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Infratentorial tumors in children – value of ADC in prediction of grade of neoplasms

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Summary

Background: The purpose of this study was to evaluate ADC values in the preoperative grading of primary infratentorial brain tumors in children.

Material /Methods: We retrospectively reviewed 50 MR examinations of patients with infratentorial tumors. All children were operated on and tumors were histopathologically proved as low-grade – 25 (24 pilocytic astrocytomas, 1 ependymoma) and high-grade lesions – 25 (19 medulloblastomas, 6 anaplastic ependymomas). In all patients with contrast-enhanced tumors, ROIs were placed in the enhanced region. In patients with non-enhancing tumors, ROIs were placed in the solid part of the lesion. Cystic, hemorrhagic and necrotic areas of tumors were excluded. Statistical analysis was performed by using a Student's t-test.

Results: Statistically significant differences were found in the comparisons of mean ADC of pilocytic astrocytomas ($1.54\times10^{-3}mm^2/s$ ±0.2) with medulloblastomas ($0.75\times10^{-3}mm^2/s$ ±0.075) and pilocytic astrocytomas ($1.54\times10^{-3}mm^2/s$ ±0.2) with anaplastic ependymomas ($0.99\times10^{-3}mm^2/s$ ±0.25). Statistical analysis including ependymomas should be discussed, because of small number of these tumors and a non-homogenous group of lesions.

Conclusions: DWI imaging and ADC map provide useful information for preoperative grading of infratentorial tumors in children.

Key words: **magnetic resonance • diffusion-weighted imaging – DWI • infratentorial tumors • children**

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Background

A conventional MRI examination allows for visualization of a proliferative lesion, and provides us with information on tumor location, its homogeneity and on signal intensity, the presence of peritumoral edema and degree of contrast enhancement. However, differentiation between low- and high-grade tumors based on MRI is still very difficult. Traditional tumors of high grade are very heterogeneous, which results from the presence of necrotic and/or hemorrhagic regions, an extensive vascular edema, strong enhancement and mass effect. However, these signs are not always present. Sometimes, low-grade tumors show features typical for more malignant tumors [1,2].

Diffusion-weighted imaging (DWI) is a very well known and a widely used method, present in a routine MRI protocol, and allowing for evaluation of a normal brain tissue or its lesions caused by ischaemia, injury, proliferation, multiple sclerosis, or abscess [3–7].

Previous reports showed usefulness of DWI imaging and of the effective (apparent) diffusion coefficient (ADC) in the diagnostics of cysts or necrotic areas. Further reports proved that ADC provides us with direct information on cellular density of tumors [8]. It was revealed that benign and malignant lesions are represented by different ADC values, with inversely proportional relation between the cellular density of a tumor and ADC value [9–14].

Table 1. Contrast enhancement in infratentorial tumors.

Tumor/enhancement	No	Slight	Inhomogeneous	Ring-like	Strong
Pilocytic astrocytoma	1	3	11	5	4
Ependymoma WHO II			1		
Ependymoma WHO II/III and III		1	2		3
Medulloblastoma	4	4	9	1	1

The aim of the work was to evaluate the usefulness of ADC in establishing the grade of infratentorial tumors in children.

Material and Methods

Brain MRI results of 50 children (18 girls and 32 boys) were subjected to a retrospective analysis. Children's age ranged from 9 months to 17 years, with a mean of 7 years and 3 months. All the patients were subjected to surgical resection of a tumor with histopathological examination of the sample. Grading was performed on the basis of WHO criteria.

We found 25 low-grade tumors (24 pilocytic astrocytomas WHO I and 1 ependymoma WHO II), 25 high-grade tumors (6 ependymomas WHO II/III and III, 19 medulloblastomas WHO IV).

The examinations were performed with a 1.5T scanner, an 8-channel surface head coil. The examination protocol included the following sequences and images: TSE T2WI (3920/102/1), FLAIR (2500/9000/111/1) [IR-inversion time/TR/TE/excitations] and SE T1WI (488/10/1) [TR-repetition time/TE-echo time/excitations]), carried out in three planes, before and after contrast medium administration (in a standard dose). Matrix: 256×256 and 256×192, field of view: 220–230 mm, slice thickness: 3–5 mm, slice interval of 30%.

