Diffusion and perfusion MR patterns of central nervous system lymphomas

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Abstract

Background. Central nervous system lymphomas (CNSLs) are rare tumors which may show variable appearance in standard magnetic resonance imaging (MRI) depending on their origin (primary or secondary) or patients' immunological status.

Objectives. The aim of the study was to analyze imaging patterns of different CNSLs, using diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI).

Material and methods. Our material consisted of 16 CNSLs (14 primary, 2 secondary, 13 immunocompetent, 3 immunodeficient) which underwent magnetic resonance (MR) examinations including DWI and T2* dynamic susceptibility contrast (DSC) perfusion (without a preload in 13 cases, with a preload in 3 subjects). In DWI, apparent diffusion coefficient (ADC), and in PWI, parameters of relative cerebral blood volume (rCBV), relative peak height (rPH) and relative percentage of signal recovery (rPSR) were analyzed within the entire tumor (mean values) and in regions with minimal diffusion (ADC_{min}) and maximal perfusion values ($rCBV_{max}$, rPH_{max} , $rPSR_{max}$).

Results. All CNSLs showed low values of ADC_{mean} (0.70×10^{-3}), ADC_{min} (0.54×10^{-3}), $rCBV_{mean}$ (0.80), $rCBV_{max}$ (1.27), rPH_{mean} (1.05), rPH_{max} (1.59), as well as high values of $rPSR_{mean}$ (1.99) and $rPSR_{max}$ (2.41). There were no significant differences in $rCBV_{max}$, as well as in all ADC, rPH and rPSR values between primary and secondary CNSLs or between tumors in immunocompetent and immunodeficient patients. Dynamic susceptibility contrast PWI with a preload resulted in significantly higher rCBV, rPH and lower rPSR values.

Conclusions. Despite various MR appearances, both primary and secondary CNSLs in immunocompetent and immunodeficient patients show very typical patterns of restricted diffusion and hypoperfusion with signal intensity curves returning above the baseline. Dynamic susceptibility contrast perfusion without a preload is recommended.

Key words: central nervous system lymphomas, diffusion-weighted imaging, perfusion-weighted imaging, magnetic resonance imaging

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Introduction

Central nervous system lymphomas (CNSLs) are an inhomogeneous group of rare brain tumors consisting of 2 main subtypes: primary and secondary CNSLs. Primary CNSLs account for approx. 7% of newly diagnosed CNS tumors.^{1–3} Recently, their incidence has increased in immunocompetent patients, though their prevalence is still higher in immunocompromised subjects, such as those with acquired immune deficiency syndrome (AIDS), after organ or bone marrow transplantations, or with inherited immunodeficiency, often due to Epstein-Barr virus (EBV) activation.^{1–6} The majority of primary CNSL tumors are of the highly aggressive diffuse large cell subtypes, usually of B-cell phenotypic origin.^{4,7,8} They are mostly intra-axial lesions located within brain parenchyma, either periventricularly within deep structures, or peripherally along leptomeningeal surfaces.^{1–3,5} They may present as solitary or multiple lesions with usually strong homogeneous enhancement. Lesions found in immunocompromised patients have more commonly multiple locations and tend to enhance less strongly, very often show ring enhancement, as well as features of bleeding and necrosis.^{3,5,6} Secondary CNSLs are metastases to the central nervous system (CNS) from systemic lymphomas, in majority of nodular type; however, metastases to the CNS from extranodal location, including very rare orbital lymphoma, are also possible.^{1–3,9,10} The high aggressiveness of systemic lymphomas, immunodeficiency and extranodal involvement predispose to CNS relapse.^{7,11} The location of secondary CNSLs in brain parenchyma is mainly similar to that of primary CNSLs. Contrary to primary CNSLs, they may also show exclusively extra-axial location within meninges or spine.^{3,9,11}

Since CNSLs may show very variable appearance, a conventional magnetic resonance (MR) examination with contrast injection is not capable of accurately distinguishing them from other intracranial lesions, including tumors, such as gliomas, metastases or even meningiomas. Advanced MR techniques, such as diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI), allow for a more detailed analysis of brain tumors and their *in vivo* differentiation.^{12–21}

Diffusion-weighted imaging is a method that evaluates water diffusion in the extracellular space in between the intact cells which constitute a barrier to free movements of water molecules. In tumors, DWI brings information on the tumor cell architecture and the parameter of apparent diffusion coefficient (ADC) is considered as a surrogate marker of tumor cellularity.^{3,16,19,20} Lower values of ADC have been reported in malignant tumors, such as high-grade gliomas, due to their high cellularity rate, and in tumors with high nuclear/cytoplasmatic ratios, such as lymphomas and medulloblastomas.^{14,17,15,21}

