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Cerebrospinal fluid changes after intravenous injection of gadolinium chelate: assessment by FLAIR MR imaging

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Abstract Fluid-attenuated inversion recovery (FLAIR) sequence is currently used in clinical practice. Some reports emphasize the possibility that, in pathologic conditions, intravenous injection of gadolinium chelates may lead to an increased signal inside the cerebrospinal fluid (CSF). The aim of this study was to evaluate the presence of CSF signal changes in pathologic conditions causing blood-brain barrier disruption or neovascularization when imaging is performed after intravenous injection of gadolinium. We obtained FLAIR sequences after gadolinium injection from 33 patients affected by different intracranial pathologies and 10 control subjects. Patients were affected by ischemic stroke in the subacute phase, from 2 to 7 days from onset of symptoms (12 patients), meningiomas (8 patients), high-grade gliomas (5 patients), previous surgical procedures for intra-axial neoplasms (5 patients), and multiple sclerosis with active plaques (3 patients). Magnetic resonance imaging was performed in patients and controls using a 1.5-T magnet, using T2- and T1-weighted FLAIR sequences. The FLAIR sequence was acquired before and 1–3 h after injection of a standard dose of gadolinium. In those patients affected by ischemic lesions, FLAIR sequences were repeated the next days and 3–4 days later. The CSF signal was visually evaluated by two readers and scored from 0 to 3 depending by the degree of enhancement. The location of CSF signal changes (close to the lesion, hemispheric, or diffuse) was also considered. The CSF signal was markedly increased after 3 h from intravenous injection of gadolinium in all the patients with stroke, in those with previous surgery, and in those with high-grade gliomas whose neoplasm's surface was in contact with the subarachnoid spaces (SAS) or ventricles; a strong enhancement was also evident inside the necrotic component of the tumor. The CSF changes were more evident close to the pathology and/or in the hemisphere involved by the pathology. Moderate CSF enhancement was observed in the SAS close to meningiomas. No signal changes were evident in all the others. In those patients with stroke imaged in the following days, CSF signal showed to be diffuse to both hemispheres the next day and returned to normal values within 2 days. In patients affected by pathologies with blood-brain barrier breakdown or neovascularization close the SAS or the ventricles, CSF changes, related to gadolinium leakage, are likely when FLAIR sequences are acquired 2–24 h after i.v. injection of the contrast. This pattern should be known in order to differentiate it from that of subarachnoid hemorrhage.

Keywords MRI · FLAIR sequence · Ischemic stroke · Cerebrospinal fluid

Introduction

The development of fluid-attenuated inversion-recovery sequence (FLAIR) and the ability to perform FLAIR with fast spin echo (fast FLAIR) has markedly improved the detection of a variety of brain disease [1]. The sensibility of FLAIR sequence is related to detection of lesions causing T2 prolongation with nulling of normal cerebrospinal fluid (CSF) background, leading to high lesion/tissue contrast [2].

The usefulness of FLAIR as compared with T2-weighted spin-echo MR imaging has been tested in a wide variety of brain diseases, including stroke [2, 3], multiple sclerosis [4, 5], infections [6, 7], hypertensive encephalopathy/reversible posterior leukoencephalopathy syndrome [8], brain neoplasms [9, 10, 11], and hypoxic–ischemic encephalopathy [12].

The FLAIR sequence has demonstrated CSF signal changes in many pathologies such as subarachnoid hemorrhage [13, 14, 15], meningitis [16], and sinus thrombosis [17]. Recently, Dechambre et al. reported CSF signal changes in FLAIR images in patients with acute stroke [18].

The present study was designed to evaluate whether i.v. injection of gadolinium may lead to CSF signal changes, as assessed by delayed acquisition of FLAIR sequences. In order to ascertain this possibility we evaluated pathologic conditions typically leading to blood-brain barrier disruption or neovascularization both in the intra and extracerebral compartment.

