Magnetic resonance imaging in epilepsy with a fast FLAIR sequence

U C Wieshmann, S L Free, A D Everitt, P A Bartlett, G J Barker, P S Tofts, J S Duncan, S D Shorvon, J M Stevens

Abstract

Objective—To assess the diagnostic value of the fast FLAIR sequence in patients with epilepsy.

Methods—One hundred and twenty eight patients with epilepsy and 10 control subjects were scanned with the fast FLAIR sequence with 5 mm slices, a coronal gradient echo (GRE) T1 weighted sequence with 1.5 mm slices and spin echo (SE) or fast spin echo (FSE) proton density and T2 weighted sequences with 5 mm slices. All images were compared by an unblinded neuroradiologist and neurologist. Fast FLAIR images of patients with hippocampal sclerosis (HS) and normal control subjects were also evaluated by two blinded independent raters.

Results—Fast FLAIR provided a high conspicuity of neocortical damage, hamartomas, dysmorphic tumours, and clear cut hippocampal sclerosis. However, the same information could be obtained from the coronal T1 and T2 weighted images. In three patients fast FLAIR showed a clearly abnormal signal when SE T2 weighted images had not been definitely abnormal. Heterotopia was less conspicuous on fast FLAIR than GRE T1 weighted images. The two blinded raters detected all but one of the patients with clear cut hippocampal sclerosis on fast FLAIR images but missed all borderline cases of hippocampal atrophy and there were two false positives. Clear cut hippocampal sclerosis was more conspicuous on fast FLAIR images than on SE T2 weighted images in most patients, but additional patients were not identified.

Conclusion—Fast FLAIR has the advantage of identifying neocortical lesions and definite hippocampal sclerosis with a short scanning time and may also demonstrate lesions when other sequences are normal in a limited number of cases. The technique was not useful, however, for identifying mild hippocampal sclerosis or heterotopia.

Keywords: magnetic resonance imaging; fluid attenuated inversion recovery; epilepsy

Fluid attenuated inversion recovery pulse sequence (FLAIR) is a sequence which nulls the CSF signal by an inversion recovery pulse and has a long TE to ensure T2 weighting. By nulling the CSF signal, a lesion usually becomes the brightest object in these images, thus enhancing conspicuity. A recent study reported the detection of several additional abnormalities including at least one histologically established dysplastic lesion by using FLAIR in patients with partial epilepsy. The sequence used, however, had a low signal to noise ratio, was prone to artefact, and the acquisition time of 20 minutes caused by the long TI and TRs limited clinical application. By using the rapid acquisition with relaxation enhancement readout (RARE) similar appearing images could be obtained in six minutes. The aim of our study was to assess the diagnostic value of this fast FLAIR sequence in epilepsy. We therefore compared fast FLAIR with a protocol of sequences which has been especially developed in recent years for patients with epilepsy.

Material and methods

PATIENTS AND CONTROLS

One hundred and twenty eight consecutive adult patients attending a tertiary referral centre for epilepsy were included in the study. Classification of the epileptic seizures was based on electroclinical data. Twenty patients had epilepsy with generalised seizures, 98 had epilepsy with partial seizures, and 10 had non-classified epilepsy. Ten normal control subjects were also evaluated.

MRI METHODOLOGY

A 1.5 Tesla GE Signa scanner (GE Medical Systems, Milwaukee, WI, USA) was used to obtain the following images:

1. Spin echo (SE) T1 weighted (TR/TE/NEX 620/16/1) sagittal images, 256 x 256 matrix and 24 x 24 field of view (FOV), 5 mm slices, 2.5 mm interslice gap.

2. Inversion recovery prepared fast spoiled gradient echo (GRE) (predominantly) T1 weighted (TR/TE/TI/NEX 17/4/2550/1, flip angle 20°) coronal images, 256 x 192 matrix, 24 x 18 FOV, 1.5 mm slices, three dimensional acquisitions.