On the other hand, PWI is a method that brings information on cerebral physiology at the capillary level (microvasculature).¹² Among the few PWI techniques, dynamic

susceptibility contrast (DSC) magnetic resonance imaging (MRI) is the most often used. Dynamic susceptibility contrast MRI provides maps of cerebral blood volume (CBV) and noninvasive mathematical measurements of relative cerebral blood volume (rCBV).^{12,22} In brain tumors, rCBV is defined as the ratio between CBV within the tumor and CBV in the white matter of the contralateral hemisphere. The rCBV parameter correlates with tumor vascularity and is increased in tumors with a high rate of pathologic neoangiogenesis.^{7,12} In glial tumors, increased rCBV ratios indicate increased malignancy, but this rule cannot be applied to extra-axial tumors. There are highly vascular extra-axial tumors with high perfusion, e.g., meningiomas, which are benign in terms of biological behavior.^{12,15,23} Apart from the CBV maps, PWI also provides perfusion curves, which give insights into the dynamics of the first pass of the contrast material through the microvasculature. An analysis of the perfusion curves has been reported to be very important in the evaluation of brain tumors, in some cases even more useful than an analysis of the CBV maps.^{12,13,17,18,24}

Accurate identification of CNSLs is crucial from the clinical point of view. Contrary to other malignant tumors, CNSLs do not undergo a surgical management, but are treated with chemotherapy.^{1,6,18,19} At the moment, brain tumors, including CNSLs, still require a biopsy, which is an invasive procedure and can cause unexpected complications.

The aim of our study was a detailed analysis of the conventional MR appearance, as well as diffusion- and perfusion-weighted images of different types of CNSLs in order to establish characteristic imaging patterns, typical for these tumors. To our knowledge, this is the first article presenting diffusion and perfusion results derived from both perfusion maps and curves in various types of CNSLs, both primary and secondary, including immunocompromised and immunodeficient patients. We also discuss the value of different DSC perfusion techniques, with and without pre-bolus, in the accurate diagnosis of CNSLs.²⁵

Material and methods

Our material consisted of 16 brain tumors diagnosed in 12 patients (5 men, 7 women) aged 6–84 years with biopsy-proven CNSLs, which were selected from a cohort of 1,060 CNS tumors evaluated with PWI and DWI in our institution in the years 2010–2015. According to the World Health Organization (WHO) system, the evaluated brain tumors were diagnosed either as primary (10 patients) or secondary (2 patients) diffuse large B-cell CNSLs (Table 1). In all patients their clinical history was carefully evaluated. Among primary CNSLs, 8 of 10 patients were found to be immunocompetent, while 2 subjects were immunocompromised (Table 1). Secondary CNSLs were metastases from a systemic nodular lymphoma or extranodal orbital lymphoma (Table 1).

Table 1. Patients' demographics and characteristics of lesions in standard MR examination

Patient	Sex	Age [years]	Immunological status	Comorbidities	Histology	Number of lesions	T1 signal	T2 signal	Edema	Enhancement	Location
primary CNSL											
1	male	78	competence	none	diffuse large B-cell lymphoma	1	hyper	iso	mild	homogenous	corpus callosum
2	female	76	competence	none	diffuse large B-cell lymphoma a	multiple (1 measured)	iso	iso	moderate	homogenous	periventricular white matter
3a, 3b	female	84	competence	none	diffuse large B-cell lymphoma	multiple (2 measured)	iso iso	iso iso	mild moderate	homogenous homogenous	disseminated: periventricular and peripheral, all lobes
4	male	73	competence	none	diffuse large B-cell lymphoma	1	hyper	hypo	mild	homogenous	peripheral, in the right parietal lobe
5	male	65	competence	none	diffuse large B-cell lymphoma	1	hypo	iso	mild	homogenous	peripheral, in the right occipital lobe
6a, 6b	female	61	competence	none	diffuse large B-cell lymphoma a	2	iso iso	hypo hypo	moderate moderate	homogenous with central necrosis homogenous	peripheral, in the left frontal lobe peripheral, in the left parietal lobe
7	female	60	competence	none	diffuse large B-cell lymphoma a	1	hypo	iso	mild	homogenous with central necrosis	peripheral, in the left frontal lobe
8a, 8b	female	73	competence	none	angiocentric diffuse large B-cell lymphoma	multiple (2 measured)	hyper hyper	hyper hyper	mild mild	homogenous homogenous	disseminated: corpus callosum, bilateral white matter along small vessels
9a, 9b	female	46	deficiency due to immunosuppressive treatment	systemic lupus erythematosus	diffuse large B-cell lymphoma	2	hyper hyper	hypo hypo	mild mild	inhomogeneous, peripheral ring inhomogeneous, peripheral ring	peripheral, in the right temporoparietal region peripheral, in the left occipital lobe
10	male	6	deficiency due to bone marrow transplantation	juvenile xanthogranuloma	B-cell lymphoma associated with EBV	1	hypo	iso	large	homogenous with central necrosis	peripheral, in the frontal lobe
secondary CNSL											
11	male	64	competence	systemic lymphoma	diffuse large B-cell lymphoma	1	hypo	hypo	non	homogenous	pituitary infundibulum
12	female	64	competence	orbital lymphoma	diffuse large B-cell lymphoma	1	hyper	hypo	large	homogenous	in the left basal ganglia

