging with contrast media is the preferred method for diagnosing brain tumors in children, showing a higher sensitivity than CT, and showing 18% of lesions not visible in CT, while only 1.4% reported inverse correlation. [1-3] Despite the high contrast resolution, in preoperative tumor grade, the sensitivity of MR is only 72.5% and its specificity is 65%.[2] Large mass effects, peritumoral edema (PTE) and necrotic or haemorrhagic areas are more typical for tumors with a high degree of malignancy, but may also be found in low grade or may be absent in high-grade lesions. [2] Contrast enhancement is also not sufficient. Almost 20% of malignant gliomas are contrast-enhanced, while one third of malignant tumors have no enhancement. This, in some cases determines incorrect evaluation of the degree of malignancy of the brain neoplasm. It should be emphasized that the classic MR examination also does not allow for the unambiguous differentiation of primary brain tumors from metastases, abscesses, lymphomas and some demyelinating lesions or ischemic areas. [2,4-6]

Therefore, it is advisable to introduce new diagnostic techniques. New, relevant information in the differentiation of cerebral focal lesions may provide diffusion weighted MR imaging (DWI). The diffusion of water molecules within brain tumors varies due to the microstructure of the lesions. One of the recognized features of tumor malignancy is its ability to rapid proliferation, which in turn leads to cellulite (increased cell density). High cell density with increased ratio of nucleus volume to cell volume, results in changes in free diffusion of water molecules in the tumor region. The greater the ratio of tumor cells and intercellular framework to extracellular space, the greater the changes in the free diffusion are observed. The aim of this study was to determine the usefulness of calculating DWI and the apparent diffusion coefficients (ADC) values in differentiation of brain neoplasms in children.

MATERIALS AND METHODS

In the study the DWI images from brain MR examinations (conducted in 2009-2012 in the Magnetic Resonance Laboratory, Voxel Medical Diagnostics Centre at the Children's University Hospital in Cracow) were analyzed. Patients were referred for MR examinations of the brain with clinical suspicion of tumor.

The criteria for inclusion in the analyzed group were:

1. Brain tumor in MR report.
2. Execution in the MR exam of the DWI sequence.
3. Histopathological result of identified brain lesion.

There were 120 cases of cerebral tumors in patients under 16 years of age, operated at Children's University Hospital in Cracow between 2009-2012. According to accepted inclusion and exclusion criteria (Table 1), as a result, 49 brain MRI examinations were analyzed.

Table1. Reasons for exclusion from the analyzed group

EXCLUSION GROUP		***NUMBER OF PATIENTS***
No DWI sequence in MR study		57
Histopathological outcome without indicate proliferative change		1
Histopathological result ambiguous	Abscess / inflammatory reaction	1
	Haemorrhage	1
Proliferative growth outside of the brain	Spinal cord tumour	4
	Bone of the frontal-parietal border	1
	Tumour of left eye socket	1
	Annular fibrosis of sculp	1
Enterogenic cyst		1
Focal cortical dysplasia		1
Hamartoma		1
Artefact in DWI imaging that makes it impossible to analyse the test		1

Based on the histopathological findings, the analyzed group was divided into two subgroups:

1. Primary benign CNS tumours (PBT).
2. Primary malignant CNS tumours (PMT).

In the group of primary benign CNS tumors there were 31 cases (20 in girls, 11 in boys) aged 2 to 17 years - mean age 9 years. A group of PMT included 18 cases (9 in girls, 9 in boys) aged 1.5 to 16 years - mean age 10 years.

In PBT group, 10 different tumor types were diagnosed, the most common neoplasm in this subgroup was capillary astrocytoma (48% of cases) and the lesions were most frequently located in the left cerebellar hemisphere (25%).

PMT group included 12 different histopathologic types. The most common tumor was glioblastoma multiforme (17% of cases), and the lesions were mainly located in the right hemisphere of the cerebellum (22% of cases).

Table 2 summarizes the location of analyzed CNS tumors. Table 3 shows histopathological types of brain neoplasms in the analyzed group.

