MRI Using Ferumoxytol Improves the Visualization of Central Nervous System Vascular Malformations

Edit Dósa, MD, PhD; Suchita Tuladhar, MD; Leslie L. Muldoon, PhD; Bronwyn E. Hamilton, MD; William D. Rooney, PhD; Edward A. Neuwelt, MD

Background and Purpose—Central nervous system vascular malformations (VMs) result from abnormal vasculo- and/or angiogenesis. Cavernomas and arteriovenous malformations are also sites of active inflammation. The aim of this study was to determine whether MRI detection of VMs can be improved by administration of ferumoxytol iron oxide nanoparticle, which acts as a blood pool agent at early time points and an inflammatory marker when taken up by tissue macrophages.

Methods—Nineteen patients (11 men, 8 women; mean age, 47.5 years) with central nervous system VMs underwent 3-T MRI both with gadoteridol and ferumoxytol. The ferumoxytol-induced signal changes on the T1-, T2-, and susceptibility-weighted images were analyzed at 25 minutes (range, 21 to 30 minutes) and 24 hours (range, 22 to 27 hours).

Results—Thirty-five lesions (capillary telangiectasia, n=6; cavernoma, n=21; developmental venous anomaly, n=7; arteriovenous malformation, n=1) were seen on the pre- and postgadoteridol images. The postferumoxytol susceptibility-weighted sequences revealed 5 additional VMs (3 capillary telangiectasias, 2 cavernomas) and demonstrated further tributary veins in all patients with developmental venous anomalies. The 24-hour T1 and T2 ferumoxytol-related signal abnormalities were inconsistent among patients and within VM types. No additional area of T1 or T2 enhancement was noted with ferumoxytol compared with gadoteridol in any lesion.

Conclusions—Our findings indicate that the blood pool agent ferumoxytol provides important information about the number and true extent of VMs on the susceptibility-weighted MRI. The use of ferumoxytol as a macrophage imaging agent in the visualization of inflammatory cells within and around the lesions warrants further investigation. (Stroke. 2011;42:1581-1588.)

Key Words: central nervous system • ferumoxytol • magnetic resonance imaging • ultrasmall superparamagnetic iron oxide nanoparticles • vascular malformations

Vascular malformations (VMs) of the brain and spinal cord have typically been classified into 4 major types: capillary telangiectasias, cavernomas, developmental venous anomalies (DVAs), and arteriovenous malformations (AVMs). Their pathogenesis involves abnormal vasculo- and/or angiogenesis. Cavernomas and AVMs are also sites of active inflammation. Various inflammatory cells (eg, neutrophils, macrophages) and mediators (eg, cytokines) have been shown to be present in these subtypes of VMs and have been demonstrated to contribute to lesion progression and rupture. Improved detection and characterization of VMs is important not just because certain types can cause serious neurological symptoms, but they are commonly mistaken for disease, resulting in inappropriate therapy.

Currently, MRI is the best modality to assess VMs. Susceptibility-weighted imaging uses a fully velocity-compensated high-resolution 3-dimensional gradient echo acquisition that uses magnitude and filtered-phase information, both separately and in combination, to create new sources of contrast. This sequence was recently found to be superior to T1- and T2-weighted MRI in detection of VMs. Ferumoxytol (Feraheme; AMAG Pharmaceuticals Inc, Cambridge, MA), an ultrasmall superparamagnetic iron oxide (USPIO) nanoparticle, developed for iron replacement therapy primarily in patients with chronic kidney disease, has seen increasing off-label use in various MRI applications. The semisynthetic carbohydrate-coated ferumoxytol has a hydrodynamic diameter of 30 nm and a long blood half-life of approximately 14 hours. Ferumoxytol is confined to the vascular compartment at early time points but subsequently becomes an inflammatory marker as it leaks across permeable vessels and is taken up by tissue macrophages hours to day(s)
after administration. It is considered to be a negative contrast material due to its strong T2* effect, but ferumoxytol also has intrinsic T1 shortening properties that can produce a positive signal using appropriate pulse sequences. Susceptibility-weighted MRI has an exquisite sensitivity to USPIOs because of T2* influencing factors. Iron oxide nanoparticles increase the visibility of both normal and tumor microvessels in the brain on T2*-weighted scans. On the other hand, for the evaluation of intracellularly trapped USPIOs in patients with central nervous system malignancies, the 24-hour T1-weighted spin echo and T2-weighted images were found to be the most helpful. The role of USPIO-enhanced MRI in patients with central nervous system VMs has not previously been investigated. We hypothesized that ferumoxytol would improve the detection of VMs using susceptibility-weighted imaging, whereas changes in signal intensity and morphology of the lesions over time on the T1- and T2-weighted sequences could provide important information about the inflammatory cell component of VMs.