DWI was performed before contrast medium administration; sequence parameters – TR/TE-2300/73, field of view: 230 mm, matrix: 128×128, slice thickness: 5mm, slice interval: 1 mm, b-values 0/500/1000 mm^2/s.

ADC was measured with a manual placement of ROIs in the solid part of the lesion. The solid part of the lesion was identified on the basis of a detailed analysis of T1-weighted images after contrast administration and T2-weighted images, including FLAIR sequence. In case of enhancing tumors, ROIs were placed in the enhanced region, while in case of non-enhancing tumors, ROIs were placed in the solid part of the lesion, identified on the basis of a FLAIR image.

The measurements were taken 3 times, and included calculation of a mean value for each lesion. ROI size was 5 pixels (approx. 50–100 mm^2).

The measurements did not include cystic, necrotic, hemorrhagic areas, or edema surrounding the tumor.

The control group (18 individuals) composed of patients at a similar age, with normal brain MRI results, referred for examination due to different clinical causes, e.g.: headaches, hypofunction of the pituitary gland. Mean ADC values were calculated in the same way.

The statistical analysis used the Student's t-test for independent samples.

Results

In most of the low-grade tumors, there was contrast enhancement (24/25). Only in one case, no contrast enhancement was found (1/25) (Table 1).

Among high-grade tumors, contrast enhancement was observed in 20 out of 25 cases, while no contrast enhancement was found in 5 out of 25 cases (Table 1). In pilocytic astrocytomas, ADC values ranged from 1.23 to 1.90×10^{-3} mm^2/s. In the group of medulloblastomas, it was 0.62–0.86×10^{-3} mm^2/s. (Figures 1 and 2).

Among high-grade ependymomas, ADC values ranged from 0.61 to 1.40×10^{-3} mm^2/s. (Table 2).

A statistically significant correlation ($P<0.05$) was found in the comparison of mean ADC values for: pilocytic astrocytomas (1.54×10^{-3} mm^2/s ±0.2) and medulloblastomas (0.75×10^{-3} mm^2/s ±0.075), as well as for pilocytic astrocytomas (1.54×10^{-3} mm^2/s ±0.2) and anaplastic ependymomas (0.99×10^{-3} mm^2/s ±0.25).

Due to a low number of ependymomas and a high heterogeneity of ADC results, the statistical analysis of this group should be discussed.

In the control group, mean ADC values for the white matter amounted to 0.78 (range from 0.61 to 0.89×10^{-3} mm^2/s); for the grey matter it was 0.84 (range from 0.74 to 1.03×10^{-3} mm^2/s).

Discussion

Preoperative differentiation of three most common infratentorial tumors in children: pilocytic astrocytoma, medulloblastoma, and ependymoma, is very important, due to different therapeutical approaches and prognosis.

A standard differentiation of infratentorial tumors with T2-weighted images shows some differences in signal intensity of the lesions. FLAIR sequence is less useful in the differential diagnosis.