Table2. Location of brain tumors in the analyzed groups

LOCATION		***PRIMARY BENIGN TUMOURS - PBT***	***PRIMARY MALIGNANT TUMOURS - PMT***
		QUANTITY	***QUANTITY***
FRONTAL LOBE	right	3	3
	left	2	0
OCCIPITAL LOBE	right	0	0
	left	1	0
TEMPORAL LOBE	right	1	1
	left	1	2
PARIETAL LOBE	right	1	0
	left	1	0
THALAMUS	right	0	3
	left	0	1
CEREBELLUM	right	4	4
	left	8	1
BRAIN STEM		3	3
POSTERIOR FOSSA		6	0

Table3. Histopathology of primary CNS tumors in the analyzed group

PRIMARY BENIGN CNS TUMOURS (PBT)		***PRIMARY MALIGNANT CNS TUMORS (PMT)***	
Type	***Quantity***	***Type***	***Quantity***
pilocytic astrocytoma	15	glioblastoma	3
pilomyxoid astrocytoma	3	primitive neuroectodermal tumour PNET	2
fibrillary astrocytoma	3	medulloblastoma	2
dysembryoplastic neuroepithelial tumour DNET	2	astrocytoma anaplasticum	2
papillary ependymoma	2	anaplastic ganglioglioma	2
ganglioglioma	2	atypical teratoid/rhabdoid tumour	1
diffuse astrocytoma	1	gliomatosis cerebri	1
hemangioblastoma	1	anaplastic astrocytoma	1
subependymal giant cell astrocytoma SEGA	1	brainstem glioma	1
ependymoma	1	embryonal carcinoma	1
		pineoblastoma	1
		germinoma	1

All MR studies were performed using the 1.5 T MR system by General Electric (GE), 8-channel GE coil. The study was

conducted in accordance with the standard MR head protocol, which includes the following sequences:

1. T2-weighted in axial plane, slice thickness 5.0 mm, spacing 3.0 mm.
2. FLAIR in axial plane, slice thickness 5.0 mm, spacing 3.0 mm.
3. DWI in axial plane, slice thickness 5.0 mm, spacing 3.0 mm.
4. 3D T1SPGR before and after i.v. administration of a contrast medium, in an axial plane, 2.0 mm slice thickness.

The DWI sequence parameters are shown in Table 4.

Table4. Diffusion sequence parameters (DWI)

PARAMETER	VALUE
PLANE IMAGING	AXIAL
SEQUENCE	EPI
NUMBER OF SLICE	22-24
REPETITION TIME	8200
ECHO TIME	97,7
FIELD OF VIEW	20
SLICE THICKNESS	5,0
SPACING	0,0
MATRIX	128X128
NUMBER OF ACQUISITION	2
MAX PARAMETER VALUE b	1500
MIN PARAMETER VALUE U b	0
NUMBER OF DYNAMIC MEASUREMENT DIRECTIONS	3

DWI source images were quantified at GE's Advantage Workstation 4.5 diagnostic facility, using the FuncTool software to reconstruct and analyze DICOM images.

For each patient in the analyzed group, DWI and ADC values were measured at the following locations:

1. **The tumor area with contrast enhancement [TC (+)]** (ROI 1 in Fig. 1a and b) selected on the 3D T1SPGR sequence images after intravenous injection of the contrast agent (T1SPGR + C). The highest contrast enhancement part was selected for analysis.
2. **The tumor area without contrast enhancement [TC (-)]** (ROI 2 in Fig. 1a and b) selected on the FLAIR sequence images, after elimination of contrast enhancing parts.
3. **The peritumoral edema [PTE]** (ROI 3 in Fig. 1a and b) selected on the FLAIR sequence images, based on the difference of the signal between the tumor and PTE. The measurement of the DWI / ADC value in the PTE area was made with the ROI located as close as possible to the neoplasm.