Materials and methods

We prospectively examined 12 patients (7 women and 5 men; mean age 69 years, age range 46–83 years) admitted to our hospital because of a clinical history and CT examinations compatible with ischemic stroke diagnosis. They were imaged in the subacute phase of the disease (2–7 days after the onset of symptoms) and showed ischemic lesions always involving the cortex and the subcortical white matter. In 9 of them follow-up MRI with FLAIR sequences (no contrast given at that time) was obtained up to 4 days; 8 patients affected by intracranial meningiomas (4 women and 4 men, mean age 39 years, age range 18–50 years); 5 patients affected by high-grade gliomas (2 women and 3 men, age range 54–71 years, mean age 63 years). In all of them surgery or biopsy subsequently confirmed the diagnosis (glioblastoma in 3 and high-grade glioma WHO III in 2); 5 patients with previous surgery for intracranial neoplasms (3 high-grade gliomas, 1 pilocystic astrocytoma, and 1 cavernoma; 2 women and 3 men; age range 24–71 years, mean age 53 years) imaged at a mean time of 7 days after surgery; 3 patients with multiple sclerosis (MS) and enhancing plaques (2 women and 1 man; age range 23–31 years, mean age 25 years).

Ten control subjects matched for age and gender were imaged as well.

In all of them (patients and controls), a standard dose of gadolinium-DTPA (0.1 mmol/kg) was injected and FLAIR sequences were acquired before injection and at the mean time of 110 min (SD 20 min) later.

Informed consent was obtained before protocol recruitment by the patients or, whenever impossible, by a spouse or guardian.

In all the patients and controls MRI was performed by means of a 1.5-T scanner equipped with echo-planar capabilities with a maximum gradient of 23 mT m^{-1}. Fast FLAIR parameters were as follows: TR/TE/no. of excitations=6700 ms/150 ms/2; TI 2200 ms; echo train length 20; field of view 24 cm; matrix 189×256; 5-mm-thick axial slices. Conventional SE axial T1-weighted images (TR 450 ms, TE 20 ms, no. of excitations 2) and turbo T2-weighted spin-echo images (TR 2000 ms, TE 120 ms, no. of excitations 2) were also acquired.

The CSF signal was analyzed by visual inspection by two readers who scored these changes (0=unchanged, 1=mild increase, 2=increased, 3=markedly increase) in the subarachnoid spaces (SAS) close to the lesion, in the same hemisphere, in both hemispheres, and, for neoplasms located close to the ventricle, inside the ventricle itself. The mean score of the two readers was considered.

Table 1 Signal intensity of cerebrospinal fluid (*CSF*) in the subarachnoid spaces (*SAS*) and ventricles on fluid-attenuated inversion recovery (FLAIR) sequences after gadolinium injection

Pathology	FLAIR sequence 110 min (SD 20 min) after i.v. injection				2 days follow-up
	SAS signal close to the lesion	SAS signal of the SAS in the same hemisphere	Signal of the SAS in the contralateral hemisphere	CSF signal inside the ventricles	
Stroke	+++	++	+	–	–
Previous surgery	++	++	+		
High-grade gliomas					
Close to SAS	+++	++	–	–	
Close to ventricles	–	–	–	+++	
Far from CSF	–	–	–	–	
Meningiomas	+	–	–	–	
Multiple sclerosis	–	–	–	–	
Control subjects	–	–	–	–	