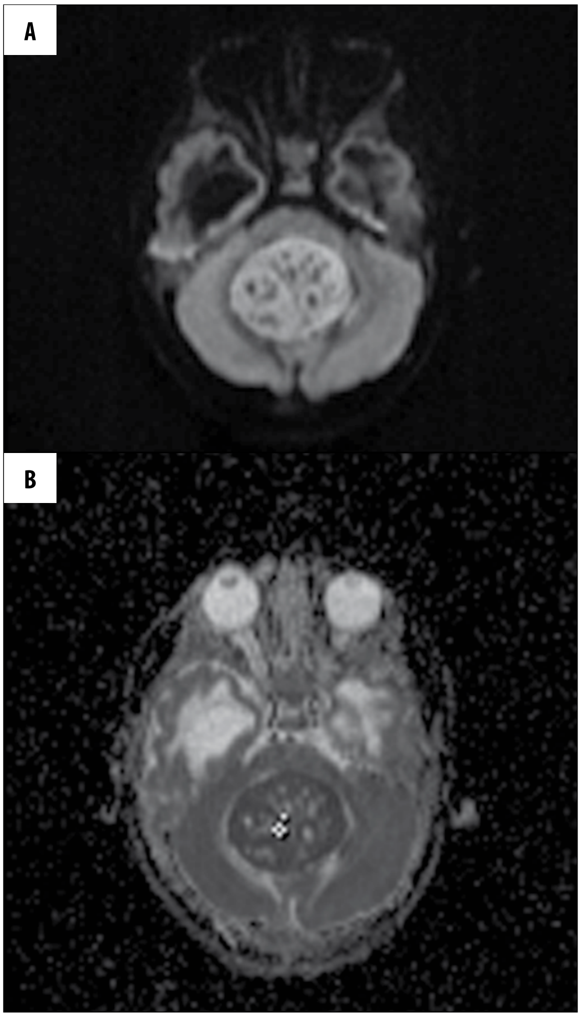

Figure 1. (**A**) DWI, (**B**) ADC=0.63×10^{-3} mm^2/s, (**C**) T1WI+C. A 10-month-old boy. Solid tumor mass obstructing the fourth ventricle. ROI placed in an enhanced part of the lesion. Very low ADC values correlating well with histopathology (medulloblastoma G IV).

Astrocytomas reveal a higher signal intensity in T2-weighted images, but not as high as the cerebrospinal fluid. Pilocytic astrocytomas frequently show much higher signal intensity than medulloblastomas. This concerns both the cystic, and the solid part of astrocytomas. Differences in signal intensity are directly connected with histological structure of the tumors. Malignant tumors with high miototic activity are hypercellular and reveal a lower signal intensity than benign tumors with a looser structure.

In typical medulloblastomas, the solid part of the tumor is isointense in comparison to the grey matter. This is connected with a higher ratio between the nuclei and the cytoplasm in tumor cells, i.e. reduction of free water molecules in this region. The observed tumor heterogeneity on the other hand is the result of formation of small cysts and calcifications.

Ependymomas are characterized with high signal heterogeneity. The solid part of the tumor produces signal similar to the one of the grey matter, while the necrotic areas and cysts present a lower signal intensity in T1-weighted images, and a higher signal intensity in T2-weighted images.

Differentiation of tumors with a standard MRI, on the basis of such criteria as: signal intensity of the mass lesion, presence of cysts, necrotic regions, peri-tumoral edema, as well as the degree of contrast enhancement or its lack, is unreliable or even impossible [15]. Both in the literature and in our material, the malignant tumors were not always getting enhanced after contrast administration, the peritumoral edema was not always present, and the cysts and/or necrotic regions were present in both malignant, and in benign tumors [15].

That is why, it is required to search for other, modern imaging methods, which would be helpful in the differentiation of the grade of brain tumors.

Diffusion-weighted imaging is a well known and a commonly used sequence which allows for visualization and differentiation of: ischemic foci in their early phase, dermoid cysts, inflammatory lesions, and proliferative processes of the CNS.

This method depends on the degree of free diffusion of water molecules in the examined environment. The extracellular space is characterized by a relative isotropy and a relatively high diffusion coefficient, as in case of the cerebrospinal fluid present in brain ventricles. The intracellular space reveals anisotropy of a different degree, depending on the number and density of the cell membranes. On the basis of the data obtained from measurements carried out in at least two sequences with a different degree of coefficient b (different amplitude and different time of gradient), ADC images are construed, with their values reflecting the degree of diffusion in a given region.

Due to the differences in diffusion rate of water molecules depending on the environment (serum, mucus, pus, solid tissue, etc.), there appeared many publications aiming to evaluate the differences in cellular density of mass lesions, and indirectly also in mitotic activity of the tumors, with