In some cases, the ROI has been corrected to avoid measuring bone tissue, necrosis, vasculature, and fluid or air filled areas.

a b

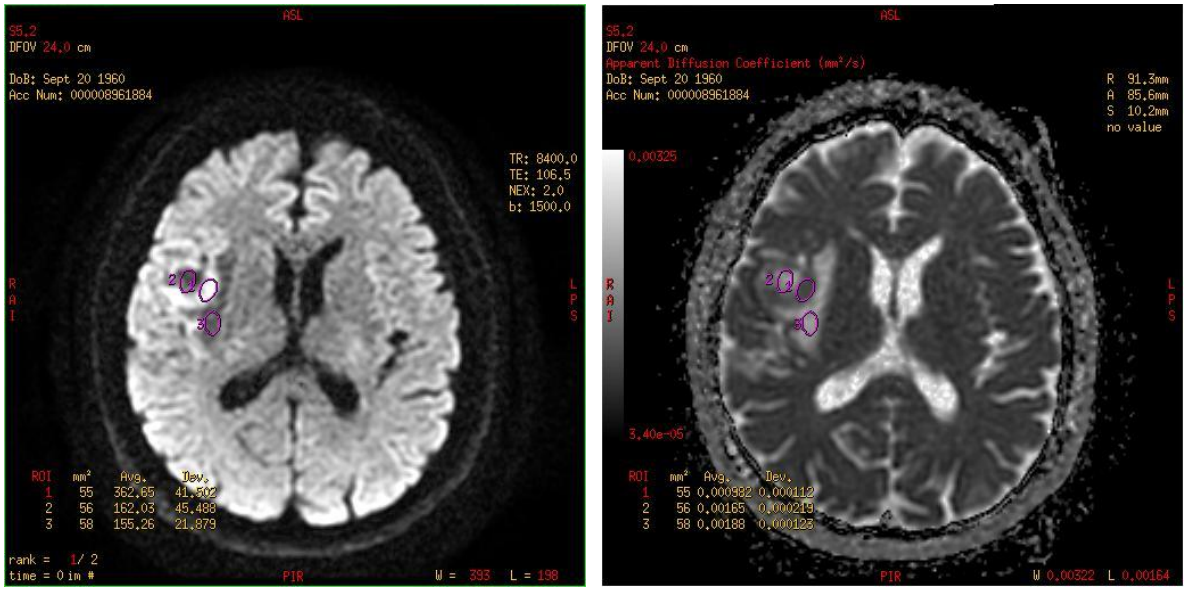

Figure 1. Head MR examination: (a) diffusion sequence (b) ADC map, with selected ROI for measurement of DWI and ADI values. ROI 1 - area of tumor with contrast enhancement; ROI 2 - tumor area without contrast enhancement; ROI 3 – peritumoral edema, PTE.

The magnitude of the ROI was adjusted to the extent of the contrast enhancement area (Tab. 5). If the lesions did not show a contrast enhancement, the ROI was adjusted to the tumor area. There was no need to use the same ROI size in all cases because, as the Bilgili study shows, the ROI size differences do not affect the received DWI signal and the ADC. [14]

Table5. Average area of the region of interest (ROI) mm^2

	AVERAGE SURFACE ROI (MIN-MAX)		*AVERAGE SURFACE ROI (MIN – MAX)*	
	TUMOR AREA WITH CONTRAST ENHANCEMENT TC(+)		*TUMOR AREA WITHOUT CONTRAST ENHANCEMENT TC(-)*	
	Primary benign tumors of the CNS (PBT).	*Primary malignant tumors of the CNS (PMT).*	*Primary benign tumors of the CNS (PBT).*	*Primary malignant tumors of the CNS (PMT).*
ROI AREA	70 (32 – 166)	58 (30 – 102)	64 (35 – 137)	81 (57 – 101)

STATISTICAL ANALYSIS

The output database was created using Excel. Statistical analysis was performed in statistical package R v.3.2.2.

