Preoperative differentiation of high grade gliomas, metastases and primary central nervous system lymphomas using perfusion and diffusion weighted MR imaging

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Aims and objectives

In standard MR examination high grade gliomas (HGG), metastases (meta) and primary central nervous system lymphomas (PCNSL) may show very similar appearance, especially when they appear as solitary enhancing lesions surrounded by a large edema (Fig. 1).

The aim of the study was to evaluate usefulness of additional MR sequences such as perfusion (PWI) and diffusion (DWI) weighted imaging in the preoperative diagnosis of these tumors.

Diffusion weighted imaging is a sensitive tool that allows quantifying of physiologic alterations in water diffusion which result from microscopic structural changes that are not detectable with anatomical MR imaging. Water diffusion can be measured with a parameter of apparent diffusion coefficient (ADC). Diffusivity of water depends primarily on the presence of microscopic structural barriers in tissue such as membranes of cell bodies, axons and myelin sheaths that can alter the random motion of water molecules. Highly cellular tumors show areas of restricted diffusion with low ADC values, thus ADC is regarded as a marker of tumor cellularity [1].

Perfusion weighted imaging is a method that brings information on cerebral physiology at the capillary level (microvasculature). Among a few PWI techniques dynamic susceptibility contrast (DSC) MR imaging is the most often used. The method is based on the measurements of the MR signal using T2*-weighted sequence during the first pass of a bolus of a paramagnetic contrast agent. DSC MRI provides maps of cerebral blood volume (CBV) and noninvasive measurements of relative cerebral blood volume (rCBV). In brain tumors rCBV is defined as the ratio between CBV in the tumor and CBV in the white matter of the contralateral hemisphere. rCBV parameter correlates with tumor vascularity and is increased in tumors with high rate of pathologic neoangiogenesis, thus rCBV is regarded as a marker of neovascularization [2]. rCBV is the most often evaluated perfusion parameter but the usefulness of other perfusion parameters derived from perfusion curves has also recently been reported [3]. One of these parameters is Percentage of Signal Recovery (PSR) which represents the percentage of signal intensity that is recovered at the end of the first pass of contrast agent relative to baseline.

We have performed a retrospective study of common malignant intracranial lesions to evaluate the diagnostic role of DWI and DSC imaging in enhancing and perienhancing regions.
**Fig. 1:** Post contrast T1-weighted (a-c) and T2-weighted (d-f) images showing very similarly appearing solitary, contrast enhancing tumors surrounded by large edema which were histologically proven to be: glioblastoma multiforme (a, d), metastasis (b, e) and lymphoma (c, f).

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Methods and materials

The study group consisted of 50 patients with biopsy proven supratentorial tumors: 20 patients with glioblastoma multiforme GBM (mean age: 57 yrs), 20 with metastases (mean age: 60 yrs) and 9 with PCNSL (mean age: 61 yrs). Ten metastases originated from lung cancer, 4 from intestinal cancer, 2 from breast cancer, 2 from renal cancer and 2 were of an unknown origin. All PCNSLs were cell-B lymphomas.

Data acquisition:

The imaging examinations were performed with 1.5 T MR unit (Signa Hdx, GE Medical Systems) using sixteen-channel coil dedicated for head and spine imaging. The standard brain protocol consisted of axial T1, T2-weighted and FLAIR images as well as coronal and sagittal T2-weighted images followed by DWI and post contrast DSC perfusion and T1-weighted images.

Diffusion weighted imaging (DWI)

Transverse single-shot echo-planar diffusion-weighted imaging was carried out using the following parameters: TE 89.9 ms, TR 8000 ms, slice thickness - 5mm, FOV 26 cm, matrix size 128 x 128, NEX - 1, diffusion sensitive gradient $b = 1000 \text{s/mm}^2$ in the three orthogonal directions, scanning time: 42 seconds. Axial DWI images were parallel to the anterior commissure-posterior commissure (AC-PC) line.

