Clinical Radiology xxx (2018) 1–11

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.clinicalradiologyonline.net

Neuroradiological findings in patients with "non-lesional" focal epilepsy revealed by research protocol

B.A.K. Kreilkamp [a,b,*], K. Das [b], U.C. Wieshmann [b], S. Biswas [b], A.G. Marson [a,b], S.S. Keller [a,b]

[a] Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, UK
[b] The Walton Centre NHS Foundation Trust, Liverpool, UK

ARTICLE INFORMATION

Article history:
Received 23 March 2018
Accepted 26 August 2018

AIM: To evaluate whether a dedicated epilepsy research protocol with expert image re-evaluation can increase identification of patients with lesions and to attempt to ascertain the potential reasons why lesions were not identified previously on earlier clinical magnetic resonance imaging (MRI).

MATERIALS AND METHODS: Forty-three patients (26 female) with focal refractory epilepsy who had failed at least two trials of anti-epileptic drug treatments were studied. Patients were recruited prospectively into the study if previous clinical MRI was deemed to be "non-lesional" by the clinicians involved in the initial assessment. Three-dimensional (3D) T1-weighted (T1W), T2-weighted (T2W), T2 fluid-attenuated inversion recovery (T2-FLAIR) sequences, and two-dimensional (2D) coronal T1-/T2W FLAIR were assessed by a neuroradiologist, including the previous clinical MRI of individual patients.

RESULTS: Twenty-nine or 43 (67%) patients remained MRI-negative after scanning with the epilepsy-dedicated protocol and image reappraisal by expert consultant neuroradiologists; however, 14/43 (33%) patients were found to have potentially epileptogenic brain lesions. The lesion that most frequently escaped the attention of clinicians was hippocampal sclerosis (nine cases, of which two had an additional focal cortical dysplasia, FCD), followed by single FCDs (two cases), and others including gliosis, encephalocoele, and amygdala enlargement (one case each). Eleven of the 14 (79%) previously "non-lesional" patients had electroencephalogram (EEG) imaging-concordant localisation features, rendering them potential candidates for resective surgery.

CONCLUSIONS: The primary factors explaining the newly identified lesions were the choice of MRI sequences, imaging parameters, data quality, lesion not reported (human factor), and loss of information through incomplete documentation. It is important for all clinicians to proceed meticulously in the detailed assessment of epilepsy-dedicated *in-vivo* MRI and discuss difficult patient cases in multidisciplinary team meetings.

* Guarantor and correspondent: B. A. K. Kreilkamp, Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, Clinical Sciences Centre, Aintree University Hospital, Lower Lane, Liverpool L9 7LJ, UK. Tel.: +44-151-529-5467.
E-mail address: b.kreilkamp@liv.ac.uk (B.A.K. Kreilkamp).

https://doi.org/10.1016/j.crad.2018.08.013
0009-9260/

Introduction

The detection of a brain abnormality on magnetic resonance imaging (MRI)[1–4] in addition to concordant focal electroencephalogram (EEG) spike discharges[5–7] has been related to good surgical outcomes, while patients with no remarkable MRI findings are rendered seizure-free less often.[7–9] Unfortunately, it is not uncommon for patients with severe seizure activity to present with an unremarkable MRI; however, it is likely that (subtle) epileptogenic lesions are not detected on routine clinical MRI and contribute to ongoing seizure activity. It is important that (1) the MRI protocol and (2) subsequent qualitative and quantitative assessment of the images is specifically tailored for patients with epilepsy so that potentially small lesions causing debilitating seizures can be detected and treated. Several publications to date have discussed the factors that can increase the accuracy of lesion detection through MRI in clinical practice.[10–13] In one study, outcome after surgery improved significantly with the introduction of an epilepsy-dedicated MRI protocol, which increased the sensitivity of epilepsy-related lesion detection (e.g., hippocampal sclerosis, HS) rather than applying a standardised MRI protocol.[11] Nevertheless, the authors state that even with a dedicated protocol, optimisation of acquisition parameters (e.g., angulation according to the presumed seizure onset zone) may be necessary for individual patients.[11] Overall, when correlating radiological findings with histopathology, neuropathological diagnoses were predicted correctly in 89% of epilepsy-dedicated MRI reports, but only by 22% of "non-expert" reports (MRI assessed by radiologists not attached to epilepsy centres) based on standard MRI.[11] Consequently, an early referral to a specialist epilepsy centre may increase the lesion detection rate. Hardware may also play a role; Phal *et al.*[14] and Winston *et al.*[15] reported an up to 30% increase in diagnostic yield of 3 T images versus 1.5 T. These results indicate that higher signal-to-noise ratio (SNR) facilitates the detection of focal epileptogenic lesions.