Continuous data were characterized by mean values with standard deviation, median, and minimum and maximum values. Descriptive characteristics are shown in Tables 6 - 7. The graphical analysis included in the diagrams (Fig. 2-3) illustrates the relationship between the described median and the mean values of the DWI signal and the ADC coefficient for each measurement location analyzed group.

Table6. Descriptive characteristics for the DWI and ADC values of primary benign CNS tumors - PBT

PBT	*TC(+)*		*TC(-)*		*PTE*	
	DWI	*ADC*	*DWI*	*ADC*	*DWI*	*ADC*
NUMBER OF ANALYZED CASES	22	22	12	12	11	11
MEDIAN	352,245	0,00170	319,370	0,00162	406,840	0,00124
MEAN	326,044	0,00158	300,717	0,00159	380,042	0,00132
STANDARD DEVIATION	127,604	0,000501	80,922	0,000436	111,0433	0,000537
MIN VALUE	78,604	0,000137	111,690	0,000984	107,350	0,000121
MAX VALUE	553,300	0,00255	392,400	0,00230	487,820	0,00225

Table7. Descriptive characteristics for the DWI and ADC values of primary malignant CNS tumors – PMT

PMT	*TC(+)*		*TC(-)*		*PTE*	
	DWI	*ADC*	*DWI*	*ADC*	*DWI*	*ADC*
NUMBER OF ANALYZED CASES	11	11	9	9	5	5
MEDIAN	335,00	0,00110	324,230	0,00109	338,630	0,00165
MEAN	480,059	0,00102	385,693	0,00115	312,358	0,00168
STANDARD DEVIATION	303,411	0,000353	208,211	0,000226	142,053	0,000100
MIN VALUE	157,570	0,000423	203,990	0,000859	161,740	0,00157
MAX VALUE	1084,400	0,00153	861,240	0,00159	493,080	0,00180

Legend to Tables 6-7 and Figures 2-3:

TC (+) - Tumor area with contrast enhancement

TC (-) - Tumor area without contrast enhancement

PTE – peritumoral edema

PBT - primary benign CNS tumours

PMT - primary malignant CNS tumours

Due to the small groups and the asymmetry of the distribution of the examined features, in statistical analyses non-parametric tests were used. To compare the DWI/ ADC median from the TC (+), TC (-) and PTE areas, for the same area [e.g. GC (+)], but measured in two different subgroups: in the BPTs and PMTs, the Mann-Whitney test was used, which is a non-parametric equivalent of Student's t-test for independent variables.

The results were considered statistically significant if the calculated probability value p did not exceed the significance level of 0.05 ($p < 0.05$).

In order to assess the usefulness of DWI signal analysis in differentiating the character of pathological CNS lesions, the statistical comparison of medians was made between:

a) The value of the DWI signal from the TC (+) area between the PBT and the PMT group,
b) The value of the DWI signal from the TC (-) area between the PBT and the PMT group,
c) The value of the DWI signal from the PTE area between the PBT and the PMT group.

In the analyzed group, the highest values of the DWI signal were observed for PBTs in the tumor area without contrast enhancement and PTE (Table 6 and Fig. 2).

A decrease in the value of the DWI signal along with the increase in the malignancy of the tumor was observed from the tumor area with contrast enhancement and PTE.

There is a small difference in the value of the DWI signal from the tumor area without contrast enhancement between the primary benign and the primary malignant CNS neoplasms (Table 8, Fig. 4).

Table8. Median values of DWI signal in analyzed group at TC (+), TC (-) and PTE ROI.

DWI	*PBT*	*PMT*
TC(+)	352,245	335,000
TC(-)	319,370	324,230
PTE	406,840	338,630

DWI - median DWI signal, TC (+) - tumor region showing contrast enhancement, TC (-) - tumor region without contrast enhancement, PTE – peritumoral edema, PBT - primary benign CNS tumors, PMT - primary malignant CNS tumors.