CNSL – central nervous system lymphoma; EBV – Epstein-Barr virus; MR – magnetic resonance; T1 – longitudinal relaxation time; T2 – transverse relaxation time.

After providing written consent, all patients underwent MR examinations of the brain with contrast injection, including diffusion and perfusion sequences. All procedures were performed in accordance with the Helsinki Human Rights consensus, and the study was approved by the Commission of Bioethics at Wrocław Medical University.

Data acquisition

All examinations were performed on a 1.5 T MR scanner (Signa Hdx; GE Medical Systems, Milwaukee, USA), using a 16-channel head-neck-spine (HNS) coil. Before contrast administration, a standard MR examination was carried out, including axial T1 (longitudinal relaxation time)-weighted images, axial, coronal and sagittal T2 (transverse relaxation time)-weighted images, as well as axial fluid-attenuated inversion recovery (FLAIR) images.

Diffusion-weighted imaging was performed using transverse single-shot echoplanar diffusion-weighted sequence with the following parameters: echo time (TE) – 89.9 ms, repetition time (TR) – 8000 ms, slice thickness – 5 mm, field of view (FOV) – 26 cm, matrix size – 128×128 , number of excitations (NEX) – 1.0, diffusion sensitive gradient – $b = 1000 \text{ s/mm}^2$ in the 3 orthogonal directions, scanning time – 42 s.

Perfusion-weighted imaging was performed with the DSC method using fast echoplanar T2*-weighted gradient echo sequence with the following parameters: TR – 1.900 ms, TE – 80 ms, FOV – 30 cm, matrix size – 192×128 , slice thickness – 8 mm without spacing, NEX – 1.0. A bolus of a 1.0 mol/L gadobutrol formula (Gadovist; Bayer Health Care, Leverkusen, Germany) in a dose of 0.1 mL/kg of body weight was injected 10 s after the start of image acquisition via a 20-gauge catheter placed in the antecubital vein. Contrast was administered with an automatic injector (Medrad; Bayer Medical Care, Indianola, USA) at a rate of 5 mL/s

and was followed by a saline bolus (20 mL at 5 mL/s). The whole perfusion imaging lasted 1 min 26 s, in which sets of images from 13 axial slices were obtained before, during and after contrast injection. After PWI, a postcontrast T1-weighted 3D sequence was performed based on contrast administered earlier in the perfusion examination.

In 2 patients, PWI was performed using the preload leakage correction method. Gadolinium contrast in a dose of 0.05 mmol/kg was administered as a prebolus 3 min before the dynamic phase of DSC T2* perfusion; it was then followed by the standard DSC technique as described above.

In the study, 1 patient (Patient 4) underwent 2 types of perfusion examinations – with (4–1) and without (4–2) a preloading bolus in the interval of 4 weeks.

Data postprocessing

In all cases, the morphological assessment of the lesions was performed on the basis of T1-, T2-weighted and post-contrast T1-weighted images, using visual inspection.

The diffusion- and perfusion-weighted images were post-processed using Functool software (ADW v. 4.4; GE Medical Systems SCS, Buc, France).