3. Fast spin echo (FSE) mild and heavily T2 weighted (TR/TEef1/TEef2/NEX 2000/38/95/1) coronal images, 256 x 192 matrix, 24 x 18 FOV, 5 mm slices, no gap (81 patients, all controls) or spin echo (SE) (TR/TE1/TE2/NEX 2000/30/120/1) weighted coronal images, 256 x 192 matrix, 24 x 18 FOV, 5 mm slices, no gap (47 patients, two...
controls). Images were obtained perpendicular to an axis drawn from the orbitofrontal cortex to the splenium, which is roughly parallel to the long axis of the hippocampus.

(4) Fast FLAIR (TR/TEf/TI/NEX 11000/164/2600/1) coronal images, 256 × 192 matrix and 24 × 18 FOV with 5 mm slices, no gap. Forty two images covering the whole brain were obtained in six minutes. Images were obtained using the same plane as in (3).

Volumetric measurements of the hippocampi and the intracranial space were performed on the GRE T1 weighted images using methods described previously. Clear cut unilateral hippocampal sclerosis was defined as asymmetry of more than 20%. Borderline hippocampal atrophy was defined as asymmetry between 10% and 20%. Hippocampal volumes were corrected for intracranial volume to identify bilateral hippocampal hippocampal sclerosis. Bilateral hippocampal sclerosis was defined as a volume more than 3 SD smaller than the mean hippocampal volume of normal controls on both sides.6

GRE T1 weighted images with 1.5 mm slices, SE, or FSE images along with the volumetric measurements were regarded as the “standard protocol”.

Images of all sequences were compared by an unblinded neuroradiologist (JMS) and a neurologist (UCW). Two blinded independent raters (SDF, ADE) inspected only the fast FLAIR images of 40 subjects. Twenty subjects had abnormal hippocampal volumes on measurement, 17 had unilateral small hippocampal volumes with asymmetry > 10%, two had bilateral symmetric small hippocampal volumes, and one had bilateral small volumes in addition to asymmetry. Twenty subjects had normal hippocampal volumes on measurement (10 control subjects and 10 patients) to evaluate the detectability of hippocampal sclerosis on fast FLAIR images.

To evaluate the conspicuity of hippocampal sclerosis on fast FLAIR images fast FLAIR and T2 weighted FSE and SE T2 weighted images of 23 patients with known hippocampal sclerosis were compared (detected by volumetric measurement) on a different day.

Results

Controls

The standard protocol was normal in all 10 control subjects. On fast FLAIR images the temporomesial structures returned a higher signal than the cortex of the cerebral convexities in seven of 10 controls. Two of these seven were rated as abnormal by the blinded raters when they rated fast FLAIR images in isolation from other data.

Although CSF suppression was generally excellent, high signal was present around the basal cisterns, the wall of the ventricles, and the aqueduct. In four control subjects the whole third ventricle returned a high signal. The white matter adjacent to the occipital horn and the CSF adjacent to the choroid also returned a high signal.

The grey matter/white matter contrast was generally less then that seen on T1 or T2 weighted images. The white matter returned a more heterogeneous signal on fast FLAIR, with a higher signal being evident in nine controls in the expected position of the corticospinal tract.

Patients

Neocortical lesions detected by the standard protocol

A non-dysgenetic neocortical lesion was shown in 22 patients by the standard protocol. (Traumatic damage (n = 5), presumed glioma (n = 2), non-specific damage (n = 10), temporal lobectomy (n = 3), Sturge-Webb syndrome (n = 1), and cyst (n = 1); additional hippocampal sclerosis was present in four patients.)

In every case the lesions were more conspicuous on fast FLAIR images and the extent of the lesion was clearly shown (fig 1). However, similar information could be obtained from conventional T1 and T2 weighted images when viewed in combination.