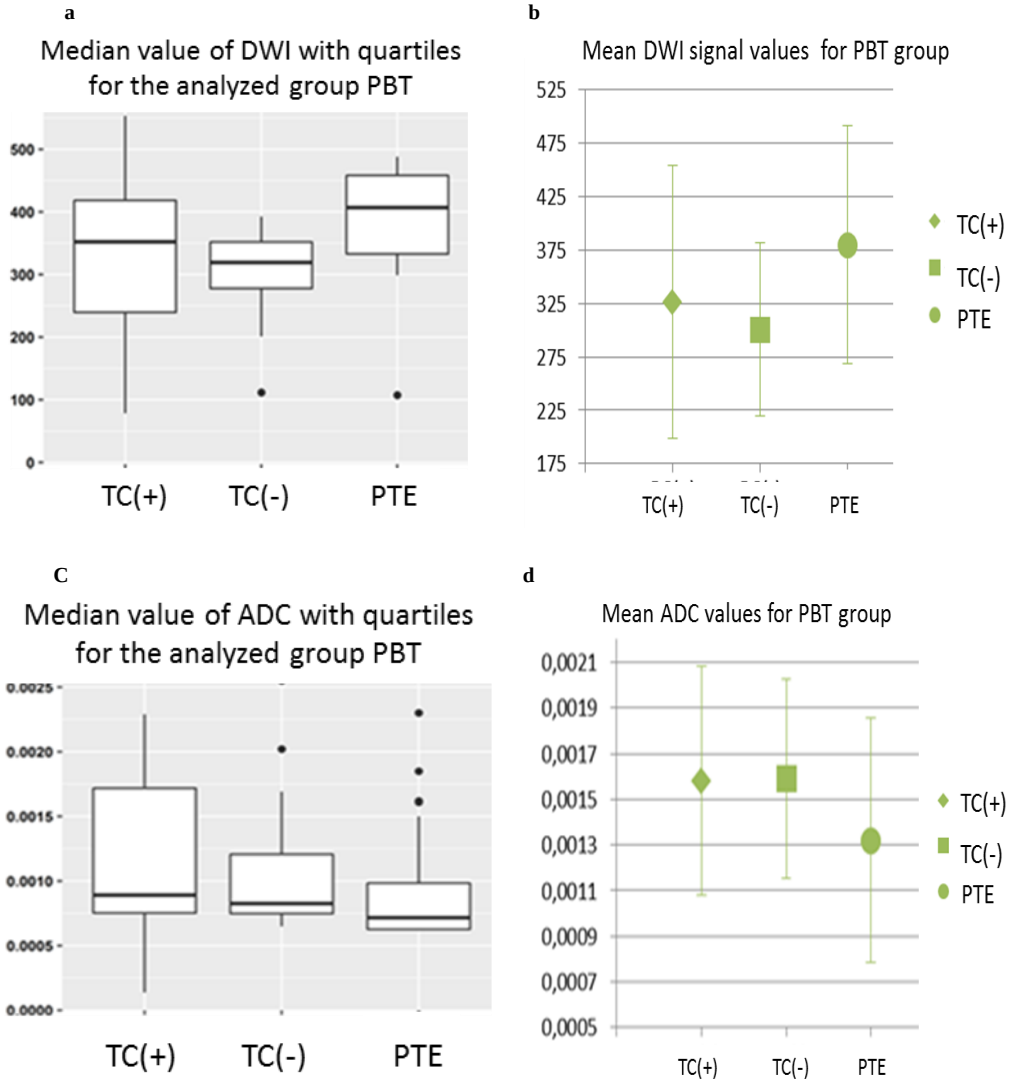

Figure 2. Graphical analysis of (a, c) median and (b, d) mean DWI signal values and ADC values for primary benign tumors - PBT.