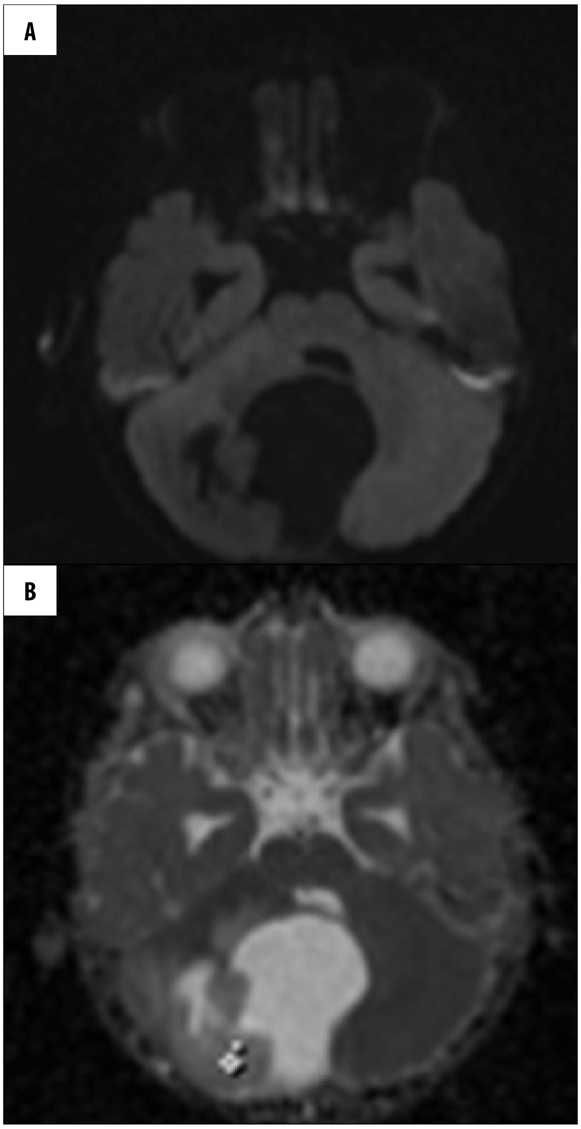

Figure 2. (**A**) DWI, (**B**) ADC=1.66×10^{-3} mm^2/s, (**C**) T1WI+C. A 2-year-old boy. Cystic cerebellar mass with a solid part. ROI placed in the solid, enhanced part of the tumor. High ADC values, correlating well with histopathology (pilocytic astrocytoma G I).

the use of diffusion degree within the lesion. In the previously published reports it was found that an increase in cellular density leads to a higher signal intensity in DWI images and a lower effective diffusion coefficient on the ADC map. Published reports have confirmed an inverse relation between the cellular density and the ADC value [5,11,16,17]. There are not many reports presenting results of DWI in tumors (including infratentorial ones) in children [11,14,18,19]. In our report, we analyzed infratentorial tumors in children, limiting our study to three most frequent (in this location) tumors: pilocytic astrocytomas, medulloblastomas, and anaplastic ependymoma.

On the basis of ADC evaluation in the presented group of patients, we showed a possibility of differentiation between pilocytic astrocytomas and medulloblastomas, as well as pilocytic astrocytomas with anaplastic ependymomas.

ADC coefficient values for different types of tumors in our patients were similar to the results of the previously published reports [11,14,19]. In most of the cases, ADC was significantly decreased in tumors of grade III and IV, and increased in benign tumors of grade I (WHO).

Our report, as well as the article by Rumboldt et al., refers only to infratentorial tumors in children [19]. The results of our analysis were very close to the ones found in the above mentioned report (Table 3). Other publications that we compared our wok to, presented total joint data on tumors in children and in adults. There were also reports showing joint data for infra- and supratentorial tumors [11,14]. Gauvain et al. included in their publication data on 5 infratentorial tumors only (2 medulloblastomas and 3 pilocytic astrocytomas) [11]. In our article, we presented data on 43 tumors of this histopathological type (19 medulloblastomas and 24 pilocytic astrocytomas). The report by Yamasaki et al. presented results on 275 tumors. However, they concerned both children and adults [14]. Tumors included in our work and selected also for our comparative analysis included: 6 pilocytic astrocytomas (age 2–35 years) and 3 ependymomas of WHO III (age 1–7 years). Moreover, the authors considered also other tumors, such as: 9 PNETs (age 5–56 years), 36 glioblastomas (age 8–81). These tumors were not included in our analysis because we limited our scope of interest to infratentorial tumors.

The above presented differences in the material selected for analysis are most probably a cause of discrepancies in the obtained results (Table 3).

When evaluating the sequence of water diffusion, especially in brains of young children, we should take into consideration all physiological differences in ADC values, connected with a lack or insufficiency of myelination of the brain and with a physiologically higher content of water in newborns and younger children. That is why, it seems

Table 2. Values of ADC in infratentorial tumors in our group of patients.