The aim of the present study was to evaluate whether an epilepsy-dedicated research protocol with expert image re-evaluation could increase identification of patients with lesions. This required patients to have no discernible brain abnormality based on a previous clinical MRI (not part of an epilepsy-dedicated research protocol). This earlier MRI was included in an evaluation of lesion conspicuity to qualitatively re-evaluate factors likely to have contributed to the new presentation of a lesion. Considering the previous reports of increased diagnostic yield using 3 T as opposed to 1.5 T MRI[14,15] and the application of epilepsy-dedicated MRI protocols,[11] the objective of this work was to determine whether the use of a dedicated epilepsy research protocol in a specialist hospital of neurology and neurosurgery would benefit lesion conspicuity and identification.

Importantly, MRI could be assessed to illustrate if MRI hardware, image signal decay due to artefacts (e.g. head motion), radiological expertise or the protocol had an influence on the individual diagnosis at the time. Failure to identify lesions earlier may have multiple reasons and may be directly linked to lesion conspicuity. The work conducted here may provide important clinical information on the number of patients who have epileptogenic lesions but have unremarkable MRI by virtue of previous imaging protocols not specialised for the detection of epileptogenic lesions. Identification of an underlying brain abnormality can potentially afford important implications for treatment consequences, such as earlier referral for epilepsy surgery for patients with medically refractory focal epilepsies. According to Wiebe and Jette,[16] surgery is effective but underused. In particular, it has been shown to be cost-effective,[17] to save lives,[18] and improve quality of life by reducing seizure frequency.[19] Consequently, epilepsy surgery with appropriate presurgical evaluation may afford many advantages over the continued use of anti-epileptic drugs (AED).

Materials and methods

The study was approved by the local ethical board for the application of MRI scanning and collection of previous clinical data in patients with refractory focal epilepsy. The epilepsy-dedicated research protocol was conducted between November 2014 and April 2016. All participants provided written informed consent. A 3 Tesla General Electric Discovery MR750 scanner (Waukesha, WI, USA) with a 32-channel head coil was used for prospective acquisition of MRI images. Forty-three patients (26 female; mean age ± standard deviation [SD] = 31.6±11, range 18–61) with focal refractory epilepsy who had failed at least two trials of AED treatments were studied. Patients were

Table 1
Demographic and clinical information.

Variable	MRI-positive patients	MRI-negative patients
N	14	29
Mean age (SD) in years, range	33.2 (10.9), 18–54	30.8 (11.2), 18–61
Sex (female/male)	10/4	16/13
Mean age at diagnosis (SD) in years, range	13.9 (11.2), 5–36	16.2 (10.1), 1–47
Mean duration of epilepsy (SD) in years, range	19.3 (14.1), 1–50	14.6 (9.6), 3–43
History of SGTCS (no/yes)	2/12	9/20
Seizure frequency (SD), per week	4.9 (9.0), 0.04–35	5.8 (10.4) 0.04–46
EEG localisation (rTL/lTL/rFL/lFL/other)	3/7/0/0/4	5/9/3/5/7
Complications at birth (unsure/no/yes)	1/12/1	2/24/3
History of brain infection (no/yes)	12/2	26/3
History of febrile convulsions (no/yes)	9/5	28/1

All participants underwent the same imaging protocol. No patient had a head trauma. Details of individual patients can be found in Table 2 and captions of Figs 1–10. TL, temporal lobe; FL, frontal lobe; r, right; l, left; EEG, electroencephalography; SD, standard deviation; SGTCS, secondary generalised tonic–clonic seizure.

Please cite this article in press as: Kreilkamp BAK, et al., Neuroradiological findings in patients with "non-lesional" focal epilepsy revealed by research protocol, Clinical Radiology (2018), https://doi.org/10.1016/j.crad.2018.08.013

recruited prospectively into the study if previous clinical MRI was deemed to be "non-lesional" by the clinicians involved in the initial assessment, which included general radiologists at other trusts and neuroradiologists at the authors' centre. Localisation of seizure onset had been thoroughly evaluated using seizure semiology and scalp EEG investigations.