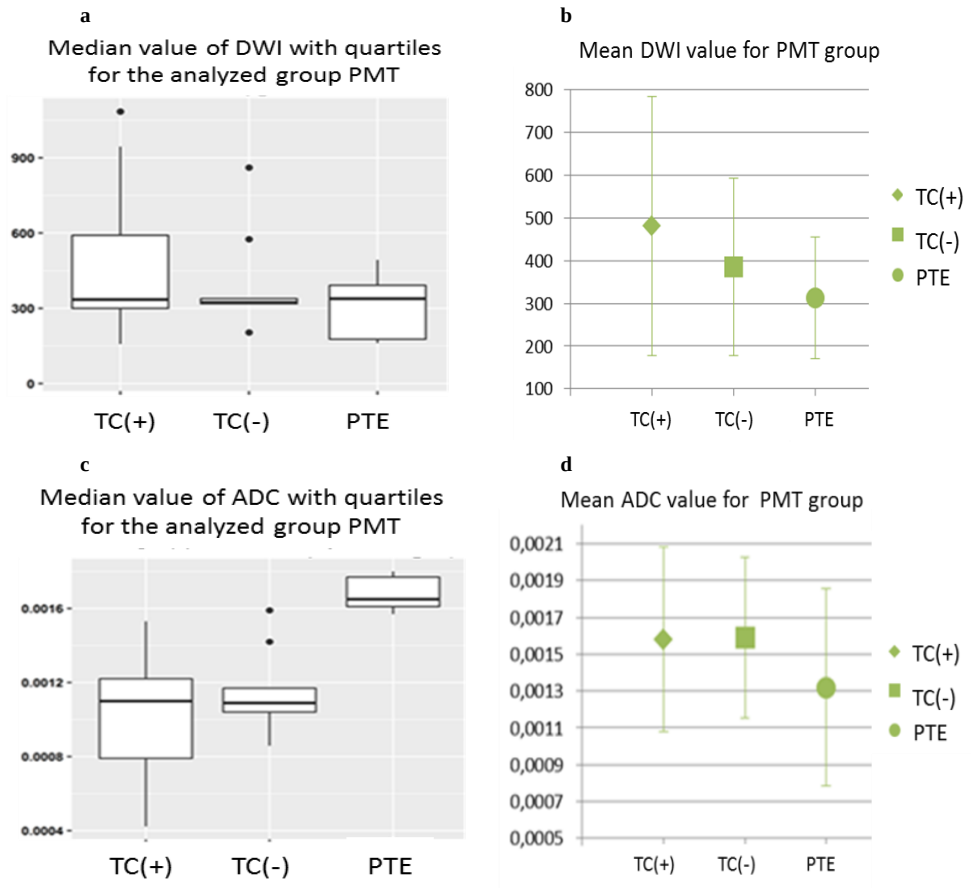

Figure 3. Graphic analysis (a, c) median and (b, d) mean DWI value and ADC values for primary malignant CNS tumors - PMT.