Dysgenetic lesions detected by the standard protocol

In 13 patients a probable dysgenetic lesion was visible (presumed laminar heterotopia (n = 3), presumed nodular subependymal heterotopia (n = 3), one with additional borderline hippocampal atrophy, polymicrogyria (n = 1), schizencephaly (n = 1), frontal pachgyria (n = 1), presumed hypothalamic hamartoma (n = 2), presumed dysembryoplastic neuroepithelial tumour (DNT; n = 2)). The schizen-
Magnetic resonance imaging in epilepsy with a fast FLAIR sequence

cephyal was evident on every sequence. On fast FLAIR images hypothalamic hamartoma and DNT returned a high signal. Both were more conspicuous on fast FLAIR than on GRE T1 weighted images. However, laminar heterotopia and nodular subependymal heterotopia were less conspicuous on fast FLAIR than on coronal GRE T1 weighted images with 1-5 mm slices or proton density weighted images and could have easily been overlooked (fig 2). Polymicrogyria and pachygyria were also less conspicuous on fast FLAIR.

Normal standard protocol MRI
The standard images of 58 patients were classified as normal. In three of these 58 patients a small area of high signal was detected on fast FLAIR images. In all three patients slight signal changes were also identified on the proton density and T2 weighted images but were considered not to be clearly abnormal (table 1). In one patient the area of signal change agreed with the clinical and EEG localisation of seizure onset. In the other patients the epilepsy had been classified as generalised.

Hippocampal sclerosis confirmed by volumetric measurements
Thirty five patients with abnormal hippocampi were detected using volumetric measurements. (Twenty eight patients had unilateral clear cut hippocampal sclerosis, detected visually and with volumetric measurements, asymmetry was greater than 20%; four patients had unilateral borderline hippocampal atrophy, detected with volumetric measurements only, asymmetry was 10%-20%; three patients had bilateral hippocampal sclerosis; corrected hippocampal volumes ranged from 1360 mm$^3$ to 1638 mm$^3$).

On most of the fast FLAIR images the sclerotic hippocampus returned a high signal and was usually more conspicuous than on SE T2 weighted images because the CSF of the temporal horn was suppressed (fig 3). However, the CSF suppression was not complete in every case and the choroid plexus often also returned a high signal. In addition, both mesiotemporal regions were brighter than the neocortex in normal control subjects as well as in the patients. To quantify the results of the visual inspection of the hippocampal region we assessed detectability and conspicuity using two blinded raters.

To assess the detectability of hippocampal sclerosis on fast FLAIR images the images of 20 randomly chosen patients with hippocampal sclerosis (13 clear cut hippocampal sclerosis, four borderline atrophy, and three bilateral hippocampal sclerosis) and 20 normal cases (10 normal controls and 10 patients, all with normal hippocampal volumes) were rated (by SLF, ADE). The raters detected all but one of the clear cut cases of hippocampal sclerosis. The case they missed also had a normal signal on SE T2 weighted images to visual inspection. They missed all cases with borderline hippocampal atrophy, one rater missed one bilateral case, and both raters had two false positive results.
To assess the conspicuousness of hippocampal sclerosis on fast FLAIR images the two blinded raters compared fast FLAIR and FSE T2 weighted images of 23 randomly chosen patients with hippocampal sclerosis (ulateral volume loss ranging from 20% to 53% in 22, one with bilateral hippocampal sclerosis) on a different day. In three patients the raters found that visual assessment of signal intensity and comparison was particularly difficult (one patient had a slight movement artefact on fast FLAIR images, one patient had bilateral hippocampal sclerosis, in one patient the images were not imaged in the standard size); these cases were excluded from comparison. In the remaining 20 patients hippocampal sclerosis was more conspicuous in > 50% (rater ADE 11 of 20, rater SLF 18 of 20). In nine cases both raters agreed on higher conspicuousness.

