The Hyperintense Acute Reperfusion Marker on Fluid-Attenuated Inversion Recovery Magnetic Resonance Imaging Is Caused by Gadolinium in the Cerebrospinal Fluid

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Background and Purpose—The hyperintense acute reperfusion marker (HARM) on fluid-attenuated inversion recovery MRI is believed to be caused by gadolinium-based contrast agents crossing a disrupted blood–brain barrier. However, this hypothesis has never been directly verified in humans.

Methods—In this study, we analyzed cerebrospinal fluid samples of patients with HARM on imaging regarding the presence and concentration of gadolinium-based contrast agents.

Results—Gadobutrol was found in concentrations of approximately 50 \( \mu \text{mol/L} \). Using phantom MRI experiments, we demonstrate that the detected concentrations are consistent with the observed HARM imaging pattern.

Conclusions—Our study yields first direct evidence in humans that the imaging phenomenon HARM is indeed caused by leakage of gadolinium-based contrast agents into the cerebrospinal fluid. (Stroke. 2012;43:259-261.)

Key Words: FLAIR ■ hyperintensive acute reperfusion marker ■ MRI

The hyperintense acute reperfusion marker (HARM) on fluid-attenuated inversion recovery (FLAIR) MRI sequences has been described as a sign for early blood–brain barrier (BBB) disruption in various clinical conditions, including acute ischemic stroke1–4 and endovascular treatment for high-grade internal carotid stenosis.5 The fact that HARM is only found on follow-up MRI if gadolinium-based contrast agents (GBCA) had been administered during a previous MRI led to the hypothesis that the hyperintense signal found in the subarachnoid space over the affected hemisphere is caused by GBCA crossing a disrupted BBB.2,3,6 This hypothesis is supported by in vitro and in vivo experiments using experimental animal stroke models but has never been directly verified in humans.7–9 In this study, we analyzed cerebrospinal fluid (CSF) samples of patients with HARM regarding the presence and concentration of GBCA. Results were then correlated with phantom MRI experiments.

Measurement of CSF Gadolinium Concentration

CSF samples were diluted with 5% nitric acid. The precipitated protein was removed by centrifugation and the gadolinium concentration was determined in the supernatant by inductively coupled atomic emission spectrometry (IRIS Advantage, Thermo, Neu Isenburg, Germany) at a wavelength of 342.247 nm. The method provided a lower limit of quantification in the CSF of 3 \( \mu \text{mol gadolinium/L} \).

Imaging Protocol

In all patients, MRI was performed using a 1.5-T system (Siemens Sonata; Siemens AG, Forchheim, Germany). The patients were investigated with a dedicated stroke MRI protocol using standard applications including FLAIR, T1-weighted, diffusion-weighted, and perfusion-weighted imaging as well as MR angiography (time of flight and contrast-enhanced MR angiography). The following parameters were used for FLAIR and T1 sequences: (1) FLAIR: 25 slices with 5-mm thickness (distance factor 20%), TR 8430 ms, TE 109 ms, TI 2500 ms, and flip angle 150°; and (2) T1-weighted spin echo sequence: 5-mm thickness (distance factor 20%), TR 690 ms,
TE 17 ms, and flip angle 70°. No fat saturation was applied. A standard paramagnetic contrast agent was used (gadobutrol, Gadovist; Bayer-Schering-Pharma, Leverkusen, Germany) at a dose of 0.1 mmol/kg body weight for perfusion sequences as well as for contrast-enhanced MR angiography (double dosing).

Phantom Imaging Experiments

According to the gadolinium concentrations found in CSF samples, phantom imaging experiments were performed using a dilution series of gadobutrol in aqueous solution with the following concentrations: no gadobutrol, 50 μmol/L, 500 μmol/L, and 1000 μmol/L of gadobutrol. Identical MRI sequences were used as described for the clinical scans.

Results

CSF Gadolinium Concentrations

Both patients with HARM on follow-up FLAIR imaging had detectable gadolinium concentrations in the CSF. In the first patient, the concentration was 38.3 μmol/L. CSF of the second patient demonstrated a similar concentration with 44 μmol/L. No gadolinium was found in the CSF of the control patient.

Phantom Imaging Experiments

In phantom imaging experiments, a complete loss of fluid-signal-suppression in FLAIR was observed at the concentration of 50 μmol/L (comparable to the concentration found in the CSF of patients). However, 10-fold higher concentrations were needed to obtain similar contrast enhancement in T1 sequences (Figure 2).

