Clinical Significance of Discrepancy between Arterial Spin Labeling Images and Contrast-enhanced Images in the Diagnosis of Brain Tumors

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Purpose: In the imaging of intra-axial brain tumors, we sometimes found areas of high signal intensity around the enhanced tumor lesions on arterial spin labeling (ASL) magnetic resonance (MR) imaging. We undertook this study to investigate the relationship between high signal intensity on ASL imaging outside the area of contrast enhancement (CE) and histological diagnosis of intra-axial brain tumors.

Methods: We examined images from 28 consecutive patients with intra-axial brain tumors who underwent ASL and CE MR imaging——three with low grade glioma (LGG), 13 with high grade glioma (HGG), six with metastasis, and six with primary central nervous system lymphoma (PCNSL)——and divided imaging findings into an “ASL dominant” group when hyperintensity on ASL was found outside the CE area and a “CE dominant” group when hyperintensity on ASL was not found outside the area of enhancement. We then analyzed the relationship between imaging findings and the histological diagnosis of the tumors.

Results: Four cases were excluded because of poor quality of ASL images, 7 cases were classified as ASL dominant, and 17 cases were classified as CE dominant. The histological diagnoses of ASL dominant cases were LGG in 3 cases, HGG in 3 cases, and PCNSL in one case. Those of CE dominant cases were HGG in 10 cases, metastasis in 5 cases, and PCNSL in 2 cases. All cases with brain metastasis were classified as CE dominant.

Conclusion: The high signal intensity outside the area of contrast enhancement is probably caused by increased perfusion or vascular proliferation, which indicates the presence of glioma or PCNSL and not metastasis. This finding indicates a new utility for ASL images in the diagnosis of brain tumors as a supplement to the conventional measurement of perfusion obtained from ASL images.

Keywords: arterial spin labeling (ASL), brain tumor, contrast enhancement, magnetic resonance imaging (MRI)

Introduction

The differential diagnosis of brain tumors is critical in determining optimal therapy and estimating prognosis.1 High grade glioma (HGG), brain metastasis, and primary central nervous system lymphoma (PCNSL) are common types of brain malignancies in adults and can manifest similar findings on conventional magnetic resonance (MR) imaging.2–5 Contrast-enhanced (CE) MR imaging and perfusion MR imaging are useful in diagnosing these tumors.3–5

Arterial spin labeling (ASL) MR imaging uses magnetically labeled arterial blood water protons as an endogenous tracer to allow visualization of
Because different types of brain tumor show different degrees of blood flow, ASL is reported useful in diagnosing brain tumors. In addition, neoangiogenesis in brain tumors could produce leaky new blood vessels from which permeation by a contrast agent could enhance tumors.

MR images acquired by ASL and CE MR imaging are distinct from each other, and the mechanisms behind the high signal intensity on ASL and contrast enhancement are different. In ASL, hyper-intensity results from tissue hyperperfusion and intravessel signals. In T1-weighted CE images, on the other hand, the enhancement effect is caused by disruption of the blood-brain barrier (BBB) and vascular structures. Therefore, the distributions of areas of hyperintensity on ASL and contrast enhancement could be different. In fact, high signal intensity on ASL is sometimes seen outside the CE area, but this finding is not well documented.

Against this background, we investigated the clinical significance of the discrepancy between the high signal intensity on ASL and the area of contrast enhancement in the imaging of brain tumors and the relationship between this discrepancy and the histological diagnosis of brain tumors.

Materials and Methods

Our local institutional review board approved this study, and informed consent was obtained from all patients prior to enrollment.

Patients

Consecutive patients who underwent CE MR imaging for the diagnosis of a suspected brain tumor for the period September 1, 2012 through March 31, 2014 were eligible for this study. From this group, we included those with low grade glioma (LGG), HGG, metastasis, or PCNSL in our analysis. Diagnoses were made histologically in the cases with glioma and PCNSL; the clinical diagnosis of metastasis was made by consensus of 2 experienced neuroradiologists (T.A., 10 years of experience; M.H., 28 years of experience). Three cases (one each of lung, breast, and colon cancer) were diagnosed clinically. A case with gliomatosis cerebri was diagnosed histologically with the addition of imaging findings. The histological diagnosis was diffuse astrocytoma, but the final diagnosis was gliomatosis cerebri because the tumor infiltrated 3 cerebral lobes and the splenium of the corpus callosum. The others were diagnosed pathologically. Twenty-eight patients (18 men, 10 women; mean age, 65 years; range, 35 to 87 years) were included in the analysis. Table summarizes patient characteristics.

Imaging protocol

Examinations were performed with a 3-tesla MR scanner (Discovery 750, GE Healthcare, Milwaukee, WI, USA) using a standard 8-channel head coil. Pre-contrast T1-weighted images, T2-weighted images, fluid-attenuated inversion recovery (FLAIR) images, diffusion-weighted images, and ASL images were acquired, and MR spectroscopy was performed. Subsequently, post-contrast T1-weighted images were acquired using a contrast agent (gadopentetic acid [Gd-DTPA], 0.1 mmol/kg; Magnevist, Bayer HealthCare, Berlin, Germany). Three-dimensional (3D) T2*-weighted angiography and diffusion tensor imaging were conducted in selected patients.