### Subjects and Methods

#### Study Population

Between March 2008 and June 2010, 11 patients with known central nervous system VMs were prospectively enrolled in this study (Protocol 1562). Additionally, 8 patients who underwent MRIs with ferumoxytol for brain tumor evaluation and were incidentally diagnosed with intracranial VMs (Protocols 1562 or 813) were retrospectively included in the analysis. Patients who were pregnant or lactating; had a contraindication to MRI examination (e.g., pacemaker); had known allergic or hypersensitivity reactions to parenteral iron, dextran, iron–dextran, or iron–

<table>
<thead>
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<th>Patient No./Gender/Age, Years</th>
<th>Protocol No.</th>
<th>Vascular Malformation</th>
<th>Lesion No.</th>
<th>With/Without Gd (n=35)</th>
<th>With Fe (n=40)</th>
<th>Lesion Location</th>
<th>Clinical Presentation</th>
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<td>Pons</td>
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<td>Headaches</td>
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<td></td>
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<td>1</td>
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</tr>
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<td>1</td>
<td>Pons</td>
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<td>2</td>
<td>Mesencephalon</td>
<td>Headaches</td>
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<td>Right temporal lobe</td>
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<td>Spinal cord</td>
<td>Bilateral lower extremity weakness</td>
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Gd indicates gadoteridol; Fe, ferumoxytol; F, female; M, male; DVA, developmental venous anomaly; AVM, arteriovenous malformation.

*The patient had chronic kidney disease; therefore, only ferumoxytol was used.*
polysaccharide preparations; had known or suspected iron overload (eg, hemochromatosis, history of multiple transfusions); or had hepatic insufficiency or liver cirrhosis were excluded. HIV-positive patients on combination antiretroviral therapy were also ineligible because of the potential for pharmacokinetic interactions with ferumoxytol. The protocols were sponsored by the National Institutes of Health and were approved by the Oregon Health and Science University Institutional Review Board. All participants provided written informed consent.

MRI Examination
The scans were performed on a 3-T whole-body MRI system (either TIM Trio, Siemens Medical Solutions, Erlangen, Germany; or Achieva, Philips Healthcare, Best, the Netherlands) with a body radiofrequency coil transmit and a 12-channel phased array head (Siemens), an 8-channel sensitivity-encoding head (Philips), or a spine matrix radiofrequency receiver coil (Siemens).

Protocol 1562 consisted of imaging on 3 consecutive days. On the first day, T1-, T2-, and susceptibility-weighted pre- and postcontrast images were acquired using gadoteridol gadolinium (III) chelate (ProHance; Bracco Diagnostic Inc, Princeton, NJ; 0.1 mmol/kg). On the following day, the same MRI sequences were obtained with ferumoxytol, which was given over 20 minutes at a constant dose of 510 mg diluted to a final volume of 34 mL of saline regardless of body weight. On the third day, the sequences were repeated in identical spatial orientation to detect ferumoxytol-induced signal changes at 24 hours. Patient 19, whose estimated glomerular filtration rate was $\frac{30}{29}$ mL/min/1.73 m$^2$, underwent only a 2-day MRI with ferumoxytol and was not studied with gadoteridol due to the risk for developing nephrogenic systemic fibrosis.