	Histopathololgy WHO	Number	Age	Mean ADC solid part ($\times 10^{-3}$ mm^2/s)	ADC from/to solid part ($\times 10^{-3}$ mm^2/s)
1.	Pilocytic astrocytoma I	24	9 months – 17 years	1.56	1.23–1.90
2.	Ependymoma II	1	1 year		1.02
3.	Ependymoma II/III	5	1–14 years	1.08	0.96–1.40
4.	Ependymoma III	1	1 year		0.61
5.	Medulloblastoma IV	19	1–14 years	0.74	0.62–0.86

Table 3. Values of ADC in comparison to previous publications.

Tumor/ ADC ($\times 10^{-3}$ mm^2/s)	Gauvain et al. 2001*	Yamasaki et al. 2005**	Rumboldt et al. 2006	Our report
Pilocytic astrocytoma	1.13–1.54	1.30–1.92	1.24–2.09	1.23–1.90
Ependymoma	0	1.03–1.22	0.97–1.29	0.61–1.4***
Medulloblastoma	0.54–0.78	0.68–0.99#	0.55–0.63	0.62–0.86

* Infra- and supratentorial tumors as a one group; ** adults and children as a one group; *** ependymomas WHO II/III and III as a one group; # PNET tumors as a one group (medulloblastoma, pineoblastoma, PNET).

important to us to compare the analysed study results in a more homogeneous age group.

Mean diffusion rate in the solid part of plocytic astrocytomas amounted in our study to 1.56×10^{-3} mm^2/s, and to 0.74×10^{-3} mm^2/s for medulloblastomas.

Similar data were published in 2006, and the mean ADC of tumors in the quoted article amounted to $1.65\pm0.27\times10^{-3}$ mm^2/s and $0.66\pm0.15\times10^{-3}$ mm^2/s, respectively [19].

In our material, we found ADC measurements to be useful in cases in which a conventional MR was ambiguous or revealed features of infiltration of adjacent structures. An example may be a 12-year-old boy with a tumor located medially in the posterior part of the skull, who revealed a quite homogeneously increased signal intensity. Standard MRI showed a potential infiltration of brain stem and cerebellar vermis. However, ADC measurements showed a mean diffusion rate within the tumor typical for plocytic astrocytoma. This was confirmed with a histopathological examination.

Cellular density of infratentorial ependymomas falls between the density of plocytic astrocytomas and medulloblastomas. The higher the grade, the higher the cellular density of ependymoma.

Mean ADC values for ependymomas ranged from 0.96 to 1.40×10^{-3} mm^2/s. Rumboldt et al. in their studies revealed mean ADC values for ependymomas ranging from 0.97 to 1.29×10^{-3} mm^2/s [19].

In case of infratentorial tumors from the group of ependymomas, there was the highest morphological diversity and a different degree of correlation between ADC measurements and histopathological results of samples collected from tumors. In a 14-year-old boy, there was a nonhomogeneously enhanced tumor, infiltrating cerebellomedullary cistern through the right Luschka's foramen. In this case, ADC values were quite high, which suggested a benign tumor. Histopathological examination showed ependymoma of mixed grade (WHO II/III), with regions of high mitotic activity accompanying more differentiated regions. We believe that tumors of histopathologically mixed type are the cause of inhomogeneous ADC results (obtained most probably from histologically different tumor regions).

High-grade ependymoma of the posterior fossa of the skull (WHO III), found in a 9-year-old boy, was isointense on T2-weighted MR images, and revealed an inhomogeneous enhancement after contrast administration, with low ADC values that correlated well with histopathological diagnosis.

Due to a low number of the analysed ADC results of the measurements of tumors from the group of ependymomas, as well as due to morphological heterogeneity of the tumors, the results in this group are not reliable and require further studies.

Our results of diffusion examined in some selected infratentorial tumors in children showed that a low mean ADC value is the most frequent in high-grade tumors, while a high one is more indicative of benign tumors.

These results are consistent with previous publications of other authors [5,10,12,13,20,21].

Conclusions

Taking into consideration the inverse proportion between the cellular density of tumors and ADC value, we may find ADC measurements useful in a routine preoperative MRI examination for differentiating the grade of infratentorial tumors in children.

Diffusion-weighted imaging is a technique available in most MRI laboratories. We opt for introduction of DWI and ADC evaluation to a standard protocol of brain examination.

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