Diffusion-weighted imaging analysis

The measurements of ADC for the whole tumor (ADC_c) and of minimal ADC (ADC_{min}) were assessed. The ADC_c values were obtained by manual outlining of the entire lesion on each slice, and then by calculating the arithmetical means from all measured ADC values. Minimal ADC was measured by placing a small region of interest (ROI) ($40\text{--}60 \text{ mm}^2$) in the location of the lowest value of this parameter on each slice; the lowest value from all the slices was chosen as the tumoral ADC_{min} . Both ADC_c and ADC_{min} values were normalized to the normal appearing white

Fig. 1. A typical multifocal primary CNSL located in the basal ganglia and the corpus callosum

A – axial T1-weighted MR image after contrast administration, showing strong enhancement; B – ADC map with restricted diffusion; C – CBV perfusion map with drawn ROIs showing hypoperfusion; D – signal intensity perfusion curve exceeding the baseline level with marked characteristic time points: S0, Smin, S1; ADC – apparent diffusion coefficient; CBV – cerebral blood volume; CNSL – central nervous system lymphoma; MR – magnetic resonance; ROI – region of interest.

matter (NAWM) of the contralateral hemisphere in order to obtain the relative values of these parameters (relative $ADC_c - rADC_c$; relative $ADC_{min} - rADC_{min}$).

Perfusion-weighted imaging analysis

The analysis was based on an evaluation of the CBV parameter on CBV maps, as well as of the values of peak height (PH) and percentage of signal recovery (PSR) derived from perfusion curves. The CBV maps were computed on a pixel-wise basis from the first-pass data as described by Rosen et al.²² The measurements of CBV were performed by placing ROIs on the CBV maps fused with post-contrast T1-weighted images in order to accurately assess the tumor core (Fig. 1). The values of PSR and PH were calculated from the perfusion curves based on formulas: $PSR = (S1 - Smin)/PH$, $PH = Smin - S0$, where: $S0$ – start of contrast passage, $Smin$ – maximal drop of magnetic susceptibility, $S1$ – measurement after 24 s from $Smin$ (Fig. 1). All CBV, PH and PSR values were normalized to values from the NAWM of the contralateral hemisphere in order to obtain relative values of all parameters: $rCBV$, relative PH (rPH) and relative PSR ($rPSR$).²³

In each tumor, the measurements of mean values of all perfusion parameters for the whole tumor core ($rCBV_c$, rPH_c , $rPSR_c$) and of maximal values of these parameters ($rCBV_{max}$, rPH_{max} , $rPSR_{max}$) were assessed. The mean values for the whole tumor were obtained by manually outlining the entire lesion on each slice (Fig. 1) and calculating the arithmetical means from all measured values. Maximal values were obtained by placing small ROIs (40–60 mm²) over several hot spots on each slice (Fig. 1). The highest value from all ROIs was chosen as the tumoral maximal value.

Statistical analysis

Comparisons of diffusion and perfusion values between different subject groups were performed using the t-test with p-values <0.05 set as the significance threshold. Diffusion and perfusion parameters were compared between primary and secondary CNSLs, as well as between primary CNSLs in the immunocompetent and immunodeficient patients. We also compared perfusion parameters acquired with and without a preloading bolus.

Results

Results of standard magnetic resonance examinations

All CNSLs (both primary and secondary) showed variable T1 and T2 appearance ranging from hypo- to hyperintense lesions (Table 1). They were mostly iso- (44%) or hypointense (44%) to the white matter on T2-weighted images, with a different range of surrounding edema (Table 1).

All immunocompetent patients showed lesions with strong homogenous enhancement, while in the immunocompromised patients a heterogenous, also ring-like, enhancement pattern was found (Table 1).

In the group of CNSLs (both primary and secondary) there were subjects with single or multiple lesions (Table 1). The location of foci was variable (Table 1). All primary CNSLs were located intra-axially within the brain parenchyma, while secondary lesions were located either intra-axially (basal ganglia) or extra-axially (pituitary infundibulum).

Diffusion results

All CNSLs showed low mean values of all evaluated diffusion parameters ($ADC_c = 0.70 \times 10^{-3}$, $ADC_{min} = 0.54 \times 10^{-3}$), which were also lower compared to NAWM ($rADC_c = 0.92$ and $rADC_{min} = 0.71$) (Table 2).

Table 2. Results of DWI measurements

Patients	ADC_c [$\times 10^{-3}$]	ADC_{min} [$\times 10^{-3}$]	$rADC_c$	$rADC_{min}$
primary CNSLs				
immunocompetent				
1	0.57	0.42	0.77	0.67
2	0.76	0.47	0.89	0.55
3a	0.81	0.56	1.05	0.72
3b	0.81	0.67	1.05	0.86
4-1	0.69	0.53	0.88	0.73
4-2	0.69	0.62	0.88	0.78
5	0.59	0.52	0.77	0.67
6a	0.65	0.57	0.89	0.78
6b	0.96	0.73	1.33	1.01
7	0.65	0.54	0.93	0.77
8a	0.58	0.47	0.77	0.62
8b	0.65	0.56	0.86	0.74
mean values	0.70	0.55	0.93	0.74
immunodeficient				
9a	0.79	0.51	1.01	0.65
9b	0.65	0.40	0.83	0.57
10	0.67	0.51	0.78	0.59
mean values	0.70	0.47	0.87	0.60
all primary CNSLs				
mean values	0.70	0.54	0.92	0.71
secondary CNSLs				
11	0.59	0.53	0.68	0.62
12	0.80	0.57	1.16	0.83
mean values	0.70	0.55	0.92	0.73
all CNSLs (primary and secondary)				
mean values	0.70	0.54	0.92	0.72