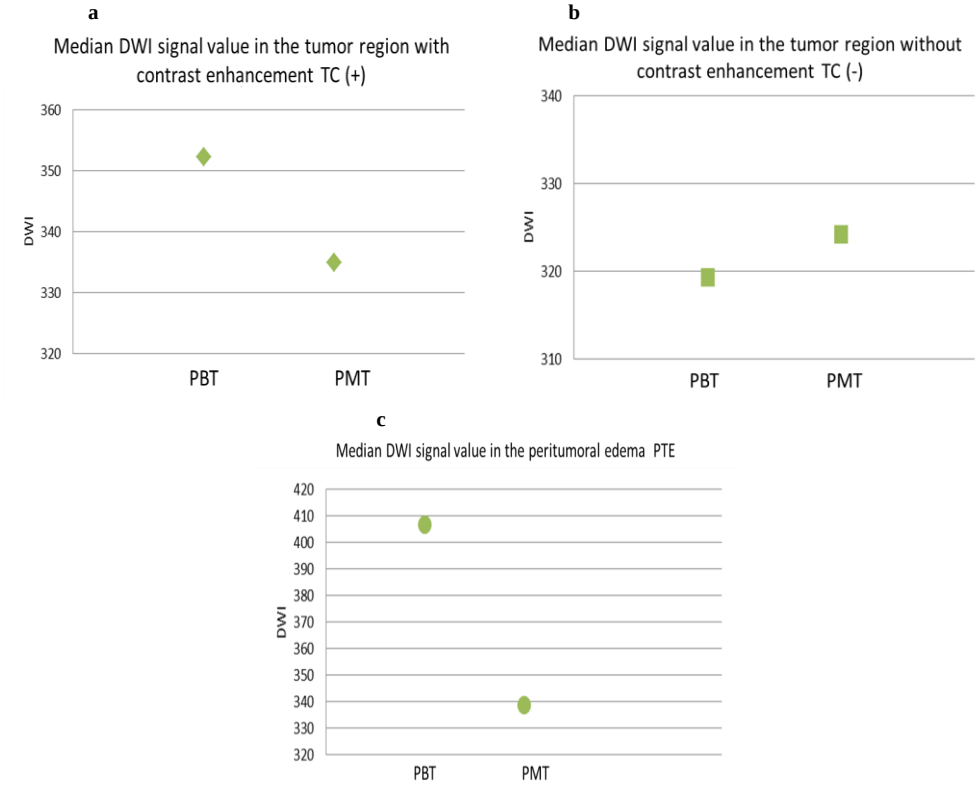

Figure 4. Graphical analysis of the comparison of median DWI signal value in the tumor region: (a) with contrast enhancement [TC(+)], (b) without contrast enhancement [TC(-)] and c) peritumoral edema (PTE). PBT - primary benign CNS tumors, PMT - primary malignant CNS tumors.

In order to assess the usefulness of the analysis of ADC values in the differentiation of the pathological CNS lesions statistical comparisons were made between:

a) The value of the ADC coefficient from the TC (+) area between the PBT and the PMT group,

b) The value of the ADC coefficient from the TC (-) area between the PBT and the PMT group,

c) The value of the ADC coefficient from the PTE area between the PBT and the PMT group.

In the analyzed group, the highest values of ADC were observed in PBTs for the location of ROI in the area of TC(+) and TC(-) (Table 6 and Fig. 3).

A decrease in the ADC coefficient was observed along with an increase in the malignancy of the brain tumor for ROI TC(+) and TC(-).

For PTE the value of ADC increases with the degree of malignancy of the brain neoplasm.

The statistical differences between the analyzed variables are summarized in Table 10.

The analysis showed statistically significant differences for the tumor area both with and without contrast enhancement between the primary benign and primary malignant CNS neoplasms.

Table9. Median values of ADC in the analyzed group at TC(+), TC(-) and PTE.

ADC	*PBT*	*PMT*
TC(+)	0,00170	0,00110
TC(-)	0,00162	0,00109
PTE	0,00124	0,00165

ADC - median value of ADC, TC(+) - tumor region showing contrast enhancement, TC(-) - tumor region without contrast enhancement, PTE – peritumoral edema, PBT - primary benign CNS tumors, PMT - primary malignant CNS tumors.

Table10. Statistical differences between analyzed variables

STATISTIC COMPARED VARIABLES	*DWI*	*ADC*
TC(+)PBT – TC(+) PMT	-	+
TC(-)PBT – TC(-) PMT	-	+
PTE PBT – PTE PMT	-	-

DWI - median DWI signal, ADC - median ADC, TC(+) - tumor region with contrast enhancement, TC(-) - tumor region without contrast enhancement, PTE – peritumoral edema, PBT - primary benign brain tumors, PMT - primary malignant brain tumors, (+) - statistically significant difference between the analyzed variables, (-) - no statistically significant difference between the analyzed variables.

Summary:

No statistically significant difference in the DWI value was found. A statistically significant difference was found in the ADC between primary benign and primary malignant CNS tumors.