The epilepsy-dedicated research protocol included a three-dimensional (3D) axial T1-weighted (T1W) fast-spin-gradient (FSPGR) with phased-array uniformity enhancement (PURE) signal inhomogeneity correction (140 sections, repetition time [TR]=8.2 ms, inversion time [TI]=450 ms, echo time [TE]=3.22 ms, flip angle=12°, with 1 mm isotropic voxel size, acquisition time: 3:48 minutes) for all participants. Axial 3D T2-weighted (T2W) turbo spin echo (TSE) with variable flip angle (CUBE) images (with PURE correction, 312 slices, TR=2,500 ms, TI = N/A, TE=71.2 ms, flip angle=90°, with 0.5 mm isotropic voxel size), and 3D sagittal CUBE T2 fluid-attenuated inversion recovery (T2-FLAIR) with PURE (312 sections, TR=6,000 ms, TI=50 ms, TE=127.1 ms, flip angle=90° with 0.5 mm isotropic voxel size) were also acquired. Additionally, T1-FLAIR coronal (52 sections, TR = N/A, TI = 920 ms, TE = 9.94 ms, flip angle = 111°, voxel size = 0.4×0.4×3mm) and a T2-FLAIR coronal image (40 sections, TR = 12,000 ms, TI = 2,713 ms, TE = 98.7 ms, flip angle=160°, voxel size = 0.86×0.86×4 mm) aligned with the long axis of the hippocampus were acquired for all patients. In those patients, who had a lesion identified on the most recent dedicated epilepsy research MRI, the previous clinical MRI was re-assessed by two expert

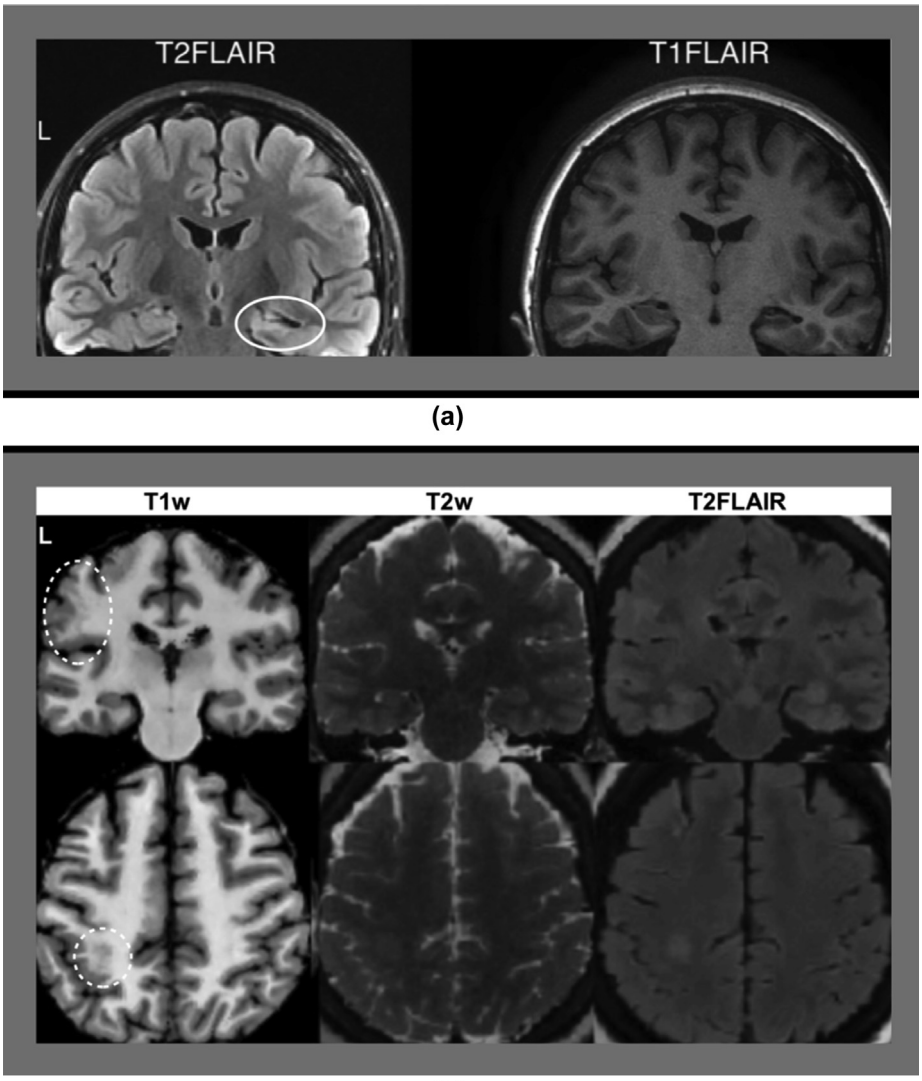

Figure 1 Common Lesions in Focal Epilepsy: Right HS shown on T2-FLAIR/T1-FLAIR (A) and FCD in the left supramarginal gyrus (top) and superior parietal lobule (bottom) (B). **(A)** HS: The T2-FLAIR image shows hyperintense signal in the hippocampal region, while the T1-FLAIR demonstrates hypointensity of the hippocampal formation with a marked volume loss. The loss of internal architecture in the right hippocampus is only marginally visible in both images. T1-FLAIR and T2-FLAIR show blurring of the parahippocampal WM, which is a frequent finding co-occurring with HS. **(B)** FCD: The related signal appears dark on T1-w and bright on T2-w/T2-FLAIR 3D volume images. The neuroradiologist's report (our center) stated that the two dysplastic sites may be interconnected. L = left. HS = hippocampal sclerosis. FCD = focal cortical dysplasia. Images acquired at our center.

