Central nervous system lymphomas characterization by MR spectroscopy and diffusion-weighted imaging

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Abstract

Purpose: To show the imaging findings in cases of central nervous system (CNS) lymphoma with conventional and functional (diffusion and spectroscopy) magnetic resonance imaging (MRI) techniques, emphasizing the contribution of advanced imaging techniques to improve diagnostic accuracy and rule out other tumors.

Materials and methods: Between June 2008 and January 2012 we studied 26 immunocompetent patients with a diagnosis of central nervous system tumor confirmed by pathology. A brain MRI was performed in these patients with conventional and functional techniques (diffusion and spectroscopy) and with gadolinium before surgery or biopsy.

Results: We included 26 immunocompetent patients, 13 men and 13 women. Eight patients had a diagnosis of primary CNS lymphoma and 18 had other tumors: glioblastoma with necrotic center (n = 9), anaplastic oligoastrocytoma (n = 3), metastases with necrosis (n = 4), and medulloblastoma (n = 2). Of the 26 lesions, 10 (8 lymphomas and 2 medulloblastomas) showed restricted diffusion, consistent with the high cellularity of both tumors. Spectroscopy showed increased lipids in all tumors. The difference among tumors was the place of measurement of lipids. Both medulloblastoma and lymphomas showed a lipid peak in the solid portion of the tumor while the remaining tumors showed lipids in the necrotic areas.

Conclusion: The combination of conventional MR imaging with and without intravenous contrast with diffusion and spectroscopy techniques improves the diagnostic accuracy of CNS lymphoma.

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Keywords: Central Nervous System; Lymphoma; Magnetic Resonance Imaging; Spectroscopy; Diffusion; Lipids

Introduction

Lymphoma of the central nervous system (CNS) is currently the third most common primary tumor of the CNS (about 5%), with an increasing incidence rate mainly due to immunodepressed conditions. This tumor is divided into two subtypes: primary lymphoma of the CNS and systemic lymphoma, with secondary CNS involvement (the most common subtype).

Primary CNS lymphoma accounts for 1 to 5% of all brain tumors and approximately 1% of all non-Hodgkin lymphomas. In immunocompetent patients, this tumor typically presents as a solitary intraparenchymal mass, although multiple lesions can occur less frequently.

Among secondary CNS lymphomas, approximately two-thirds present as leptomeningeal spread and one-third shows parenchymal disease. In the latter, imaging findings are similar to the findings in primary CNS lymphoma; therefore, it is impossible to discriminate between primary and secondary lymphoma on the basis of neuroimaging alone.

Conventional magnetic resonance (MR) imaging may show characteristic findings, but they are not conclusive in SNC lymphoma when there is parenchymal involvement. It usually appears as a circumscribed, oval or round lesion of periventricular location. On T1-weighted imaging, the lesion is slightly hypo- or isointense to gray matter, with some mass effect due to its size; meanwhile on T2-weighted imaging, it is typically iso-/hypointense. Intravenous (IV) contrast enhancement is typical but may vary: in immunocompetent patients homogenous enhancement occurs in approximately 90%, while the rest shows ringlike enhancement. In immunocompromised patients, 75% show ringlike enhancement.

Despite the above reported characteristics, none of these findings will unequivocally differentiate CNS lymphomas from other neoplasms. For this reason, functional techniques, namely diffusion and spectroscopy are very useful. In diffusion-weighted imaging, lymphomas often show restricted diffusion, since they are highly cellular tumors: they have a higher signal inten-
The purpose of this study is to demonstrate that an adequate analysis of conventional and functional techniques (diffusion and spectroscopy) in brain MR imaging may contribute to differentiate CNS lymphoma in immunocompetent patients from other tumors.

**Materials and methods**

**Design**

Observational, retrospective and analytical cross-sectional study.

**Population**

Immunocompetent patients with a diagnosis of CNS tumor who had had a gadolinium-enhanced conventional MRI scan.
of the brain with spectroscopy showing a positive lipid curve performed prior to surgery or biopsy sample collection.

**Period**
From June 2008 to January 2012.

**Imaging techniques**
Scans were performed using a 1.5T magnetic resonance scanner (Siemens Avanto and Philips Achieva). Sequences were performed according to our institutional protocol for SNC tumors: axial FLAIR, axial T2-weighted imaging, axial gradient-echo (GRE), sagittal T1-weighted imaging and volumetric T1-weighted imaging after intravenous contrast administration. Diffusion-weighted sequences had a coefficient of b0 and b1000, and an ADC map. In all cases, intravenous gadolinium (20 ml injection) was used as contrast material, and multivoxel or monovoxel spectroscopy were performed (the latter for infratentorial tumors) with PRESS sequence and intermediate (135 ms) and short (30 ms) echo times. Voxels were placed in such a way that the tumor site could be compared with the contralateral healthy parenchyma (in the case of monovoxel, another voxel was placed on the contralateral healthy side).