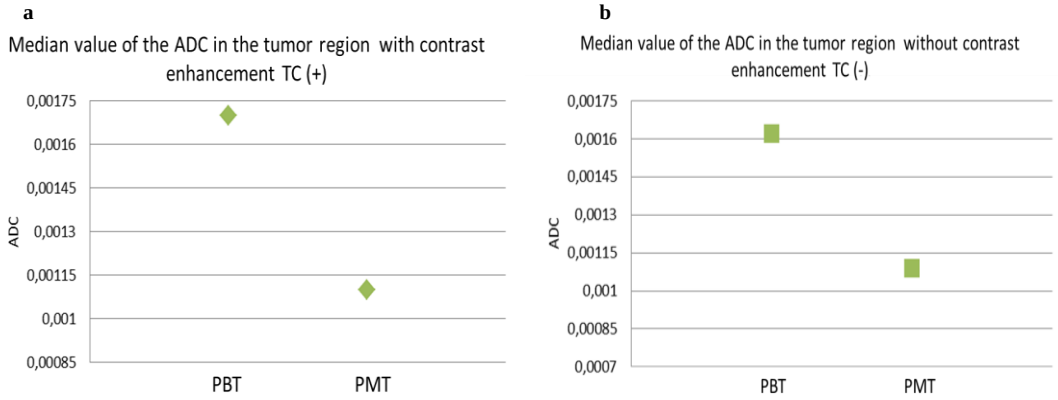

Figure 5. Graphical analysis of the median value of the ADC in the localized group of interest (ROI) in the tumor region (a) with contrast enhancement [TC(+)], (b) without contrast enhancement [TC(-)] and c) peritumoral edema (PTE). PBT - Primary benign CNS tumors, PMT - primary malignant CNS tumors.

DISCUSSION

Many reports suggest an increasing value of MR diffusion imaging with the assessment of ADC in the diagnosis and differentiation of brain tumors. [13,15-17,23,24] According to the majority of published studies PTBs are characterized by a higher ADC value compared to primary malignant neoplasms of CNS. [9,15-17] It is believed that the high cell density of primary malignant

tumors is the cause of changes in tumor diffusion and reduction of ADC values. The ADC coefficient correlates with the total surface / volume of the nuclei and the degree of malignancy - the primary malignant tumors of the central nervous system are characterized by higher cell density and lowering of the ADC. [20,21]

There are not many studies devoted to diffusion studies of brain tumors in children. In the limited available literature on this topic, the authors indicate that the value of ADC decreases with the increase of the neoplasm's grade of malignancy. Conducted in 2010, a study by a Polish team from the Children's Health Centre in Warsaw showed that benign primary brain tumors are characterized by higher ADC values compared to primary malignancies of CNS. [18] These differences were statistically significant. In the research of Porto team (published in 2013), the authors also received higher values of ADC in the group of brain PBTs than in the group of primary malignant ones. These results were confirmed in subsequent studies of Kralik team in 2014. [19,22]

In our study, it was also shown that the value of ADC in primary benign is lower compared to primary malignant brain tumors in children. The obtained mean values of the ADC coefficient for PBTs were slightly different from the results of Jurkiewicz but for malignant tumors, the ADC mean value was similar. A larger spread of results is most probably associated with greater histopathological variety of tumors in our study - 10 in the PBTs and 12 in the PMTs different histologic types of brain neoplasms. In the study of Jurkiewicz team, only one histopathological type of the benign brain tumor (pilocytic astrocytoma) and two of PMTs (ependymoma and medulloblastoma) were analyzed. However, the differences observed in our study between cerebral tumors with different grade of malignancy are statistically significant in the same way as in the Jurkiewicz team report.

CONCLUSION

The obtained results from statistical comparisons between variables and observed trends allow to state that, in the group of patients under 16 years, in the area of brain tumor, the intensity of the DWI signal increases, and the ADC value decreases with the increase of tumor malignancy.

Unfortunately, although the values obtained between the primary benign and the primary malignant brain tumors differ significantly, no statistically significant difference was found. The large variety of histopathological types of the analyzed brain neoplasms is likely to influence the dispersion of the obtained results. Also the limit value of the DWI signal and the ADC ratio between the primary benign and the primary malignant CNS tumors were not possible to establish in our study.

Research on this field should be continued on larger group of cases (ex. in a multicenter study).

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