+++ to + Strong to mild enhancement of CSF signal; – no enhancement

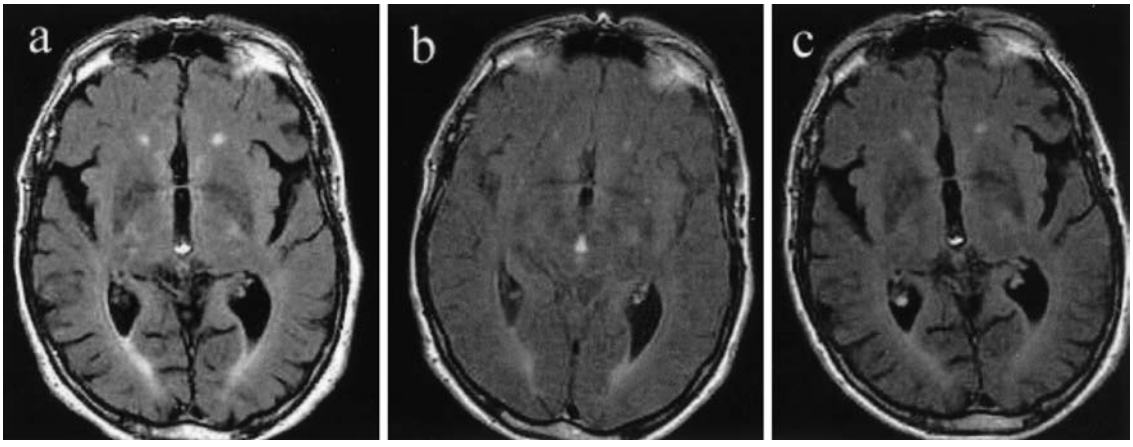

Fig. 1 **a** Fast fluid-attenuated inversion recovery (FLAIR) performed in a patient with an ischemic stroke 4 days after the clinical onset of symptoms (the lesion is not shown in this slice). **b** In the follow-up MRI performed with the same sequence 2 h later, cerebrospinal fluid (CSF) signal is diffusely increased in subarachnoid spaces with consequent lesser contrast between brain cortex and CSF itself. **c** The CSF signal returned to normal value 2 days later

Results

The results are summarized in Table 1.

In the patients with ischemic stroke, FLAIR sequence obtained after i.v. injection demonstrated an increase of signal intensity in the SAS. The enhancement was either diffuse to both hemispheres (Fig. 1) or higher in the SAS close to the lesion (Fig. 2). In all cases it demonstrated progressive normalization within 2 days (Fig. 1).

In the patients with previous surgery a strong enhancement of the poroencephalic cavity and of SAS closely located was also shown (Fig. 3).

In patients with high-grade gliomas strong enhancement of the CSF was shown only when the surface of the lesion was in contact with the SAS or the ventricles (Fig. 4). When present, the necrotic components of the neoplasm strongly enhanced after contrast injection as well (Fig. 4). The enhancement of the CSF was higher in those SAS close to the lesion and in the hemisphere ipsilateral to the lesion itself.

Mild CSF enhancement close to the lesion was shown in meningiomas (Fig. 5) which themselves enhanced after contrast injection.

No changes of CSF signal were observed in MS patients and controls.

Discussion

It is well known that FLAIR sequence is very sensitive to the CSF changes occurring in different pathologic conditions. Subarachnoid hemorrhages (SAH), sinus thrombosis, and meningitis may lead to an increase of CSF signal [13, 14, 15, 16, 17]. In a study by Singer et al. [16] FLAIR sequence demonstrated to be highly sensitive for the diagnosis of SAS disease being superior to gadolinium-enhanced T1-weighted MR imaging. Although these data have important implications, especially because FLAIR is performed without the cost of contrast agent, the sequence appeared to be nonspecific for acute SAH. Similar results were reported by Tsuchiya et al. [19] in meningeal carcinomatosis. These authors also demonstrated that contrast-enhanced FLAIR images can sometimes surpass contrast-enhanced T1-weighted images in their quality.

Animal experiments illustrated the extreme sensitivity of FLAIR imaging to changes in the T1 relaxation of CSF that became apparent even at gadolinium concentrations of 0.007 mmol/l [20]. The extreme sensitivity of FLAIR imaging can also be appreciated by the fact that there is evidence to suggest that breathing 95% oxygen can change the relaxation time of CSF to modify its appearance on FLAIR images [21]. This is due to the fact that the sequence is designed to nullify the normal CSF signal and any condition allowing the composition of CSF to change leads to an increase of signal. T1-weighted sequences were reported to be influenced by changes of CSF content (e.g., gadolinium concentration) as well, but the sensitivity of FLAIR is much higher [22].

Recently, Dechambre et al. described 5 patients with hyperintense CSF signal on FLAIR images in acute stroke [18]. The hypothetical explanation proposed by the authors could be a disruption of the blood-brain barrier resulting in leakage of protein and gadolinium chelates, or both, in the SAS.

Using different models, Jackson and Hayman [23] and Mathews et al. [24] proposed that an underlying leakage of small amounts of gadopentetate dimeglumine from damaged pial vessels is the mechanism for the increased fast FLAIR contrast between surface collections of gadopentetate dimeglumine and surrounding normal CSF and adjacent gray matter.