Patients on Protocol 813 underwent MRI examination on 2 consecutive days. On Day 1, axial T1-, T2-, and susceptibility-weighted precontrast and susceptibility-weighted postcontrast images were acquired using ferumoxytol, which was injected intravenously at a dose of 1 mg/kg diluted 1:1 with normal saline and was followed by gadoteridol administration (0.1 mmol/kg) within 15 minutes (mean, 13.5 minutes; range, 11 to 15 minutes). After the T1-weighted postgadoteridol sequences, additional diluted ferumoxytol was given at a dose of 3 mg/kg. The patients were rescanned 24 hours later for the assessment of delayed ferumoxytol-caused signal changes.

Multiple time points were all completed in the same MRI instrument for each participant. The patients were monitored closely for 2 hours after ferumoxytol administration and were followed up for 1 month.

Brain MRI acquisition parameters are presented in the online supplement (http://stroke.ahajournals.org).

Image Analysis
The ferumoxytol-caused signal changes were assessed at 2 time points: 25 minutes (range, 21 to 30 minutes) and 24 hours (range, 22 to 27 hours). Any signal intensity change exceeding the signal intensity of normal white matter on the ferumoxytol-enhanced T1-weighted images was termed as USPIO-induced signal increase (hyperintensity). Any signal intensity drop below the signal intensity of normal white matter on the postferumoxytol T1-, T2-, or susceptibility-weighted images was rated as USPIO-induced signal loss (hypointensity).

The gadoteridol and ferumoxytol-enhanced images from each patient were evaluated in a matched-pair fashion and were analyzed by 2 neuroradiologists in consensus. The categorization of VMs on MRI was based on previously established and well-accepted standards.1 2 3 The 3- to 5-mm hypointense lesions seen only on the postferumoxytol susceptibility-weighted images were considered as a capillary telangiectasia if they had an irregular border and/or an
arborizing (tree-like) appearance; otherwise, they were recorded as a cavernoma.

Results

A total of 19 patients (11 men, 8 women; mean age, 47.5 years; age range, 9 to 74 years) were included in the analysis. Six patients had a capillary telangiectasia, 1 had both capillary telangiectasias and cavernomas, 4 had only cavernomas, 7 had a DVA, and 1 patient had a spinal cord AVM. Thirty-five lesions were detected on the pre- and postgadoteridol images, whereas 40 were seen on the ferumoxytol sequences. Patient demographics, number, location, and clinical presentation of the VMs are shown in the Table.

All of the image sets from each of the 19 evaluated patients were technically adequate for assessment. There were no adverse events attributed to either contrast material.

Capillary Telangiectasias

Seven patients with 9 lesions were studied in this group (Table). Six of 9 capillary telangiectasias demonstrated both gadoteridol enhancement and 24-hour ferumoxytol-induced signal changes (Figures 1 and 2). Early 25-minute T1 and T2 signal abnormalities were noted only in 1 patient after ferumoxytol administration (Figure 2). Ferumoxytol resulted either in a signal increase (5 of 9) or in a signal dropout (1 of 9) on the T1-weighted images at 24 hours. Five lesions became iso- and 1 hypointense on the T2-weighted sequences 24 hours after ferumoxytol injection. All capillary telangiectasias showed prominent signal loss with ferumoxytol on the susceptibility-weighted images (Figures 1 through 3A–B).

Cavernomas

Five patients had cavernomas. A total of 21 lesions was noted with gadoteridol and an additional 2 lesions were found on the postferumoxytol susceptibility-weighted sequences (Table; Figure 3C). Eighteen of 23 lesions presented as 2- to 4-mm hypointensities on the T2- and/or susceptibility-weighted...
weighted scans. Five cavernomas, which had a T1 iso-, T2 hyperintense core and a T2 hypointense rim on the precontrast images, showed mixed ferumoxytol-related signal changes on the T1-weighted images at 24 hours in addition to the T2- and susceptibility-weighted signal loss. In this group of cavernomas, 4 of 5 lesions demonstrated 25-minute T1 signal increase; among them, 1 had a T2 signal decrease as well (Figure 2).

Developmental Venous Anomalies
Seven patients, each with an isolated DVA, were evaluated in this group (Table). The T1-weighted MRI scans with both contrast agents showed a typical caput medusae appearance of DVAs: a classic small cluster of tributary veins draining into a dilated collector vein. The lesions were visible on both the pre- and postferumoxytol T2- and susceptibility-weighted images, but the ferumoxytol scans demonstrated additional tributary veins in all patients compared with the precontrast sequences (Figure 4). The ferumoxytol-induced signal loss was more prominent at 25 minutes than at 24 hours.