Please cite this article in press as: Kreilkamp BAK, et al., Neuroradiological findings in patients with "non-lesional" focal epilepsy revealed by research protocol, Clinical Radiology (2018), https://doi.org/10.1016/j.crad.2018.08.013

Table 2
Patient demographic/clinical information and recent MRI findings for patients with newly diagnosed epileptogenic lesions.

ID	Sex	Age (years)	Infection/febrile convulsion	Onset (age, years)	Duration (years)	EEG	Type	Frequency (per week)	Finding
22	F	54	No/no	5	50	Right TL	SPS, SGTCS, CPS	2	Right HS & small-vessel disease
24	F	39	Yes/yes	36	2.5	Right TL	SGTCS	0.5	Right HS & right cerebello-pontine angle cystic lesion – epidermoid
25	M	47	No/no	34	13	Bilateral TL	A, SGTCS, CPS	2	Bilateral HS
27	F	38	No/yes	7	31	Left TL	CPS, SGTCS	0.5	Left HS
38	F	30	No/no	15	15	Left TL	SGTCS	1	Left HS
51	F	43	No/yes	6	37	Left TL	SGTCS, CPS	2	Left HS & left TL pole FCD & small-vessel disease/Rasmussen's/encephalitis
56	F	23	Yes/no	6	17	Right TL	A, CPS	2.5	Right HS and right parahippocampal FCD
59	F	27	No/no	6	21	Bilateral FL	CPS, SGTCS	7	FCD in left supramarginal gyrus & left parietal lobule
61	F	36	No/yes	30	6	Left TL	SGTCS	0.04	Left temporal encephalocoele
65	M	22	No/no	5	17	Left TL	A, CPS, SPS, SGTCS	6	FCD/gliosis in right superior frontal gyrus
66	M	18	No/no	10	8	Left TL	CPS, SPS, SGTCS	1	Left HS
69	M	29	No/no	10	19	Right TP	CPS, SGTCS	7	Right cortical gliosis (widespread)
81	F	40	No/yes	7	33	Left TL	A	2	Left HS
84	F	19	No/no	18	1	Left FT	CPS, SGTCS	35	Left amygdala enlargement

Bold patient IDs indicate that the previous MRI was available for assessment (n=8).
F, female; M, male; HS, hippocampal sclerosis; SPS, simple partial seizures; SGTCS, secondary generalised tonic–clonic seizures; A, absence seizures; CPS, complex partial seizures; TL, temporal lobe; FL, frontal lobe; TP, temporoparietal; FT, frontotemporal; FCD, focal cortical dysplasia.

neuroradiologists. This included data from patients acquired on 1.5 and 3 T systems, with and without dedicated clinical epilepsy protocols. The previous clinical MRI images were re-evaluated in order to determine the factors influencing the accuracy of visual lesion detection. Two neuroradiologists with long-term experience in evaluating MRI of patients with epilepsy performed reassessment of the images independently from one another. Demographic and clinical information for all patients are summarised in Table 1.

Results

Twenty-nine of the 43 (67%) patients remained MRI negative after assessment of the epilepsy-dedicated MRI by the consultant neuroradiologists; however, 14/43 (33%) patients were found to have potentially epileptogenic brain lesions, such as HS and focal cortical dysplasia (FCD), shown in Fig 1. Diagnostic information for these patients is presented in Table 2.

All available images are presented in the results sections along with clinically relevant information for each patient. Eleven of the 14 (79%) previously "non-lesional" patients had EEG imaging-concordant localisation features (except for patients 59, 65, and 84) rendering them potential candidates for resective surgery. Surgical candidacy had been assessed during the multidisciplinary team meetings that consider results from MRI, neurophysiological, and neuropsychological evaluation. For eight of the 14 patients (57%) previous MRI examinations (from the authors' centre and another) were available for