In our study FLAIR sequences confirmed an increased CSF signal in most of the patients when FLAIR

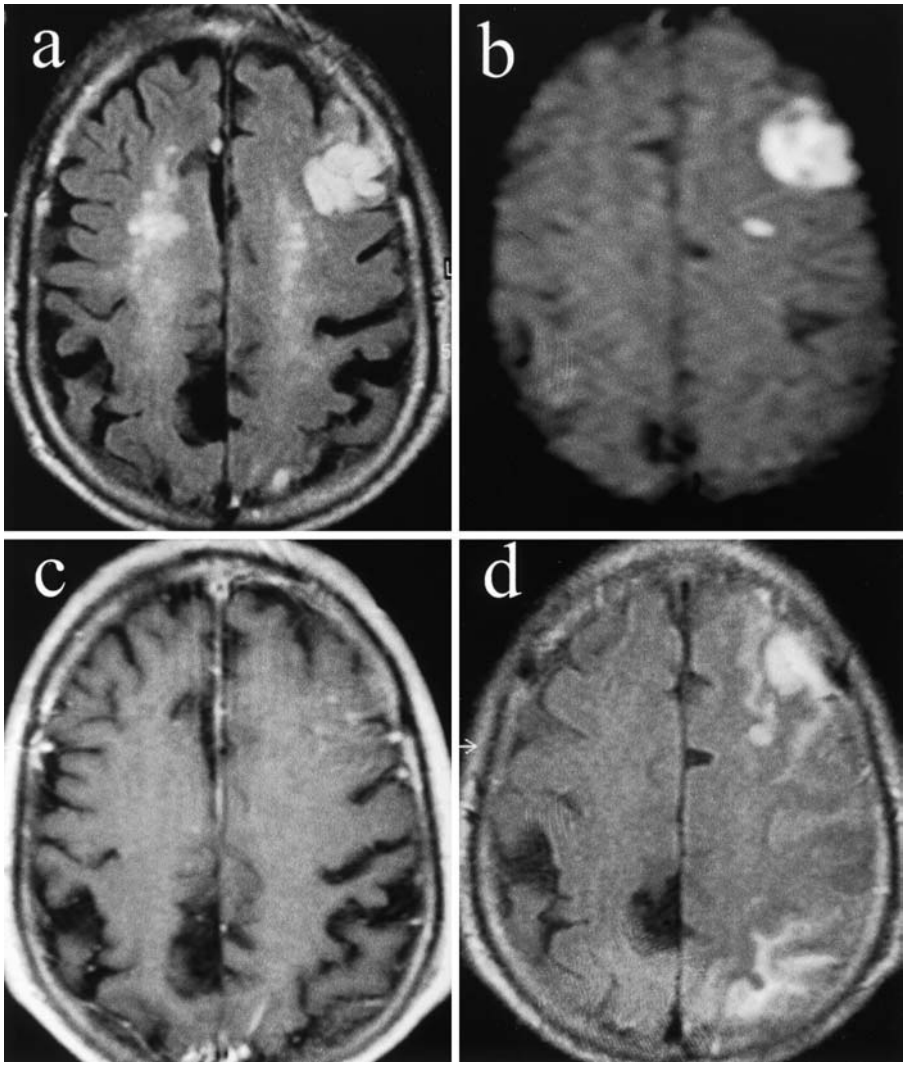

Fig. 2 Subacute (36 h) ischemic stroke is shown by **a** fast-FLAIR sequence and **b** diffusion-weighted imaging. Mild cortical enhancement is evident on **c** postcontrast T1-weighted image. **c** Delayed fast FLAIR (2 h later) clearly shows the CSF signal increase mostly in the ipsilateral hemisphere