Arteriovenous Malformation
Patient 19, who had chronic kidney disease, presented with a 6-month history of progressive lower extremity weakness. The patient underwent spine MRI examination without gadolinium administration before enrollment in the ferumoxytol study. The noncontrast T2-weighted images showed abnormally increased intrinsic cord signal extending from the conus to upper thoracic levels. Dorsal flow voids were also visible (Figure 5B). The abnormal tangle of blood vessels on the spinal cord was hyperintense on the T1-weighted scans and hypointense on the T2- and T2*-weighted images after ferumoxytol administration (Figure 5D). Similar to the DVAs, the ferumoxytol-induced signal loss at 25 minutes was the most prominent. Thoracic spinal angiography revealed a dural arteriovenous fistula at T10 along with prominent venous dilatation.

Discussion
Susceptibility-weighted imaging is a relatively new technique that exploits the T2* relaxation differences between deoxy-
In contrast to the USPIO-related signal loss on the susceptibility-weighted images, the presence of T1 and T2 signal abnormalities varied among and within VM types, which can be due to differences in vessel size and intraluminal flow rate. We also noted intraluminal discrepancy between the existence of T1- and T2-weighted ferumoxytol enhancement in some telangiectasias and cavernomas. One possible explanation for this finding is the known dose-dependency of USPIO-induced signal changes. Whereas iron oxide nanoparticles result in T2 shortening at higher concentrations, their T1 shortening effect peaks at lower concentrations; thus, at doses applied in this study, the iron accumulation was not concentrated enough to cause decreased T2 signal in all lesions.

We have previously reported in patients with glioblastoma multiforme that both the intensity and volume of ferumoxytol enhancement increase with time. In these subjects, the USPIO-related signal intensity peaked at 24 to 28 hours, and at that time, the ferumoxytol enhancement also extended beyond the tumor border delineated by gadoteridol. The iron staining of biopsy samples, obtained from patients with brain tumors who underwent image-guided surgery, demonstrated that the iron oxide nanoparticles had been trapped by peritumoral macrophages and reactive astrocytes 24 to 36 hours after their administration. Based on these observations, we hypothesized that the 24-hour ferumoxytol scans would provide information about the inflammatory cell component of VMs. However, in patients with DVAs and in case of spinal cord AVM, the ferumoxytol was still in the intraluminal space at 24 hours. In those cavernomas, that had both 25-minute and 24-hour signal abnormalities, no change in the volume and morphology of ferumoxytol enhancement was noted between the 2 time points. Moreover, no additional area of T1 or T2 enhancement was seen with ferumoxytol compared with gadoteridol in any of the lesions. It is unclear whether these findings indicate that there was ferumoxytol uptake in the phagocytic cells but at low concentrations or that there were few macrophages to endocytose the USPIOs. Alternatively, the evaluation of intra- and perilesional macrophages in cavernomas and AVMS may require later time points than in the high-grade glioma study. The interpretation of postferumoxotyl T1- and T2-weighted images in patients with capillary telangiectasias is challenging. Five of 9 lesions had only 24-hour ferumoxytol enhancement, and there was just 1 capillary telangiectasia that had both 25-minute and 24-hour ferumoxytol-related signal abnormalities. No definite explanation can be given for this observation. Because capillary telangiectasias are typically devoid of reactive astrocytes and macrophages, we speculate that the absence of 25-minute enhancement and presence of 24-hour signal changes represent delayed wash-in and wash-out of the large-molecular-weight ferumoxytol.