ASL imaging was performed by pseudo-continuous ASL sequence using a stack of spirals with

<table>
<thead>
<tr>
<th>No. of cases (male)</th>
<th>Mean age, years (range)</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGG 3 (1)</td>
<td>45.3 (35–58)</td>
<td>3 oligodendrogliomas</td>
</tr>
<tr>
<td>HGG 13 (10)</td>
<td>67.8 (41–87)</td>
<td>one anaplastic astrocytoma, one gliosarcoma, 10 glioblastomas, one gliomatosis cerebri</td>
</tr>
<tr>
<td>Metastasis 6 (4)</td>
<td>64.3 (48–77)</td>
<td>2 lung cancers*, 2 breast cancers*, one gastric cancer, one colon cancer*</td>
</tr>
<tr>
<td>PCNSL 6 (3)</td>
<td>67.3 (55–78)</td>
<td>6 diffuse large B-cell lymphomas</td>
</tr>
</tbody>
</table>

HGG, high grade glioma; LGG, low grade glioma; PCNSL, primary lymphoma of the central nervous system. *Three cases were diagnosed clinically (one each, lung, breast, and colon cancer). The others were diagnosed pathologically.
3D fast spin echo imaging sequences with parameters: 512 sampling points on 8 spirals; field of view (FOV), 24 cm; reconstructed matrix, 64 × 64; repetition time (TR), 4632 ms; echo time (TE), 10.5 ms; number of excitations, 2; post-labeling delay (PLD), 1525 ms; slice thickness, 4 mm; number of slices, 36; and acquisition time, 3 min 15 s. In-plane resolution was 3.6 × 3.6 mm.

Post-contrast T₁-weighted images were acquired using 3D spoiled gradient recall acquisition in the steady state (3D-SPGR) with parameters: FOV, 24 cm; matrix, 384 × 256; TR, 10.4 ms; TE, 4.4 ms; flip angle, 15°; slice thickness, 1.2 mm; number of slices, 140 to 160; and acquisition time, 3 min 8 s to 4 min 5 s. Enhanced images were acquired in the sagittal plane and reconstructed in the axial plane. Slice thickness was 4 mm, and in-plane resolution of reconstructed images was 1.2 × 0.9 mm. Contrast-enhanced 3D-SPGR was performed about 5 min after injection of contrast material.

Image analysis

Two experienced neuradiologists (T.A. and M.H.) analyzed all imaging data. In post-contrast T₁-weighted images, the area of tumor enhancement was selected from the area where tumor invasion was suspected on T₂-weighted and FLAIR images, and the area of hyperintensity was then selected by comparison with normal white matter on the ASL image from the same area where tumor invasion was suspected on the T₂-weighted and FLAIR images. Imaging findings were then divided into 2 groups, designated “ASL dominant” when hyperintensity on ASL was found outside the area of contrast enhancement and “CE dominant” when hyperintensity on ASL was not found outside the CE area (Figs. 1, 2). Given a partial volume effect due to in-plane resolution (ASL, 3.6 × 3.6 mm; CE T₁WI, 1.2 × 0.9 mm), “ASL dominant” was defined when ASL hyperintensity extended 4 mm or more from the area of contrast enhancement, and “CE dominant” was defined otherwise. We compared diagnosis and imaging findings.

Results

We excluded 4 cases with poor quality of ASL images. In this study, 21 of 24 (87%) cases showed enhancement on CE T₁WI, and 3 cases (13%; oligodendrogliomas) did not.

Seven cases were classified as ASL dominant and 17 cases as CE dominant (Figs. 3, 4, 5). The histological diagnosis of ASL dominant cases was LGG in 3 cases, HGG in 3 cases, and PCNSL in one case. The histological diagnosis of CE dominant cases was HGG in 10 cases, metastasis in 5 cases, and PCNSL in 2 cases.

All cases with brain metastasis were classified as CE dominant, and all cases with LGG (histology, oligodendroglioma) were classified as ASL dominant. Cases with HGG and PCNSL showed both ASL dominant and CE dominant features.

Representative case

A follow-up ASL image acquired in one case with gliomatosis cerebri showed an ASL dominant pattern on initial analysis (Fig. 5A–C). Biopsy proved the histological diagnosis of the tumor was diffuse astrocytoma, but the final diagnosis was gliomatosis cerebri because the tumor infiltrated the right temporal, parietal, and occipital lobes.
and the splenium of the corpus callosum. The patient initially refused treatment and underwent close follow-up. One month after initial imaging, left hemiplegia appeared and MR imaging demonstrated a new ring-like enhancement (Fig. 5D) where the hyperintensity had been observed on ASL images. Chemoradiotherapy including temozolomide was started, but the areas of contrast enhancement and of high signal intensity on ASL were enlarged in the second follow-up study performed one month after initiation of treatment.