ADC_c – apparent diffusion coefficient for the whole tumor;
 ADC_{min} – minimal ADC; CNSL – central nervous system lymphoma;
 DWI – diffusion-weighted imaging; $rADC_c$ – relative ADC_c ;
 $rADC_{min}$ – relative ADC_{min} .

Individual analysis of all subjects showed that 5 out of 16 tumors (31%) revealed ADC_c values similar or slightly higher compared to NAWM (Patients: 3a, 3b, 6b, 9a, 12) while 11 out of 16 tumors (69%) showed lower values, indicating restricted diffusion within the entire tumor core (Table 2). When analyzing ADC_{min} , only 1 subject (Patient 6b) revealed values similar to NAWM. In all other cases, which is 94% of subjects, the values of ADC_{min} were lower than NAWM, which indicated restricted diffusion.

There were no statistically significant differences in all evaluated ADC values between primary and secondary CNSLs, or between immunocompetent and immunodeficient subjects with primary CNSLs (Table 2).

Table 3. Results of PWI measurements

Patients	rCBV _c	rCBV _{max}	rPH _c	rPH _{max}	rPSR _c	rPSR _{max}
DSC perfusion without a preload bolus						
primary immunocompetent CNSLs						
1	0.72	1.02	1.20	1.59	1.55	1.80
2	0.40	0.83	0.99	1.30	1.95	2.11
3a	0.45	0.52	0.74	1.10	1.48	1.54
3b	0.91	1.85	0.83	1.14	1.47	2.43
4-2	0.81	1.11	1.22	1.41	1.50	1.85
5	0.53	1.70	0.97	1.76	2.49	3.95
6a	0.31	0.44	1.05	1.29	1.95	2.10
6b	0.53	0.87	0.80	1.85	3.24	3.25
7	1.41	1.65	1.43	1.89	1.31	1.51
mean values	0.67	1.11	1.03	1.48	1.88	2.28
primary immunodeficient CNSLs						
9a	1.12	2.17	1.49	3.01	1.49	1.67
9b	0.93	1.04	1.32	1.70	1.23	1.29
10	0.43	0.79	0.84	0.86	3.78	5.83
mean values	0.82	1.33	1.22	1.86	2.17	2.93
all primary CNSLs						
mean values	0.71	1.17	1.07	1.58	1.95	2.44
secondary CNSLs						
11	1.69	2.22	0.79	1.76	2.28	2.28
12	1.06	1.66	0.98	1.62	2.12	2.12
mean values	1.38	1.94	0.89	1.69	2.20	2.20
all CNSLs (primary and secondary)						
mean values	0.80	1.27	1.05	1.59	1.99	2.41
DSC perfusion with a preload bolus						
8a	2.35	3.34	3.24	4.11	1.54	1.82
8b	1.95	2.60	2.13	2.55	1.46	1.46
4-1	2.01	2.81	2.32	2.97	0.97	1.05
mean values	2.10	2.92	2.56	3.21	1.32	1.44
all DSC examinations (with and without a preload bolus)						
mean values	1.04	1.58	1.31	1.81	1.87	2.24

DSC – dynamic susceptibility contrast; PWI – perfusion-weighted imaging; rCBV_c – relative cerebral blood volume for the whole tumor; rCBV_{max} – relative maximal CBV; rPH_c – relative peak height for the whole tumor; rPH_{max} – relative maximal PH; rPSR_c – relative percentage of signal recovery for the whole tumor; rPSR_{max} – relative maximal PSR.

Perfusion results

All CNSLs examined using the DSC perfusion method without a preloading bolus showed low mean values of rCBV_c, rCBV_{max}, rPH_c, rPH_{max}, as well as high values of rPSR_c and rPSR_{max}, indicating hypoperfusion and overshooting of perfusion curve above the baseline level (Table 3).