**Images review**
A radiologist specialized in neuroradiology reviewed the images obtained. First, the morphological features of the lesion were reviewed. T1-, T2-weighted and FLAIR sequences provided data on the shape, size, location, presence of perilesional edema and

![Image](image_url)

Figure 2 (a) axial T2-weighted imaging; (b) axial T1-weighted imaging with intravenous contrast; (c) diffusion coefficient b1000; (d) apparent diffusion coefficient map; and spectroscopy with (e) short echo time and (f) intermediate echo time. Primary lymphoma of the central nervous system in a 70-year-old immunocompetent female patient is evidenced. The lesion, partially involving the head of the caudate nucleus, has an intra- and extraventricular location, appears isointense on T2-weighted imaging and shows an intense homogeneous enhancement after intravenous contrast administration, with restricted diffusion. Spectroscopy in short echo time reveals the lipid curve, while the intermediate echo time shows a neo-proliferative pattern with increased choline and decreased N-acetylaspartate levels.
characteristics of the intratumoral components (solid, necrotic or mixed); while the GRE sequence was used to identify any blood component in the lesion. Diffusion was interpreted as positive (also known as restricted diffusion) when there was a higher signal on b1000 images than on the healthy contralateral brain parenchyma, and low signal on the ADC map. If there was no signal drop on the ADC map, diffusion was considered to be negative. Images obtained with intravenous contrast were analyzed on the basis of the presence or absence of enhancement of the target lesion.

Data obtained from spectroscopy were then reviewed. Reports were performed considering the Cho and NAA curves in the intermediate echo time and the lipid curve in the short echo time. The increase in the Cho curve and the decrease in the NAA peak, compared with the healthy contralateral side, were markers of tumor. Then, lipid curve results were separately interpreted. For this interpretation, the morphological site (necrotic or solid portion of the tumor) where the voxel was placed was taken into account. The presence or absence of a curve was defined as positive or negative for lipids, respectively.

Figure 3 (a) axial T2-weighted imaging; (b) axial T1-weighted imaging with intravenous contrast; (c) diffusion coefficient b1000; (d) apparent diffusion coefficient map; and spectroscopy with (e) short echo time and (f) intermediate echo time. Glioblastoma multiforme in a 54-year-old male patient. The dorsal frontal and right posterior expansive lesion of necrotic appearance with peripheral enhancement exhibits perilesional edema. Diffusion-weighted imaging shows facilitated diffusion in the inner part of the lesion, while spectroscopy reveals in the short echo time a lipid curve in the necrotic portion of the tumor and in the intermediate echo time a neo-proliferative pattern with an increase in choline and a decrease in N-acetylaspartate levels.
Pathology data
A pathologist specialized in neuropathology evaluated the samples obtained by biopsy in some cases and surgical pieces in others.

Statistical method
Continuous variables were expressed as means, with standard deviation or interquartile range depending on its distribution, and categorical variables were expressed as percentages (with 95% confidence interval). In addition, continuous variables were compared using the T test or Mann-Whitney test and categorical variables were compared using Fisher’s test or the Chi-square test. Statistical significance was set at p < 0.05.

Results
From June 2008 to January 2012, 26 cases (13 male and 13 female) with a diagnosis of CNS tumor confirmed by pathol-

Figure 4 (a) coronal T1-weighted imaging with intravenous contrast; (b) diffusion coefficient b1000; and (c) apparent diffusion coefficient. Adult medulloblastoma in a 26-year-old male patient. The solid lesion on the left cerebellar hemisphere shows post-contrast enhancement. Diffusion-weighted imaging shows restricted diffusion, while (d) spectroscopy shows an increase in choline and a marked decrease in N-acetylaspartate levels. A lipid curve is noted (arrow).
ogy were studied. These patients had had conventional MR imaging of the brain performed with gadolinium and functional techniques of diffusion and spectroscopy before surgery of biopsy sample collection.

In 5 of the 26 patients, the reason why the scan had been ordered was not available, but in the remaining 21 patients, the reasons were: aphasia (n = 3), ataxia (n = 3), epilepsy (n = 3), neurological deficit (n = 8) and findings with no clinical symptoms (n = 4).

We evaluated eight immunocompetent patients with primary CNS lymphomas (figs 1 and 2), 3 women and 5 men, with an age range between 21 and 92 years old (mean: 71 years). The remaining 18 patients, 10 men and 8 women, had an age range between 19 and 63 years (mean: 51 years). Diagnoses included: glioblastoma with a necrotic center (n = 9) (fig. 3), anaplastic oligoastrocytoma (n = 3), metastasis with necrosis (n = 4) and medulloblastoma (n = 2) (fig. 4).