Discussion
The capability of fast FLAIR to demonstrate structural abnormalities varied considerably and depended on the aetiology. Neocortical brain damage and lesions diagnosed as presumed hamartomas and DNT were always more conspicuous on fast FLAIR. Takehara et al reported a similar result for the detection of tubers in tuberous sclerosis.

Fast FLAIR was inferior to coronal GRE T1 weighted images with 1.5 mm slices in detecting nodular subependymal heterotopia and laminar heterotopia because of the low grey matter/white matter contrast, and fast FLAIR was inferior to GRE T1 weighted images in detecting polymicrogyria and pachygyria because of the thicker slices. Heterotopia, polymicrogyria, and pachygyria often underlie apparent "cryptogenetic" epilepsy. Heterotopia may be associated with hippocampal sclerosis, as in one of our patients. Patients with heterotopia and hippocampal sclerosis often are not seizure free after temporal lobectomy; thus the detection of exclusion of heterotopia is important in the presurgical evaluation.

Clear cut hippocampal sclerosis (asymmetry > 20%) was detectable on fast FLAIR images in nearly all cases, because of the high signal returned by the sclerotic hippocampus. Hippocampal sclerosis is usually associated with a high signal on T2 weighted images making an abnormality on T2 weighted images an important diagnostic criterion for hippocampal sclerosis. In most, but not all, cases clear cut hippocampal sclerosis was more conspicuous on fast FLAIR images than on SE or FSE T2 weighted images. In theory, a hippocampus with a high T2 signal should be the brightest (and most conspicuous) object on fast FLAIR images because the CSF signal of the temporal horn should be suppressed. On SE T2 weighted images the CSF of the temporal horn returns high signal which has to be distinguished from the hippocampal signal. Thus hippocampal sclerosis should always be more conspicuous on fast FLAIR images compared with SE T2 weighted images. However, on some fast FLAIR images the CSF suppression was incomplete in the temporal horn and the choroid plexus also returned a high signal; in these cases the sclerotic hippocampus was not more conspicuous on fast FLAIR images than the T2 weighted images.

One patient with clear cut hippocampal sclerosis on volumetric measurements was missed by the two raters because the signal was not abnormal. This case also had a normal signal on visual inspection of SE T2 weighted images but in fact yielded a measured T2 value on subsequent T2 mapping which was outside the normal range. Nevertheless, hippocampal sclerosis is not in every case associated with a change in T2 relaxation and an increased signal is not specific for sclerosis but may also occur in other types of pathology such as neoplasias and dysplasia. Therefore, the estimation of hippocampal volume loss which is associated with hippocampal sclerosis, either visually or with volume measurements, is equally important. Volume loss was not reliably assessable on fast FLAIR images because of the relatively low resolution and the large slice thickness (5 mm).

In addition to these problems the raters failed to recognise all cases of borderline hippocampal atrophy (asymmetry 10%–20%) on fast FLAIR images and called two false positive results. This may be explained by the fact that the mesiotemporal region was always brighter than the neocortex on fast FLAIR images and there was a high interindividual variability in signal intensity in control subjects making it difficult to decide whether the signal was pathological in borderline cases.

Hippocampal sclerosis is the most common lesion in temporal lobe epilepsy. The probability of a seizure free outcome after temporal lobectomy is greater for patients with hippocampal sclerosis than for patients with normal histological findings. Magnetic resonance imaging with contiguous thin coronal T1 weighted images and coronal T2 weighted images improves the sensitivity of detecting hippocampal sclerosis, and further improvement is possible with quantitative methods such as volumetric measurements and T2 mapping. Fast FLAIR increases the conspicuousness of clear cut hippocampal sclerosis but in this study it seemed not to be as sensitive as quantitative methods, and although fast FLAIR indeed may be useful for MRI units which lack the resources to carry out adequate quantification, borderline hippocampal atrophy and bilateral hippocampal sclerosis will remain difficult to detect.