Primary CNSLs showed significantly lower ($p = 0.02$) values of rCBV_c (mean 0.71; range 0.31–1.41) compared to secondary CNSLs (mean 1.38; range 1.06–1.69). The values of rCBV_{max} in secondary CNSLs were slightly higher compared to primary CNSLs, but the difference did not reach the significant level ($p = 0.08$) (Table 3). The values of rCBV_{max}

in primary CNSLs ranged from 0.44 to 2.17, while in secondary CNSLs from 1.66 to 2.22. Only 3 out of 14 tumors (21.4%) showed values of rCBV_{max} higher than 1.75, but not exceeding 2.22. There were no significant differences in the values of perfusion parameters derived from perfusion curves between primary and secondary CNSLs.

When immunocompetent and immunodeficient patients were compared with primary CNSLs, no differences were found in the values of all perfusion parameters between these 2 groups.

Compared to DSC without a preload bolus, primary CNSLs, which were examined using a preload bolus, revealed statistically higher ($p < 0.001$) mean values of rCBV_c (mean 2.10; range 1.95–2.35), rCBV_{max} (mean 2.92; range 2.6–3.34), rPH_c (mean 2.56), and rPH_{max} (mean 3.33), as well as significantly lower rPSR measurements (Table 3). Patient 4 examined with both perfusion techniques also showed significantly different results of all perfusion parameters with higher rCBV and rPH values as well as lower rPSR values in the DSC technique with a use of a preloading bolus (4–1) compared to the follow-up examination without a preload (4–2) (Table 3).

Discussion

Our study based on the group of 16 CNSLs tumors showed a great variety of radiological appearances on conventional MR sequences, which is typical for these tumors. We observed a wide

Fig. 2. Primary CNSLs (in immunocompetent patients) mimicking other tumors such as meningioma (A–D) and metastases (E–H)

All CNSLs show strong homogeneous enhancement on postcontrast T1-weighted images (A, E), restricted diffusion on ADC maps (B, F), low perfusion on CBV maps (C, G) and a typical shape of the perfusion curves above the baseline (D, H).

ADC – apparent diffusion coefficient; CBV – cerebral blood volume; CNSL – central nervous system lymphoma.

range of signal changes on T1- and T2-weighted images, different patterns of contrast enhancement, as well as different numbers and locations of tumoral foci.

T2 hypointensity is reported to be one of the very characteristic features of CNSLs, attributed to their high nuclear/cytoplasmatic ratio.^{1–3,14} In the group of our subjects, we found low T2 signal in 44% of all CNSLs, T2 isointensity also in 44% of CNSLs, while high T2 signal only in 12% of all subjects. T2 hypointensity was found in all groups of evaluated primary and secondary lymphomas, as well as in immunocompromised and immunocompetent subjects. In our study, all subjects with CNSLs with competent immune system revealed solid and homogenous contrast enhancement (84.6%), which was also reported in the literature.^{1–3,14} On the other hand, immunocompromised individuals showed inhomogeneous enhancement, including a peripheral ring-like pattern. This inhomogeneity is found to be typical and is explained by lower focal cellularity, resulting from tumor necrosis in patients with depressed immunity.^{1–3,14,16} The number of lesions in each patient varied from a single tumor found in all subject groups to multiple foci characteristic for primary CNSLs in immunocompetent patients. Almost all evaluated tumors showed an intra-axial location, either peripherally, or within deep structures, except for 1 case of secondary lymphoma within pituitary infundibulum, which is also consistent with literature reports.^{2,3}

To summarize the findings of standard MR examinations, in our study, primary CNSLs in immunocompetent patients were intra-axial lesions with various T2 signal, as well as strong and solid enhancement, with a tendency to appear in multiple foci. On the other hand, primary CNSLs in immunodeficient patients appeared as T2 hypo- or isointense lesions with inhomogeneous enhancement, including a ring-like pattern with peripheral intra-axial location, while secondary CNSLs were lesions with very similar MR appearance to primary CNSLs in immunocompetent subjects, apart from their tendency to appear in an extra-axial location.

As presented above, CNSLs in our study were a highly variable group of tumors in standard MR imaging, mimicking other focal brain lesions. All cases of single lesions required differentiation from other brain tumors, including gliomas and even meningiomas due to their tendency to contact with meningeal surfaces (Fig. 2 A–D). Multiple homogenous masses with diffuse surrounding edema were highly suggestive of metastases (Fig. 2 E–H), while multiple disseminated lesions strongly mimicked inflammatory changes or angitis in 1 case (Patient 8).