Perfusion weighted imaging (PWI)

DSC MR imaging was performed using gradient echo planar T2* -weighted sequence with the following parameters: TR = 1.900 ms, TE = 80 ms, FOV = 30 cm, matrix = 192 x 128, slice thickness = 8 mm without spacing, NEX - 1.0. Ten seconds after the start of the image acquisition a bolus of a 1.0-mmol/l gadobutrol formula (Gadovist, Schering Bayer Pharma) in a dose of 0.2 mmol/kg of body weight (as indicated by the producing company) was injected via 20-gauge catheter placed in the antecubital vein. Contrast administration was performed using an automatic injector (Medrad) 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 minute and 26 seconds in which sets of images from 13 axial slices parallel to the anterior commissure-posterior commissure plane were obtained before, during and after contrast injection.

After dynamic studies postcontrast T1-weighted 3D images were performed using contrast administered for perfusion examination.
During the whole MR examination the subjects were instructed to keep their eyes closed. No sedation or anesthesia were used in any of the patients.

Image postprocessing

The DWI and PWI images were postprocessed using Functool software (ADW 4.4, GE Medical Systems).

Diffusion weighted imaging

Measurements of ADC for the whole tumor (mean ADC) and measurements of minimum ADC (min ADC) were assessed. Mean ADC values were obtained by manual outlining of the entire tumor on each slice and then by calculating the arithmetical means from all measured ADC values (Fig. 2). Min ADC value was measured by placing small ROI (40-60 mm$^2$) in the location of the lowest value of this parameter in the whole tumor (Fig. 2).

Perfusion weighted imaging

The analysis was based on evaluation of CBV values as well as a parameter of percentage of signal recovery (PSR) derived from a perfusion curve. PSR was calculated based on a formula: $\text{PSR} = \frac{S0 - S1}{S0 - Smin}$, where: $S0$ - start of contrast passage, $Smin$ - maximum drop of magnetic susceptibility, $S1$ - measurement after 24 seconds from $Smin$ (Fig. 2).

All CBV and PSR values were normalized to the normal appearing white matter of the contralateral hemisphere, obtaining relative values of perfusion parameters: (rCBV, rPSR).

Measurements of perfusion parameters were processed for the whole tumor core (mean rCBV, mean rPSR) and for locations with the highest values of rCBV within a tumor core. Values of parameters from the whole tumor were obtained by manual outlining of the entire tumor on each slice (Fig.2) and subsequently calculating the arithmetical means from all the measured values. Maximum rCBV values were obtained measuring perfusion parameters in locations of the highest values using small ROI (40-60 mm$^2$) (Fig.2).

In the hyperperfused tumors DWI and PWI analysis was also performed in the peritumoral non-enhancing area of T2-hyperintensity obtaining mean ADC and min ADC as well as mean rCBV, mean rPSR and max rCBV in the manner similar to the measurements within the tumor core (Fig. 3).
Fig. 2: Regions of interest (ROIs) placed on ADC (a) and CBV (b) maps: large ROIs outlining the entire tumor core and small ROIs in the regions of minimum ADC values and maximum CBV values. Green ROI on the CBV map is placed in the normal appearing white matter of the contralateral hemisphere to obtain relative CBV values (rCBV). C-signal intensity perfusion curve with marked baseline (yellow line) and significant time points (S0 - start of contrast passage, Smin - maximum drop of magnetic susceptibility, S1 - signal intensity after 24 seconds from Smin).

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Fig. 3: Regions of interest (ROIs) placed on ADC (a) and CBV (b) maps: large ROIs outlining the entire non-enhancing T2-hyperintense zone and small ROIs in the regions of minimum ADC values and maximum CBV values.
Results

Measurements from the tumor core:

There were no significant differences between GBM and metastases in the values of: max rCBV values (4.8 and 5.3, respectively), mean rCBV (2.26 and 3.01, respectively), mean rPSR (1.21 and 0.97, respectively), mean ADC (0.99 and 1.09, respectively) and min ADC (0.76 and 0.83, respectively) (Fig. 4).