The location of lymphomas was: periventricular (n = 3), subcortical (n = 2), splenium of corpus callosum (n = 1), striate body and thalamus (n = 1) and the cerebellar hemisphere (n = 1); while the other tumors were located in: cerebral hemispheres (n = 12), deep gray matter (n = 1), fourth ventricle (n = 1), cerebellar hemisphere (n = 1), brainstem (n = 1), and multiple supra- and infratentorial lesions (n = 2).

Two imaging patterns were found: 9 neoplasms showed solid lesions (7 lymphomas and 2 medulloblastomas), while the remaining 17 were mixed (solid with necrotic areas).

All lesions enhanced after IV contrast. Restricted diffusion areas were found in 10 out of 26 lesions: all lymphomas (including the mixed pattern one, as solid sites showed positive diffusion) and the 2 medulloblastomas. All other lesions did not show restricted diffusion, but on the contrary, those with a necrotic center exhibited facilitated diffusion.

The spectroscopy showed an increased in Cho, a drop in NAA and an elevated lipid curve in all 26 lesions. Lipid was found in the solid portion of the tumor in 10 of the 26 neoplasms (8 lymphomas and 2 medulloblastomas), while in the other 16, it was a finding associated with the site of tumor necrosis. Results of the statistical analysis are shown in Table 1.

**Discussion**

It is important to differentiate the diagnosis of CNS lymphoma from other neoplasms because the prognosis and therapy of this tumor are different. Although conventional MRI can provide data that may help in diagnosis, it is not specific enough to categorize this tumor.

Diffusion-weighted imaging provides data on tumor cellularity because cells constitute a barrier to free diffusion of water. This is the reason why highly cellular tumors, such as lymphoma, show restricted diffusion.

Our series was consistent with literature reports, as all lymphomas showed restricted diffusion, including those with a mixed component (which exhibited positive diffusion in solid sites). However, this finding is not specific to lymphomas; medulloblastomas also showed restricted diffusion in this study (an expected finding considering the intrinsic high cellularity of the tumor, the reduced extracellular space and high nuclear/cytoplasmic ratio).

MR spectroscopy showed in all lesions a neo-proliferative pattern (consistent with literature reports), with an increase in Cho levels and a decrease in NAA. Even if the Cho/NAA ratio can predict the degree of malignancy, it fails to differentiate the histological lineage, as it was the case in this study. As regards the lipids curve, all lesions showed an increase, but a differential histological diagnosis could be established because the site where the lipid peak occurred was analyzed.

**Table 1:** Baseline characteristics and magnetic resonance imaging.

<table>
<thead>
<tr>
<th></th>
<th>Lymphoma (n = 8)</th>
<th>Non-lymphoma (n = 18)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Gender*</td>
<td>F= 5, M= 3</td>
<td>F = 8, M = 10</td>
<td>0.673</td>
</tr>
<tr>
<td>Age (years)</td>
<td>71</td>
<td>51</td>
<td>0.08</td>
</tr>
<tr>
<td>MRI solid lesion*</td>
<td>7</td>
<td>2</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>MRI mixed lesion*</td>
<td>1</td>
<td>16</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>MRI positive diffusion*</td>
<td>8</td>
<td>2</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Spectroscopy positive for lipids*</td>
<td>8</td>
<td>18</td>
<td>NS</td>
</tr>
<tr>
<td>Site where lipids were found*</td>
<td>S = 8</td>
<td>S = 2, N = 16</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>MRI enhancement after IV contrast*</td>
<td>8</td>
<td>18</td>
<td>NS</td>
</tr>
</tbody>
</table>

F (female); M (male); S (solid); N (necrosis); NS (not significant). * absolute frequency. a Median.
while tumors of glial lineage and metastases showed an increase in the curve of necrotic areas, lymphomas and medulloblastomas showed such increase in solid portions. Lymphomas and medulloblastomas exhibited similar features. Both appeared as solid lesions with restricted diffusion (both are hypercellular), thus precluding diffusion from helping in the differential diagnosis. In addition, both showed an increase in the lipids curve (both being solid lesions), so it was not possible to differentiate one entity from the other on the basis of the short echo time spectroscopy. Despite these similarities, there are other findings that help to differentiate between both lesions: medulloblastoma is a pediatric tumor typically located in the posterior fossa.

**Conclusion**

Conventional MRI with and without intravenous contrast in combination with diffusion and spectroscopy techniques in the presence of a solid parenchymal mass that enhances with IV contrast and shows restricted diffusion and lipid peak on spectroscopy improves the diagnostic accuracy of lymphoma.

**Conflicts of interest**

The authors declare no conflicts of interest.

**References**