As mentioned by Haldorsen et al. and also confirmed by an analysis of our material, standard MR imaging is not sufficient to unequivocally differentiate CNSLs from other brain lesions, thus newer advanced imaging techniques

should be added to aid the accurate diagnosis of these tumors.³ Several techniques have been reported to improve the differentiation of CNSLs, including DWI, PWI, MR spectroscopy, and diffusion tensor imaging (DTI).^{12,16,19,20} To our knowledge there are still no reports on a detailed analysis of both DWI and PWI in various CNSLs, including primary and secondary disease, as well as various immune status of evaluated patients.

Diffusion-weighted imaging is an imaging technique which may provide information regarding tumor cellularity and biology, based on the fact that cells constitute a barrier to water diffusion. Highly cellular tumors such as lymphomas tend to demonstrate a restriction of water diffusion, and thus decreased values of the ADC parameter.^{16,18–20} In our study, an analysis of DWI results showed low mean values of ADC_c and ADC_{min} in the group of all evaluated subjects, which is consistent with previous reports.^{16,18–20} We also looked at individual subjects and revealed that in 69% of all evaluated lymphomas, the ADC_c values were lower than in NAWM, indicating homogeneously restricted diffusion within the entire tumor load, and when searching for areas of the lowest ADC values (ADC_{min}), 94% of evaluated lesions showed small regions of restricted diffusion.

In our study, we also did not find any significant differences in all evaluated ADC values between primary and secondary, or between immunocompetent and immunodeficient subjects with primary CNSLs, which indicates that restricted diffusion is a consistent DWI finding in all CNSLs. We did not find any other DWI studies comparing primary and secondary lymphomas in the literature. On the other hand, Zacharia et al. evaluated the ADC parameters in immunocompetent and immunodeficient primary CNSLs but without detailed comparisons between these 2 groups of patients.¹⁶ They focused on comparisons between lesions with homogenous, inhomogeneous and ring-like enhancement, reporting restricted diffusion in all tumors except for 2 ring-enhancing lesions, which led to an incorrect diagnosis of the infection. It has to be stressed that in our study of ring-enhancing lymphomas, all DWI parameters were obtained from the periphery of these lesions and in all cases we found large areas of restricted diffusion. It is crucial to identify correctly areas of restricted diffusion in inhomogeneously enhancing lymphomas, since this is a characteristic feature of these tumors, which can be used to differentiate them from others, such as gliomas or metastases, which show higher ADC values or only small areas of restricted diffusion consistent with the most malignant parts of these tumors.^{6,14,17,18,21}

In the next part of our study, we also evaluated the results of perfusion examinations. In the majority of cases, we used the DSC perfusion method without a preload, which is the most often performed perfusion technique in the evaluation of focal brain lesions. Relative CBV is the most important perfusion parameter in the evaluation of brain tumors, which correlates with their regional vascularity and

is increased in tumors with a high rate of pathologic neoangiogenesis.¹² Since most brain tumors are in some parts inhomogeneous, the parameter of $rCBV_{max}$ is the most important and commonly used in everyday practice as the one reflecting the most malignant areas within a tumor core (the so-called hot spots). In glial tumors, increased $rCBV$ ratios indicate increased malignancy, but this rule cannot be applied to other tumors, for example meningiomas, which are highly perfused lesions, but benign in terms of biological behavior, or lymphomas, which are malignant lesions with relatively low perfusion values. Low values of $rCBV$ in lymphomas can be explained by the histopathological appearance of these tumors – their high cellularity, complete absence of neoangiogenesis and angiocentric growth pattern.¹² In our study, similarly to previous reports, low mean values of $rCBV$ (both $rCBV_c$ and $rCBV_{max}$) ranging from 0.44 to 2.22 were found within all evaluated lymphomas.^{3,12–14} Several studies have demonstrated that glioblastomas (GBMs) and metastases may reach very high $rCBV_{max}$ values of 3.0 or even 10.0, mainly due to a high concentration of microvessels,^{12,24} and $rCBV$ of 1.75 has been set as the threshold value differentiating low-grade and high-grade gliomas.^{26,27} It has to be pointed out that 79% of all CNSLs in our study showed $rCBV_{max}$ values <1.75 , similarly to low grade gliomas, and 21% revealed $rCBV_{max}$ values >1.75 , but not exceeding 2.22, which is very unusual for high-grade gliomas, metastases or meningiomas. Though lymphomas may strongly mimic high-grade gliomas, metastases or even meningiomas in their conventional MR appearance, they show low perfusion values similarly to low-grade gliomas, which may be a very helpful feature in the correct differential diagnosis of these lesions.