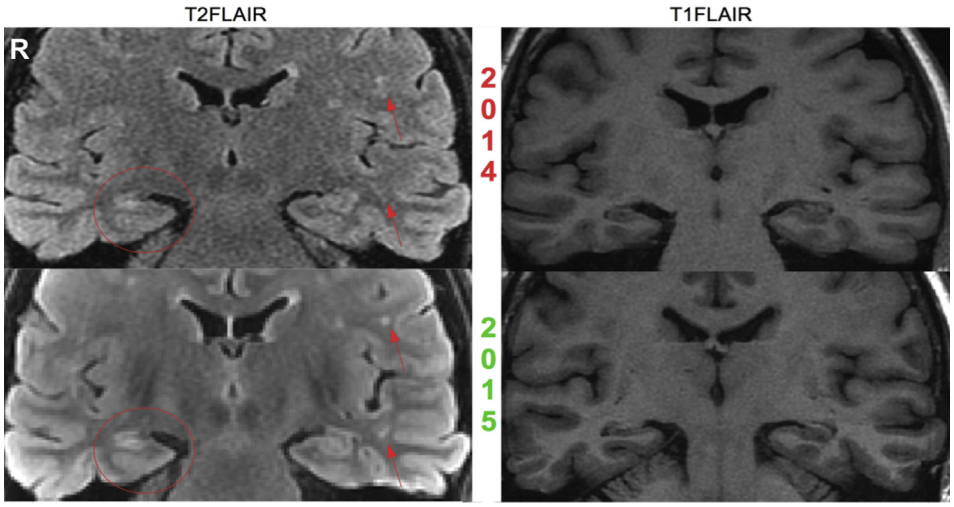

Figure 2 Patient 22: right HS and Small-Vessel Disease. In 2014 this patient received a dedicated epilepsy protocol at our center. Although the T1-FLAIR coronal sequence shows a comparable quality relative to the most recent 2015 T1-FLAIR, Small Vessel Disease and right HS were not detected by the neuroradiologist. HS and WM lesions related to small vessel disease are increasingly conspicuous on the most recent T2-FLAIR image relative to the 2014 T2-FLAIR image, the latter of which suffers from lower SNR. R = right.

Please cite this article in press as: Kreilkamp BAK, et al., Neuroradiological findings in patients with "non-lesional" focal epilepsy revealed by research protocol, Clinical Radiology (2018), https://doi.org/10.1016/j.crad.2018.08.013

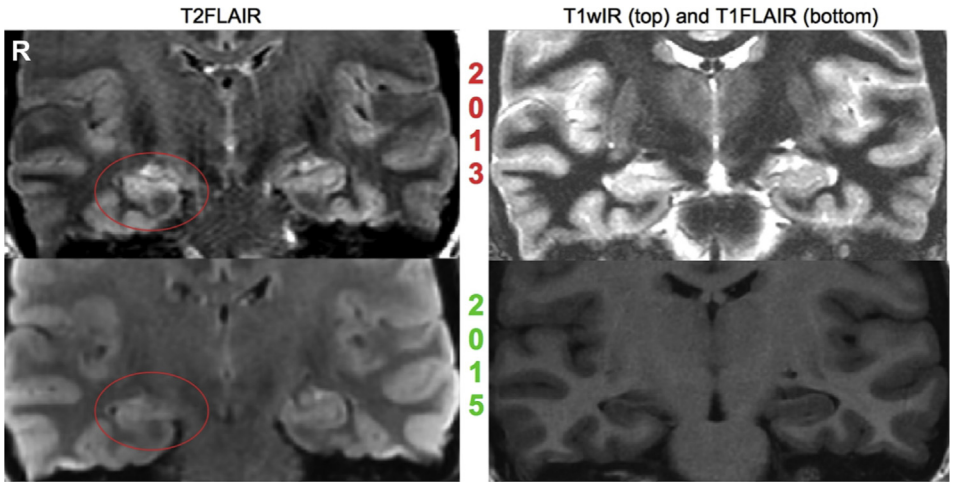

Figure 3 Patient 24: right HS. While early images do not show clear evidence of HS, the expert neuroradiologist termed this as "small right hippocampus" without explicitly diagnosing HS. This was inappropriately documented and this information did not reach the consultant neurologist. In the later image right HS was re-diagnosed. R = right.

retrospective evaluation. The remaining images could not be retrieved as they had been acquired at other hospitals. This section initially presents the eight cases with a new identifiable lesion for whom previous MRI studies were available (Figs 2–9). Subsequently, the remaining six cases for whom previous MRI was not obtainable are presented (Fig 10). The reasons for lesions not being reported in this dataset were multifactorial and were due to the following factors (Table 3): (1) general technical issues affecting image quality and lesion conspicuity: (i) low SNR (Fig 2) and movement artefacts (Fig 3) have contributed to loss of lesion conspicuity on the T2-FLAIR images. Consequently, the lesion was not identified as HS (Figs 2 and 3); (ii) the previous MRI, which was not part of a dedicated epilepsy research protocol, had technical issues, and therefore, did not clearly show the lesion (poor angulation along the long axis of the hippocampus, Fig 7; large section thickness, Figs 8 and 9); (2) human factors leading to lesions not being identified: (i) the clinical team previously evaluating the patient cases did not document lesion (Figs 5 and 6); (ii) the standard MRI was reviewed and reported as "non-lesional" by a general radiologist, although the lesion was visible (Fig 7); (iii) loss of information during communication: the neuroradiologist referred to the abnormality without stating "hippocampal sclerosis", and subsequently, the information was documented inappropriately (Figs 3 and 4). Rather, the hippocampi for these patients were referred to as "small", e.g., "small appearance of the left hippocampus" (patient 24) and "bilateral small hippocampi" (patient 25).