Compared to metastases and GBM, PCNSL showed significantly lower max rCBV (0.97) and mean rCBV values (0.53), significantly higher mean rPSR (2.25) as well as lower values of mean ADC (0.73x10^{-3}) and min ADC (0.55x10^{-3}) (Fig. 4).

Comparing PCNSLs to GBMs and metastases, there was no overlap in the values of max rCBV and mean rCBV (sensitivity and specificity 100%) (Fig. 5).

There was a certain overlap in values of mean rPSR, mean ADC and min ADC between PCNSLs and the combined group of metastases and GBMs (Fig. 5).

Measurements from the peritumoral zone:

In the peritumoral region GBM showed significantly higher values of max rCBV compared to metastases (1.9 and 0.8, respectively), without any differences in the values of mean rCBV as well as mean ADC and min ADC (Fig. 6).

There was a slight overlap in the values of max rCBV between GBM and metastases (range: 0.28-3.75 and 0.53-0.9, respectively). Twenty percent of GBM similarly to metastases did not show areas of high max rCBV values in the peritumoral zone.
Fig. 4: Mean values of diffusion and perfusion measurements within the tumor core in patients with GBM, metastases and lymphoma. The table shows similar results for GBM and metastases and significantly different results for lymphoma.

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<table>
<thead>
<tr>
<th>Results from the tumor core</th>
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<tr>
<td>max rCBV</td>
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</tr>
<tr>
<td>GBM</td>
</tr>
<tr>
<td>PCNSL</td>
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<td>p = 0.002</td>
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Fig. 5: Detailed results of diffusion and perfusion measurements within the tumor core in patients with GBM, metastases and lymphoma.

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**Fig. 6:** Mean values of diffusion and perfusion measurements within the peritumoral non-enhancing T2-hyperintense zone in patients with GBM and metastases. The table shows significantly higher values of max rCBV in GBM compared to metastases.

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<table>
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<tr>
<th></th>
<th>max rCBV</th>
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<th>mean rPSR</th>
<th>mean ADC</th>
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<tbody>
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<td>0.59</td>
<td>1.19</td>
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</tr>
<tr>
<td>GBM</td>
<td>1.9*</td>
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</table>
Conclusion

In our study we evaluated DWI and perfusion parameters in both enhancing and perienhancing regions in common malignant brain lesions such as GBM, metastases and PCNSL.

Differentiation of lymphoma from GBM and metastases

Evaluating the tumor core, we found very similar results of all evaluated parameters in GBM and metastases and significantly different results in PCNSL.

In our study, similarly to previous reports [3-6], GBM and metastases occurred to be hyperperfused tumors with partial return of the perfusion curves to the baseline, with no diffusion restriction while PCNSL appeared to be tumors with low values of rCBV and very characteristic high rPSR values and diffusion restriction (Fig. 7-9). High rPSR values mean that the perfusion curve in lymphomas can go above the baseline what is known as overshooting and has been published before [3, 6] (Fig. 7).

Variability in perfusion patterns among GBM, metastases and lymphomas is linked with different vascularization of these lesions seen in histologic studies.

The microvasculature noted in GBM is characterized by glomeruloid capillaries, vascular hyperplasia as well as BBB disruption. Capillaries in metastases are similar in their structure to those from the primary tumors and have no similarity to normal brain capillaries, show prominent capillary fenestration and complete lack of BBB. Lymphomas, on the other hand, show angiocentric growth pattern, form multiple thick layers around the host vessels with invasion of the endothelial cells and the vessel lumen without neovascularization [7].