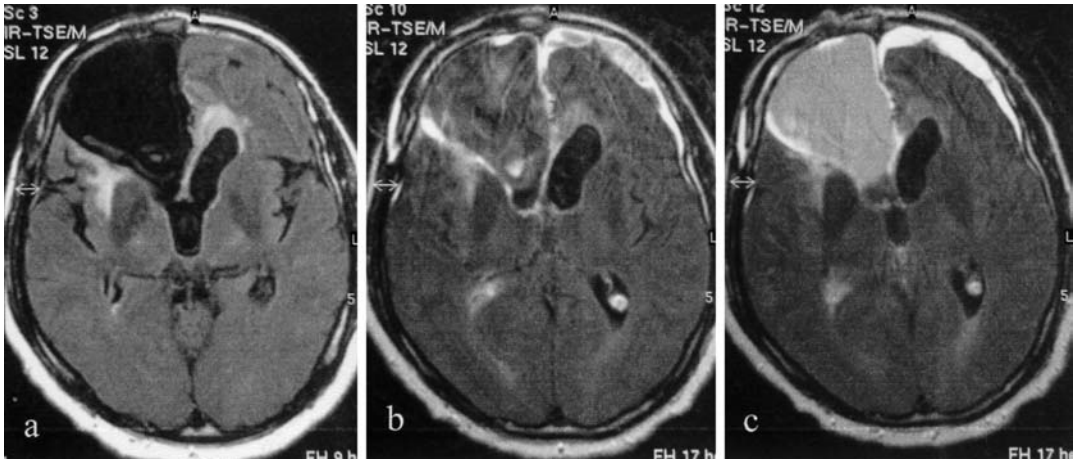

Fig. 3 **a** Fast-FLAIR sequence obtained in a patient with previous surgery for glioblastoma in the frontal region. Follow-up **b** 2 and **c** 3 h later. A diffuse enhancement of the poroencephalic lesion is evident also extending in the adjacent subarachnoid spaces (SAS) and subdural effusion

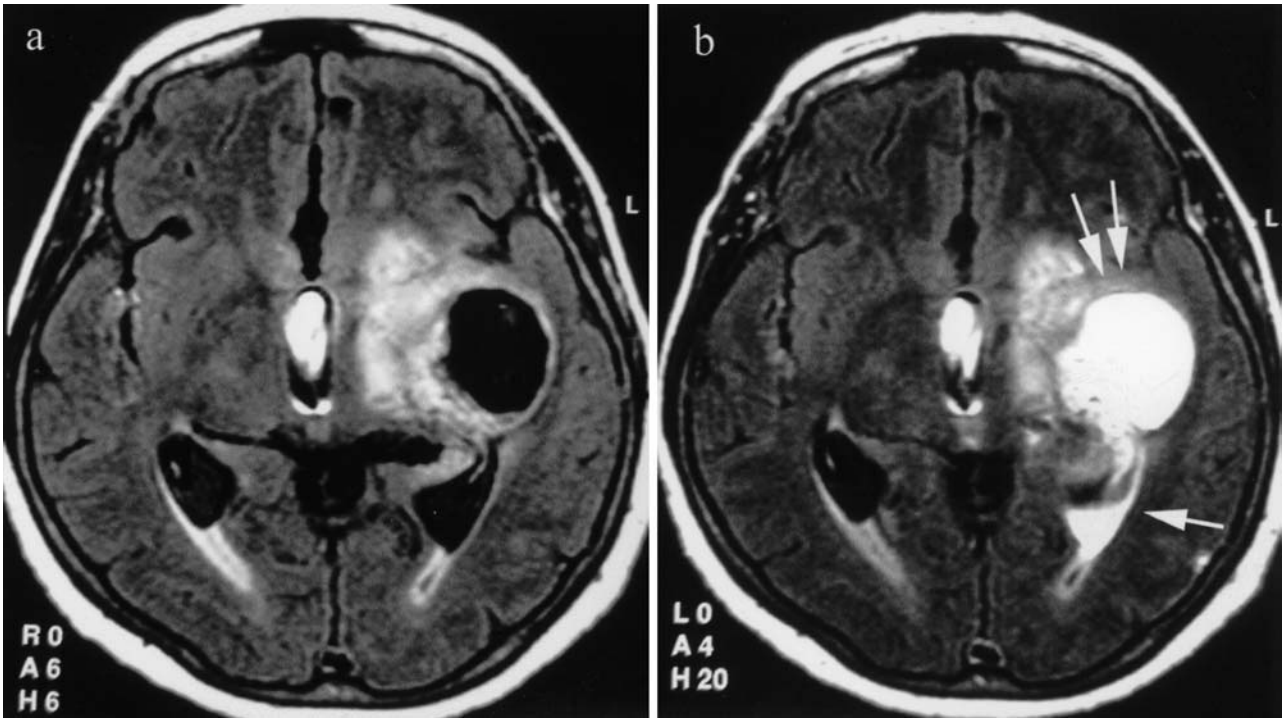

Fig. 4 **b** Strong enhancement of the necrotic component of glioblastoma (*arrows*) associated to gadolinium leakage in the occipital horn of the lateral ventricle (*arrow*). **a** Precontrast fast-FLAIR sequence