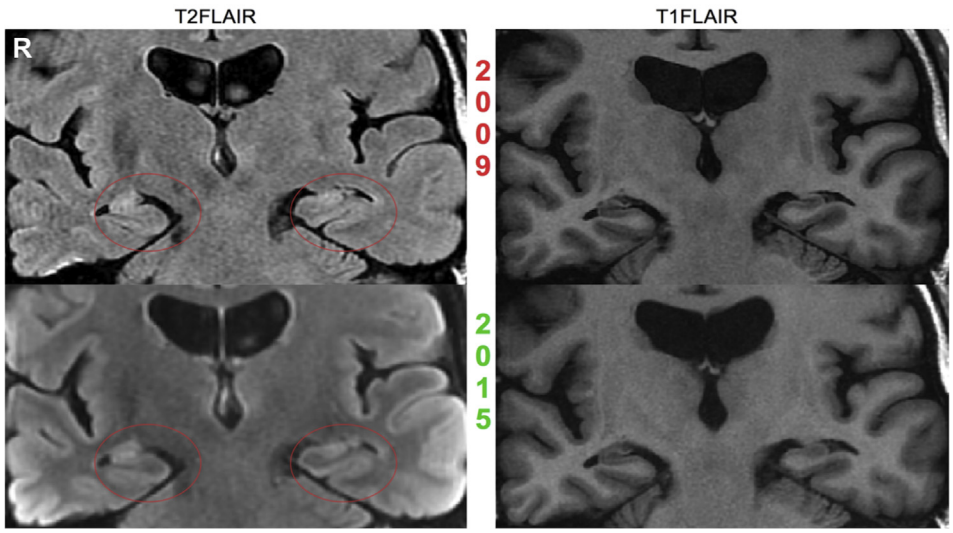

Figure 4 Patient 25: bilateral HS. The images from 2009 show bilateral HS as demonstrated by hyperintensity on T2-FLAIR and volume loss on T1-FLAIR; this was referred to as "bilateral small hippocampi" by the expert neuroradiologist. This was inappropriately documented and the information did not reach the consultant neurologist. In 2015 the patient was diagnosed with bilateral HS. R = right.

Please cite this article in press as: Kreilkamp BAK, et al., Neuroradiological findings in patients with "non-lesional" focal epilepsy revealed by research protocol, Clinical Radiology (2018), https://doi.org/10.1016/j.crad.2018.08.013

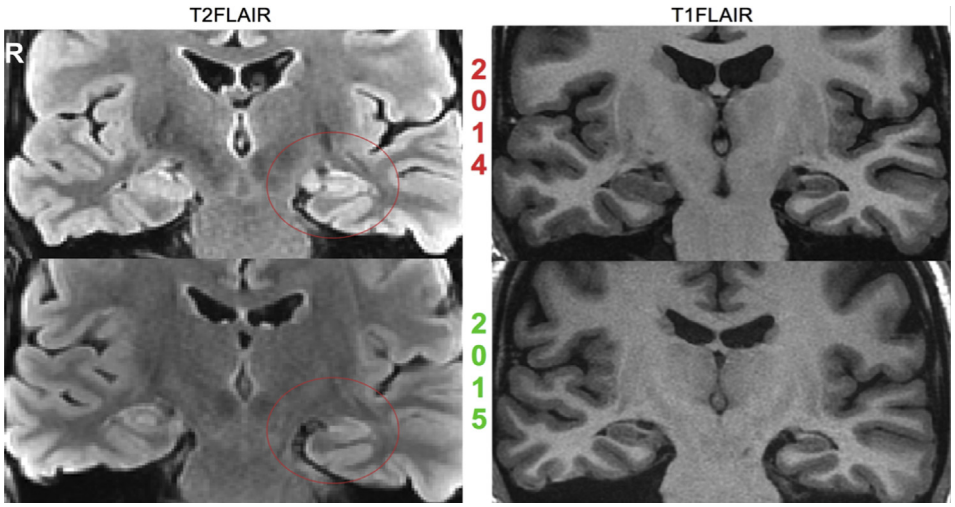

Figure 5 Patient 38: left HS. Despite signal hyperintensity on T2-FLAIR and volume loss on T1-FLAIR, HS was only diagnosed in 2015. Lesion conspicuity was similar for both MRI sessions. R = right.