The dose of USPIO agent has a substantial impact on image quality. The most important limitation of this study is that 2 different ferumoxytol doses were applied. In 14 of our 19 participants, ferumoxytol was injected at a constant dose of 510 mg (approximately 7 mg/kg in a 70-kg patient), whereas in 5 patients, it was given at a dose that could not be calculated due to the absence of body weight information.
of 4 mg/kg. High doses are advantageous in the evaluation of tissue uptake of USPIOs on the T1- and T2-weighted sequences but can result in some loss of resolution of venous structures due to a decrease in the signal-to-noise ratio on the T2*-weighted images and vice versa with low doses.8 The blooming effect of USPIO nanoparticles (the USPIO-enhanced region may be much larger than the area of nanoparticle uptake) is also dose-dependent; therefore, the optimization of ferumoxytol dose for the visualization of VMs on the susceptibility-weighted images is crucial and currently underway.

Conclusions
We have shown here that the blood pool agent ferumoxytol improves the detection of central nervous system VMs on the susceptibility-weighted MRI. Because ferumoxytol has a good biocompatibility profile, has no known long-term toxicity, and in contrast to the gadolinium-based contrast agents it can be safely given to patients with decreased renal function, it seems to be a promising tool for the diagnosis and follow-up of VMs. The use of ferumoxytol as a macrophage imaging agent in the visualization of inflammatory cells within and around the lesions requires further investigation.

Sources of Funding
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Disclosures
AMAG Pharmaceuticals, Inc provided the study drug ferumoxytol free of charge. Oregon Health and Science University has received a sponsored research agreement from AMAG to conduct clinical trials of MRI with ferumoxytol. None of the authors has financial interest in this agent or in its developer, AMAG.

References

Figure 5. Spinal cord arteriovenous malformation. A–D, Sagittal T1- (A), T2- (B), and T2*-weighted images (C) obtained before and T2*-weighted images obtained 25 minutes after ferumoxytol administration (D). The T2*-weighted image shows abnormally increased intrinsic cord signal. Dorsal flow voids are visible (arrows). The abnormal tangle of blood vessels on the spinal cord is hypointense with ferumoxytol on the T2*-weighted images (arrowheads).


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SUPPLEMENTAL MATERIAL
Magnetic resonance imaging using ferumoxytol improves the visualization of central nervous system vascular malformations

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Supplemental Methods

Brain MRI Acquisition Parameters

**Siemens:** 1) Axial 2D T₁-weighted SE [repetition time (TR), 900 ms; echo time (TE), 10 ms; field of view (FOV), 180 x 240 mm²; acquisition matrix, 192 x 256; number of slices, 44; slice thickness, 2 mm; interslice gap, 0 mm]. 2) Axial 2D T₂-weighted turbo spin echo (TSE) (TR, 9000 ms; TE, 93 ms; turbo factor, 9; FOV, 180 x 240 mm²; acquisition matrix, 192 x 256; number of slices, 49; slice thickness, 2 mm; interslice gap, 0 mm). 3) Axial 3D T₂*-weighted GRE [TR, 28 ms; TE, 20 ms; flip angle (FA), 15°; FOV, 187.5 x 240 mm²; acquisition matrix, 298 x 448; number of slices, 72; slice thickness, 1.2 mm; interslice gap, 0 mm].

**Philips:** 1) Axial 2D T₁-weighted SE (TR, 900 ms; TE, 9.5 ms; FOV, 240 x 240 mm²; acquisition matrix, 212 x 268; number of slices, 44; slice thickness, 2 mm; interslice gap, 0 mm). 2) Axial 2D T₂-weighted TSE (TR, 4500 ms; TE, 93 ms; turbo factor, 14; FOV, 240 x 240 mm²; acquisition matrix, 209 x 268; number of slices, 44; slice thickness, 2 mm; interslice gap, 0 mm). 3) Axial 3D T₂*-weighted fast field echo (TR, 31 ms; TE, 41 ms; FA, 15°; FOV, 240 x 240 mm²; acquisition matrix, 284 x 400; number of slices, 72; slice thickness, 1.2 mm; interslice gap, 0 mm).

The slices were positioned parallel to the long axis of the corpus callosum.