Additional lesions in cases with a completely normal standard protocol MRI were not detected by fast FLAIR in our study. Usually, an abnormal fast FLAIR signal was associated with abnormalities on the other sequences. In only three patients fast FLAIR showed a clearly abnormal signal, when SE T2 weighted images were suspicious but not definitely abnormal (table 1). By contrast with this result, Bergin et al reported additional lesions detected by FLAIR in 30% of their patients. The different findings of the two studies may be explained by several factors.
Magnetic resonance imaging in epilepsy with fast FLAIR sequence

Table 2  Summary of fast FLAIR findings

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Appearance on fast FLAIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothalamic hamartomas</td>
<td>High signal, more conspicuous than on SE T2 images</td>
</tr>
<tr>
<td>DNT</td>
<td>High signal, more conspicuous than on SE T2 images</td>
</tr>
<tr>
<td>Low grade glioma</td>
<td>High signal, more conspicuous than on SE T2 images</td>
</tr>
<tr>
<td>Brain damage</td>
<td>High signal, more conspicuous than on SE T2 images</td>
</tr>
<tr>
<td>Sturge-Weber syndrome</td>
<td>Cortical lesion conspicuous</td>
</tr>
<tr>
<td>Clear cut HS</td>
<td>High signal in all but one case</td>
</tr>
<tr>
<td>Borderline hippocampal atrophy</td>
<td>Signal similar to controls</td>
</tr>
<tr>
<td>Schizencephaly</td>
<td>Detectable, not conspicuous</td>
</tr>
<tr>
<td>Heterotopic grey matter</td>
<td>Not conspicuous</td>
</tr>
<tr>
<td>Pachygyria, polymicrogyria</td>
<td>Difficult to detect</td>
</tr>
</tbody>
</table>

Clear cut HS = hippocampal sclerosis with asymmetry > 20%; borderline hippocampal atrophy = with asymmetry of 10-20% on volumetric measurement; DNT = dysembryoplastic neuroepithelial tumour.

Firstly, Bergin et al implemented the sequence differently; using a 1·0 Tesla Picker MR-scanner, their TR value was half as long as ours and they did not employ the RARE readout. The TR and TE values used in our sequence have been optimised for the detection of white matter lesions in multiple sclerosis but may have been suboptimal in the detection of lesions relevant in epilepsy. The echo spacing of the RARE readout may also have been suboptimal in our sequence, perhaps causing edge related artefacts.

Secondly, Bergin et al (their study was smaller than ours and had no control subjects), described lesions in the amygdala and the adjacent hippocampus (accounting for five of 11 additional cases). With the fast FLAIR sequence we noted a high interindividual signal variation in the temporomesial region in control subjects. The temporomesial region also returned a higher signal than the neocortex on fast FLAIR images in control subjects. Consequently, slight signal changes in the amygdala were not regarded as abnormal in our study.

Probably most important, however, is that we compared the fast FLAIR with a different protocol of sequences than Bergin et al. We applied a volume acquisition sequence with a slice thickness of 1·5 mm, performed hippocampal volumetric measurements, and obtained the T2 weighted images perpendicular to the long axis of the hippocampus. Bergin et al used T1 and T2 weighted axial and coronal sequences with 6 mm slice thickness. The sensitivity for hippocampal sclerosis is higher on sequences with thin slices. Thus the chance to detect additional hippocampal sclerosis with fast FLAIR was lower in our study.

Table 2 summarises our results.

In conclusion, the major advantages of fast FLAIR are increased conspicuity of neocortical lesions and clear cut unilateral hippocampal sclerosis; fast FLAIR may also demonstrate lesions when other sequences are normal in a few cases. Heterotopia, borderline hippocampal atrophy, and subtle cortical dysplasia may be missed on fast FLAIR.

We acknowledge Drs SJ Riederer and JN Rydberg of the Magnetic Resonance Laboratory of the Mayo Clinic, Rochester, MN, USA, who made available to us the fast FLAIR sequence used in this work.