In-vivo MRI is the most reliable and frequent imaging method used to provide information on macroscopic brain structure, and in the presence of varying data quality, it is often impossible for neuroradiologists to evaluate the definite presence of lesions. The lesion that most frequently escaped the attention of clinicians was HS (nine cases, of which two had an additional FCD), followed by FCDs (two cases), and others including gliosis, encephalocoele, and amygdala enlargement (one case each).

The previous images for patients 27, 51, 59, 69, 81, and 84 could not be retrieved. All lesions reported for these patients were conspicuous on the most recent images acquired using the dedicated epilepsy research protocol (Fig 10). So far, five patients (patient 22 with right HS; 38 with left HS; 56 with right HS; 66 with left HS; 81 with left HS) have received ipsilateral temporal lobectomies. All resected specimens had histological confirmation of HS.[20] These patients have been followed up at various time points after surgery (2 years, 2 years, 1 year, 3 months, and 1 week, respectively) and classified according to the International League Against Epilepsy (ILAE) outcome classifications.[21] Patients 22, 56, 66, and 81 are currently seizure free (ILAE I). Patient 38 no longer experiences secondary generalised tonic–clonic seizures (SGTCS), and now experiences one short (<10 seconds) focal seizure per week, which represents a substantial improvement (ILAE III). Three other patients (51, 59, and 61) are still being considered for surgery.

Discussion

The objective of the present study was to employ an epilepsy-dedicated MRI protocol in a cohort of patients with refractory focal epilepsy who were deemed previously to be non-lesional on clinical MRI. Thirty-three percent of all patients recruited had a newly identified brain lesion. The primary factors explaining the newly identified lesions were the choice of MRI sequences, imaging parameters (in particular, no previous use of a dedicated epilepsy research protocol, including the lack of angulation orthogonal to the long axis of the hippocampus and large section thickness),

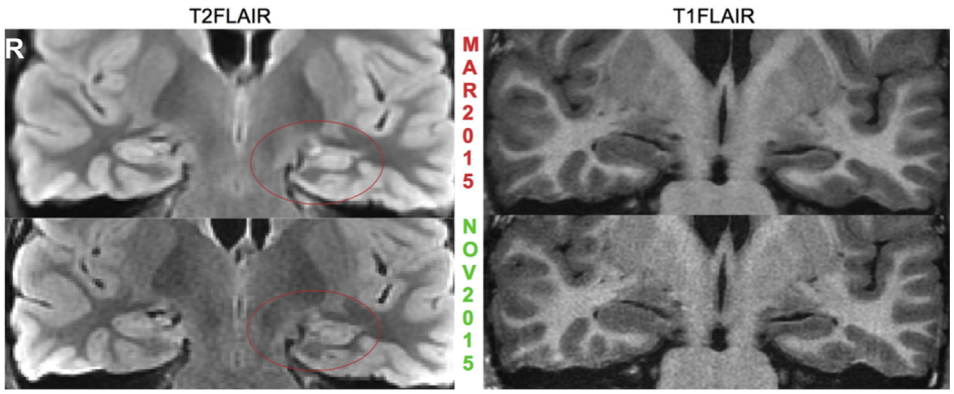

Figure 6 Patient 66: left HS. This patient received comparable quality of epilepsy-dedicated imaging in March and November 2015. However, HS was only diagnosed on the later images, which show hyperintensity on T1-FLAIR and HA on T1-FLAIR. Lesion conspicuity was similar for both MRI sessions. R = right.

Please cite this article in press as: Kreilkamp BAK, et al., Neuroradiological findings in patients with “non-lesional” focal epilepsy revealed by research protocol, Clinical Radiology (2018), https://doi.org/10.1016/j.crad.2018.08.013