Lymphomas show very characteristic perfusion pattern with low rCBV values and the overshooting of the perfusion curve measured with high rPSR values. Since low rCBV values can be explained with hypovascularization of lymphomas, the exact explanation of high rPSR values is difficult and not fully understood. The so called overshooting of the perfusion curve 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. The T2* effects lead to lower signal intensity recovery while T1 effects cause higher signal-intensity recovery. In lymphomas probably the T1 effects due to an extensive accumulation of contrast material in the interstitial space dominate the T2* effects and cause the characteristic overshooting from baseline. Other physiologic factors such as blood flow, blood volume, vascular permeability, and leakage space or the interplay between these factors may also lead to high PSR [3].
In the study by Mangla et al, rPSR was found to be the most useful perfusion parameter in differentiation lymphomas from GBM and metastases. In contrary, in our study the most useful parameters were both mean rCBV and max rCBV values.

In our study lymphomas differed from GBM and metastases also in diffusion characteristics. Lymphomas were shown to be tumors with restricted diffusion what can be explained with very high cellularity of these lesions with small extracellular space [8]. GBM and metastases showed only areas of restricted diffusion what is associated with regional higher cellularity, in gliomas usually in the most malignant parts of lesions [8].

Differentiation of lymphomas from GBM and metastases has important clinical usefulness since lymphomas are tumors treated with chemotherapy unlike GBM or metastases which are treated with extensive surgery, chemo- and radiotherapy. The preoperative diagnosis of lymphoma is important because it can avoid extensive surgery limiting the surgical procedure to a biopsy necessary for treatment decisions.

Differentiation of GBM from metastases

Since metastases and GBM tend to show very similar perfusion and diffusion patterns due to similar rate of neovascularization and cellularity within the enhancing parts of these tumors, these measurements cannot be used to accurately differentiate these tumors. In our study we found that only evaluation of the peritumoral perienhancing regions in GBM and metastases can be useful in preoperative diagnosis of these lesions. Of all evaluated perfusion and diffusion parameters only values of max rCBV have been found to be of the highest significance. GBM showed areas of significantly higher max rCBV values in the perienhancing region indicating increased neovascularization outside the tumor core. It has to be stressed that 20% of GBM did not show this typical pattern of hyperperfusion in the perienhancing region and were thus indistinguishable from metastases showing only very low r CBV values around the tumor core indicative for pure vasogenic edema.

These results are in accordance with previous studies as well as histopathologic studies of GBM and metastases which showed infiltrative nature of GBM with increased neoangiogenesis in the perienhancing regions and pure vasogenic edema without neoplastic infiltration around metastases [3, 9].

Summary

In our opinion PWI and less significantly DWI can provide additional information helpful in distinguishing GBMs, metastases and PCNSLs. While interpreting perfusion results it is important to analyze both rCBV values and the shape of perfusion curves. In hyperperfused tumors it is important to evaluate both a tumor core and a peritumoral zone. Lymphomas are hypoperfused tumors with characteristic shape of perfusion curve exceeding the baseline and with diffusion restriction. Metastases and GBM are hyperperfused tumors with the perfusion curve showing only partial return to the baseline.
and with only focal diffusion restriction. Infiltrative growth of GBM can be depicted in PWI by showing areas of hyperperfusion within the perienhancing zone.

The most useful parameter is max rCBV which enables to differentiate all lymphomas from metastases and GBM on the basis of measurements from the tumor core as well as 80% of GBM from metastases on the basis of measurements from the peritumoral zone.

In our opinion DWI and especially PWI as easy and fast to perform techniques should be incorporated in MR protocol of all intracranial tumors.
Fig. 7: Primary central nervous system lymphoma appearing as (a) a solitary enhancing tumor, with characteristic (b) diffusion restriction (low ADC values), (c) hypoperfusion (low rCBV values) and (d) perfusion curve returning above the baseline level (high PSR values).

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Fig. 8: Solitary metastasis (a) with fascilitated diffusion on the ADC map (b), hyperperfusion on the CBV map (c) and a perfusion curve with only partial return to the baseline level (d).

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**Fig. 9:** Glioblastoma multiforme appearing as a small cortical enhancing tumor (a). CBV map (b) and CBV map overlaid on T2-weighted image (c) show hyperperfusion of the tumor itself (white arrows) and also within the peritumoral zone (black arrows) what is a feature differentiating GBM from a metastasis.

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