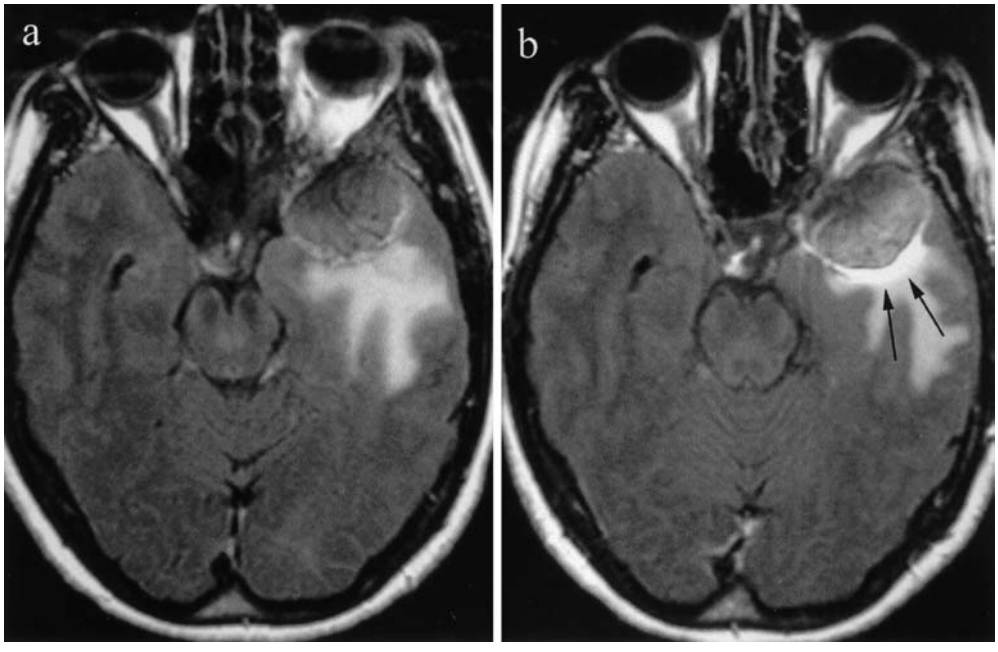

Fig. 5 **b** Mild enhancement in the SAS close to a meningioma 2 h after gadolinium injection (*arrows*). **a** Precontrast fast-FLAIR sequence

sequences were obtained after i.v. injection. In all the patients with pathologies leading to a breakdown of the blood-brain barrier or with new vessel formation close to the SAS or ventricles, an increased signal of the CSF was shown after gadolinium injection. Moreover, in the same cases the enhancement was higher close to the lesion and/or in the ipsilateral hemisphere. This may lead to the conclusion that CSF changes are evident only for those lesions with neovascularization or blood-brain barrier breakdown located close to the CSF.

This pattern was not evident in patients with white matter disease and lesion enhancement (MS patients with active plaques), in normal subjects, and even in those patients with high-grade gliomas without contact with the CSF.

Although gadolinium chelates were recently found in the CSF of dogs undergoing intravenous injection of gadolinium [22] with CSF concentration dependent on the i.v. dose, we did not find changes of signal in the SAS compatible with gadolinium leakage in normal subjects or in those without lesions close to the CSF. It is possible that the standard dose of gadolinium used is not enough to be detected by FLAIR sequences in these conditions.

The signal changes observed in the CSF (as assessed in patients with stroke) returned to normal within 2 days. It is likely that gadolinium slowly diffuses in the SAS during the first hours following injection and is resorbed within 48 h.

The knowledge that, in pathologic conditions with blood-brain barrier breakdown or neovascularization, gadolinium can leak in the SAS and cause CSF signal changes may help in the differential diagnosis with other pathologies leading the CSF signal to increase (especially SAH). It is therefore important to remember that whenever FLAIR sequences are acquired after i.v. injection of gadolinium (from 1 to 24 h) CSF signal changes might be related to this phenomenon.

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