Subsequently, we also evaluated the perfusion curves of CNSLs. Low rPH and high $rPSR$ values were observed in the majority of cases. High $rPSR_{max}$ in lymphomas is consistent with an overshooting of the signal intensity curve above the baseline level, which was observed in 100% of our cases. The $rPSR$ ratio was reported by Mangla et al. to be the most sensitive and specific feature in the differentiation of lymphomas from GBMs and metastases.¹² Furthermore, there are other reports of significantly reduced PSR in metastases and GBMs compared to CNSLs, reflected in the perfusion curve not crossing the baseline.^{12,14}

Since hypoperfusion in lymphomas can be explained by hypovascularization and the absence of neoangiogenesis, the exact explanation of the signal intensity curve returning above the baseline level is difficult and not fully understood.^{12,14} It is probably due to gadolinium extravasation into the interstitial space and complex T1 and T2 effects, which can alter the shape of the perfusion curve. T2 effects lead to lower signal intensity recovery, while T1 effects cause higher signal intensity recovery.^{12,28} In lymphomas, T1 effects, probably due to an extensive accumulation of contrast material in the interstitial space, dominate over T2 effects and cause the characteristic overshooting from the baseline.^{12,28,29} However, so far, no definite explanation has been

Fig. 3. A patient with a single CNSL lesion in the right parietal lobe examined with 2 DSC perfusion techniques with (A–C) and without (D–F) a preloading bolus

Axial T1-weighted MR images (A, D) after contrast administration, showing strong enhancement. The CBV perfusion map with a preload (B) shows hyperperfusion compared to hypoperfusion seen on the CBV map without a preload (E). The perfusion curve after a preload (C) exceeds the baseline compared to the perfusion curve without a preload, which does not reach the baseline (F).

CBV – cerebral blood volume; CNSL – central nervous system lymphoma; DSC – dynamic susceptibility contrast; MR – magnetic resonance.

given for overshooting in lymphomas in DSC perfusion without a preload. This phenomenon is probably caused by several factors and a complex interplay between them.¹²

Moreover, in our study we also compared all perfusion parameters between primary and secondary CNSLs, as well as between immunocompromised and immunocompetent patients. Secondary CNSLs revealed significantly higher $rCBV_c$ values compared to primary CNSLs, but still lower than 1.75. There were no other significant differences in any other perfusion parameters derived from CBV maps or perfusion curves among all evaluated patients subgroups. To our knowledge there are no reports in the literature that compare perfusion parameters in various lymphoma subgroups.

The last part of our investigation was to compare the results of 2 different perfusion techniques – with and without a preload bolus of contrast. The perfusion results after a preload indicated hyperperfusion of the evaluated lymphomas (high $rCBV$ and rPH values) and showed the perfusion curves with only a partial return to the baseline level (low $rPSR$ values). These results differed significantly from the values obtained in the perfusion technique without a preload.

In a few previous studies their authors have also analyzed CNSLs in PWI with a preload.^{15,25,30} Preload dosing techniques have been proposed to minimize and correct for T1-weighted leakage due to blood–brain barrier, as well as T2- and/or T2*-weighted imaging residual effects characteristic for DSC perfusion techniques without a preload. These techniques are useful in differentiating between post-treatment radiation injury and recurrence of high-grade gliomas, where the blood–brain barrier disruption is significant and can lead to an underestimation of $rCBV$ measurements.^{7,9,23} On the other hand, a preload in CNSLs elevates their CBV values and effaces the characteristic perfusion curve, making them more similar to perfusion characteristics of high-grade gliomas, metastases or meningiomas. Therefore, in our opinion this technique brings a disadvantage in the case of lymphomas, because it makes their differentiation from other tumors impossible.^{15,25,30}

A good practical example illustrating the differences between DSC methods with and without a preload is the case of Patient 4, who was examined with both techniques. The initial examination with a preload resulted in high $rCBV$ values with $rCBV_{max}$ reaching 2.81 and a wrong diagnosis

of a metastasis (Fig. 3 A–C). The follow-up examination without a preload presented typical perfusion characteristics of CNSLs, such as hypoperfusion and the perfusion curve returning above the baseline level, which enabled the correct diagnosis of lymphoma confirmed later in biopsy (Fig. 3 D–F).

Conclusions

Despite their various appearances in conventional MR examinations, CNSLs (both primary or secondary and in patients with different immunological status) show very typical patterns in DWI and PWI without a preload bolus, such as diffusion restriction and hypoperfusion with the signal intensity curves returning above the baseline, respectively. These features enable us to differentiate CNSLs from other brain tumors, such as high-grade gliomas, metastases or meningiomas. In our opinion, advanced MR techniques such as DWI and PWI without a preload, as methods easy to perform and interpret, should be routinely incorporated in the initial workup of all brain tumors.

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