**Discussion**

Our results show that the difference in findings between ASL and CE MR imaging supplement the findings of conventional imaging in predicting tumor histology. The high signal intensity on ASL outside the CE area on MR imaging indicated the specific histology of the brain tumor, that is, glioma or lymphoma, thereby providing new helpful information to consider alongside conventional imaging findings.

In brain tumors, the area of high signal intensity on ASL usually shows a CE effect. In this study, 17 of 24 cases (71%) showed enhancement in the area of hyperintensity on ASL, but 7 cases (29%) showed no enhancement or a smaller area of enhancement in the lesion with high intensity on ASL, which we called the “ASL dominant” pattern. We observed this pattern in cases of glioma and PCNSL but not in metastasis. Generally, invasion of glioma and lymphoma is seen around the CE area,\(^{14}\) where blood flow is increased.\(^{3,15,16}\) One reason for the hyperintensity on ASL is increased perfusion, which could not be detected on CE MR imaging. Another reason is the signal from vessels. Noguchi and associates reported that areas of high vascular density showed a high signal in ASL images in glioma cases.\(^{17}\) In addition, stagnant flow could contribute to the hyperintensity on ASL termed “arterial transit artifact.”\(^{13}\) Though we assumed that this hyperintensity on ASL reflects hyperperfusion in the brain tumor, we could not exclude the possibility of arterial transit artifact. Comparison of ASL with dynamic susceptibility perfusion would help identify the cause of ASL hyperintensity.

In this study, we classified all cases with oligodendrogloma as ASL dominant, so it may be that this ASL dominant pattern is characteristic of oligodendroglomas. On the other hand, another common LGG in adults, low grade diffuse astrocytoma, is a tumor with relatively lower perfusion than oligodendrogloma.\(^{18,19}\) Thus, we should remember that LGG could represent low signal intensity on ASL. About two-thirds of our cases showed the CE dominant pattern, and all cases with metastasis were classified into this group. Metastatic invasion into the brain tended to be localized to the area of contrast enhancement, which was a different feature from glioma and PCNSL. The CE dominant pattern may indicate more dominant destruction of the BBB in the lesion than increased tumor blood flow, which is considered a characteristic of neovasculature in some metastatic brain tumors.

Previous papers reported the utility of ASL in the preoperative diagnosis of brain tumors as equal to or less than that of dynamic contrast perfusion.\(^{10,11}\) If our imaging findings are considered, the diagnostic performance of ASL is better than that indicated by these previous studies.

We were able to perform follow-up ASL study in a case with gliomatosis cerebri, in which ASL showed hyperperfusion in initial imaging where contrast enhancement did not exist. Follow-up MR imaging revealed multiple areas of ring-like enhancement in the area of hyperperfusion. This case raised the possible superiority of ASL to CE MR imaging for detecting tumor dedifferentiation in the early phase of gliomatosis cerebri.

We did not compare findings in ASL images with...
those in a cerebral blood flow (CBF) map acquired by a dynamic susceptibility contrast perfusion study, a standard technique for analyzing perfusion in brain tumors. One difference between the ASL image and CBF map is the signal intensity of vessels. Vessels generally show no signal in ASL images but appear hyperintense on a CBF map. We believe no “CBF map dominant” finding has been reported and that recognition of such a finding would be difficult because it could be masked by intravessel hyperintensity in normal vessels. Investigation of the discrepancy among ASL images, CBF maps, and CE MR imaging is a potential direction for future research.

Limitations of this preliminary study include our small number of patients, so statistical power to detect a difference was weak. Further study is needed to determine the implications of the discrepancy between ASL and CE MR imaging findings in the diagnosis of brain tumors. In addition, the ASL images had low signal-to-noise ratios and low spatial resolution, and a weak ASL signal could easily disappear because of the noise and partial volume effect. Therefore, patterns of cases with weak ASL signal outside the area of contrast enhancement could be misinterpreted as CE dominant. For ASL, we used one fixed PLD, a parameter that indicates the time between labeling blood protons and image acquisition that affects the occurrence of intravascular hyperintensity. Use of a longer PLD might have decreased the ASL dominant finding. Nowadays, we can acquire multiple ASL images with different PLDs in one acquisition. This sequence could be helpful to determine the reason for discrepancy between ASL and CE T1WI. In addition, use of better quality ASL images acquired with a longer acquisition time might have yielded more subtle hyperintensity that would have altered the present results. We chose the scan parameters based on the limited scan time permitted in a normal clinical setting.

Conclusion

We analyzed the discrepancy between ASL and contrast-enhanced MR images and found that an
ASL dominant pattern indicated glioma or PCNSL and not metastasis. This finding indicates a new utility for ASL images in the diagnosis of brain tumors as a supplement to conventional perfusion measurement obtained from ASL images.

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