Spine MRI Acquisition Parameters

**Siemens:** 1) Sagittal 2D T₁-weighted TSE (TR, 700 ms; TE, 10 ms; turbo factor, 5; FOV, 362.5 x 400 mm²; matrix size, 278 x 384; number of slices, 15; slice thickness, 3 mm; interslice gap, 0.3 mm). 2) Sagittal 2D T₂-weighted TSE (TR, 3600 ms; TE, 106 ms; turbo factor, 31; FOV, 400 x 400 mm²; matrix size, 307 x 384; number of slices, 15; slice thickness, 3 mm; interslice gap, 0.3 mm). 3) Sagittal 2D T₂*-weighted GRE (TR, 179 ms; TE, 5.7 ms; FA, 25°; FOV, 400 x 400 mm²; matrix size, 240 x 334; number of slices, 15; slice thickness, 3 mm; interslice gap, 0.3 mm). 4) Axial 2D T₁-weighted SE (TR, 900 ms; TE, 10 ms; FOV, 180 x 240 mm²; matrix size, 192 x 256; number of slices, 44; slice thickness, 2 mm; interslice gap, 0 mm). 5) Axial 2D T₂-weighted TSE (TR, 9000 ms; TE, 93 ms; turbo factor, 9; FOV, 180 x 240 mm²; matrix size, 192 x 256; number of slices, 49; slice thickness, 2 mm; interslice gap, 0 mm). 6) Axial 3D T₂*-weighted GRE (TR, 28 ms; TE, 20 ms; FA, 15°; FOV, 187.5 x 240 mm²; matrix size, 298 x 448; number of slices, 72; slice thickness, 1.2 mm; interslice gap, 0 mm).

The sagittal sequences were acquired as a cervico-thoracic and a thoraco-lumbar part with an overlap of at least three vertebral bodies. The axial images were planned along a line parallel to the intervertebral disc spaces.
フェルモキシトールを用いた MRI により中枢神経系血管奇形の可視化が向上する

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背景および目的: 中枢神経系血管奇形（VM）は異常な血管発生および／または血管新生に起因する。海綿腫および動静脈奇形も活発な炎症を起こす部位である。本研究の目的は、早期時点では血液プール造影剤の機能を果たし、組織マクロファージにより取り込まれると炎症マーカーの機能を果たすフェルモキシトール酸化鉄ナノ粒子の投与により、MRI での VM 検出が向上するかどうかを明らかにすることであった。

方法: 中枢神経系 VM を有する 19 例の患者（男性 11 例、女性 8 例、平均年齢 47.5 歳）を対象に、ガドテリドールとフェルモキシトールの両方を用いて 3-T MRI を施行した。T1、T2、および磁化率強調画像に認められるフェルモキシトール誘発性の信号の変化を、25 分（範囲: 21 ~ 30 分）および 24 時間（範囲: 22 ~ 27 時間）の時点で解析した。

結果: ガドテリドール投与前後の画像に 35 個の病変（毛細血管拡張症 6 例、海綿腫 21 例、動静脈奇形 7 例、静脈性血管奇形 1 例）が認められた。フェルモキシトール投与後の磁化率強調シーケンスでは、さらに 5 箇所の VM（毛細血管拡張症 3 箇所、海綿腫 2 箇所）が明らかになり、静脈性血管奇形を有するすべての患者にさらなる支流静脈が認められた。24 時間 T1 および T2 のフェルモキシトールに関連した信号異常は、患者間および VM タイプ内で一貫性がなかった。いずれの病変でも、ガドテリドールと比較してフェルモキシトールでの T1 または T2 強調の追加領域は認められなかった。

結論: 本研究の結果は、血液プール造影剤フェルモキシトールが、磁化率強調 MRI による VM の数および正確な範囲について重要な情報を提供することを示すものである。病変内および病変周辺の炎症細胞の可視化のためのマクロファージ造影剤としてのフェルモキシトールの使用については、さらなる検討を行う必要がある。

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図 5

脳腫瘍形成の例。A～D: フェルモキシトール投与前に撮影した矢状断 T1 強調画像（A）、T2 強調画像（B）、および T2* 強調画像（C）と、フェルモキシトール投与後 25 分後に撮影した T2* 強調画像（D）。T2 強調画像には内因性脳腫瘍信号の異常な増加が認められる。脳側の無信号域が確認できる（矢印）。T2* 強調画像では、フェルモキシトールにより脳腫瘍の異常なもつれが低信号となる（矢頭）。