Discussion

The term “HARM” was introduced by Warach and colleagues in patients with ischemic stroke receiving serial MRIs in the acute phase. It describes an imaging phenomenon of hyperintense signal of the subarachnoid CSF space, which was already noted in patients with compromised cerebral perfusion, including cases of acute ischemic stroke1–4 and patients with hyperperfusion syndrome after carotid artery stenting5 or temporary balloon occlusion of the carotid artery.10

HARM is believed to be a marker for early disruption of the BBB. Gadobutrol, like other clinically used GBCA, with a molecular weight of 605 D and a Stokes-Einstein radius of approximately 5 to 7 Å, does not cross the intact BBB.8 However, animal experiments using transient middle cerebral artery occlusion have shown that opening of the BBB and crossing of GBCA may occur after reperfusion.8 In humans, HARM is considered to reflect such a BBB breakdown and subsequent enhancement of the CSF space by GBCA. The evidence however remains mainly indirect but is supported by MRI studies,6 the signal characteristics as well as the observations that the hyperintense signal never corresponds

Table. Dosing of GBCA and Time Intervals for Imaging Studies and CSF Sampling

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>GBCA Dose First MRI, mmol/kg</th>
<th>GBCA Dose Second MRI, mmol/kg</th>
<th>Time Between First and Second MRI, h</th>
<th>HARM on Second MRI</th>
<th>Time Between Second MRI and CSF Sampling, min</th>
<th>Estimated GFR (MDRD Formula), mL/min</th>
<th>Detected CSF Gadolinium Concentration, μmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.2</td>
<td>0.2</td>
<td>44</td>
<td>Yes</td>
<td>70</td>
<td>&gt;60</td>
<td>38.3</td>
</tr>
<tr>
<td>2</td>
<td>0.2</td>
<td>0.2</td>
<td>36</td>
<td>Yes</td>
<td>100</td>
<td>&gt;60</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>0.2</td>
<td>0.2</td>
<td>47</td>
<td>No</td>
<td>90</td>
<td>&gt;60</td>
<td>0 (&lt;3)</td>
</tr>
</tbody>
</table>

GBCA indicates gadolinium-based contrast agents; CSF, cerebrospinal fluid; HARM, hyperintense acute reperfusion marker; GFR, glomerular filtration rate; MDRD formula, Modification of diet in renal disease formula.
to either hypointensity on MR gradient echo imaging or hyperattenuation on CT, which rules out blood as a cause of the increased signal.\textsuperscript{2,3} In addition, HARM is not found in patients without prior exposure to a GBCA.

Our experiments yield the first direct evidence in humans by measuring gadobutrol concentrations in the CSF. In both patients with HARM in our study, gadobutrol concentrations in the CSF were approximately 50 μmol/L. We therefore performed phantom imaging measurement using FLAIR as well as T1 sequences to test whether in vitro signal would correspond to the signal pattern found in patients. At the measured concentration (50 μmol/L), experiments confirmed a strong enhancement in FLAIR without corresponding enhancement in T1 sequences. This effect may be explained by the methodological basis of FLAIR, which suppresses the CSF signal by long inversion times and thus “nulling” the fluid signal. Even a slight change in “target T1” with shortening of T1 by low concentrations of gadobutrol disrupts the fluid signal suppression of FLAIR sequences. In contrast, the same slight shortening of T1 by the low-contrast agent concentration does not yet result in a comparably strong signal change in T1-weighted sequences. Our observation is supported by previous reports in which the sensitivity of FLAIR for low-contrast concentrations is >10-fold higher than for T1 imaging.\textsuperscript{2,7,9} Mathews and colleagues performed similar phantom experiments and found strong hyperintensity on FLAIR for gadolinium concentrations as low as 10 μmol/L. As observed in our experiments, comparable hyperintensity on T1 imaging was only found with gadolinium concentrations >100 to 500 μmol/L.\textsuperscript{7} Mamourian et al reported similar findings. In addition, their study detected GBCA in the CSF of healthy dogs after intravenous administration of higher GBCA doses (0.3 mmol/kg).\textsuperscript{9}

There are limitations to our study, most notably the low number of patients examined. However, complexity of the detection method as well as invasiveness of the diagnostic procedure limits the feasibility of larger case numbers. We were only able to use CSF of HARM patients undergoing lumbar puncture for other clinical indication and with the lack of therapeutic consequence, it is not justifiable to perform CSF sampling just for gadolinium concentration measurements. In addition, our MRI protocol consists of 2 bolus of GBCA to perform perfusion imaging as well as contrast-enhanced MR angiography. Thus, a higher dose of gadobutrol (“double dosing”) is applied, which may lead to increased visibility of HARM and a higher CSF concentration of gadobutrol.\textsuperscript{9}

In conclusion, our study yields first direct evidence in humans that the imaging phenomenon HARM is indeed caused by leakage of GBCA through a disrupted BBB. Further studies are needed to evaluate the clinical significance of the marker and its use as a surrogate parameter for BBB permeability in clinical studies.\textsuperscript{4}

Disclosures
T.F. is employed by Bayer Schering Pharma, the manufacturer of Gadovist.

References
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