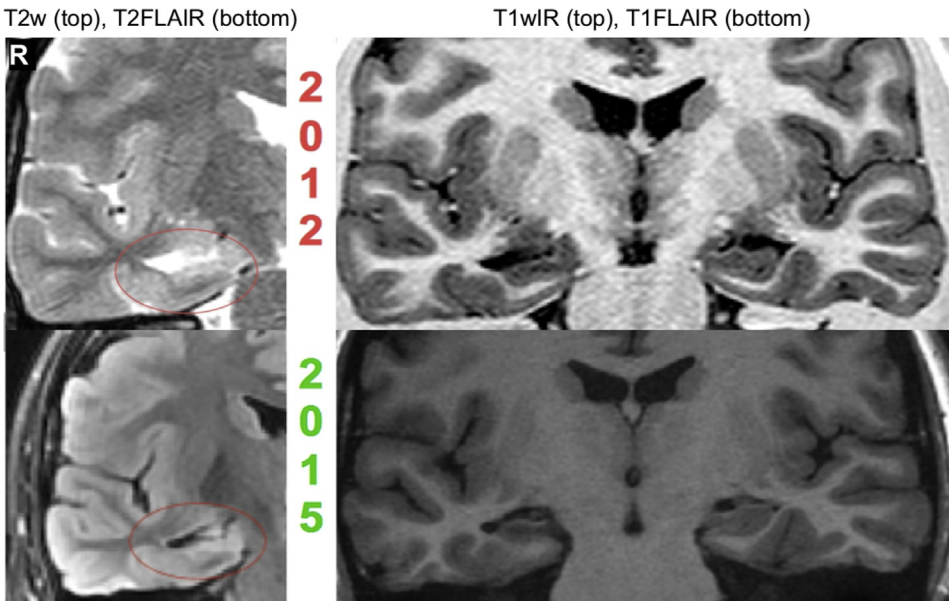

Figure 7 Patient 56: right HS with parahippocampal WM blurring. In 2012 this patient received imaging at a general hospital (left: T2-w; right: T1-w Inversion Recovery) with an angulation not orthogonal to the long axis of the hippocampus. HS and parahippocampal WM blurring are more conspicuous on the epilepsy research image of 2015 (left: T2-FLAIR; right: T1-FLAIR), particularly relative to the contralateral hemisphere. R = right.

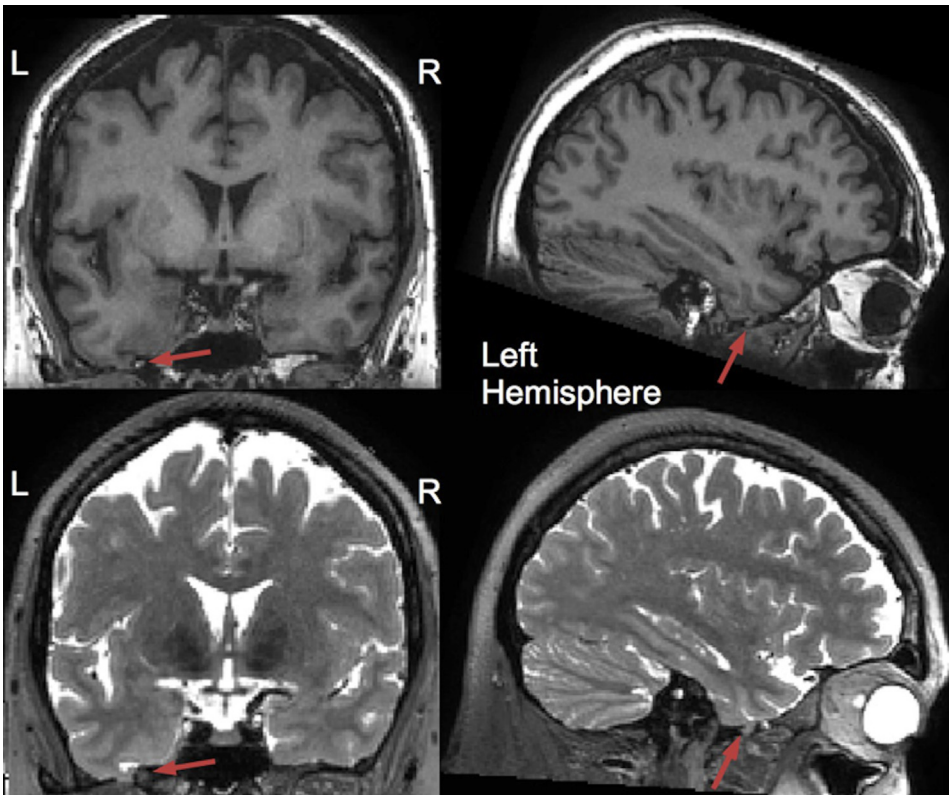

Figure 8 Patient 61: left temporal encephalocele. Left temporal encephalocele was diagnosed based on a 3D volume T2-w acquisition, which is not routinely acquired in the evaluation of patients with epilepsy at our center but was part of the study's dedicated epilepsy research protocol. Note how the lesion is more conspicuous on the T2-w image (below) compared to the T1-w (top). Diagnosis was later confirmed with computed tomography imaging. Older MRIs (all 2D) with large slice thickness (~5 mm) from 2009 failed to reveal this abnormality. L = left; R = right.

Please cite this article in press as: Kreilkamp BAK, et al., Neuroradiological findings in patients with "non-lesional" focal epilepsy revealed by research protocol, Clinical Radiology (2018), https://doi.org/10.1016/j.crad.2018.08.013

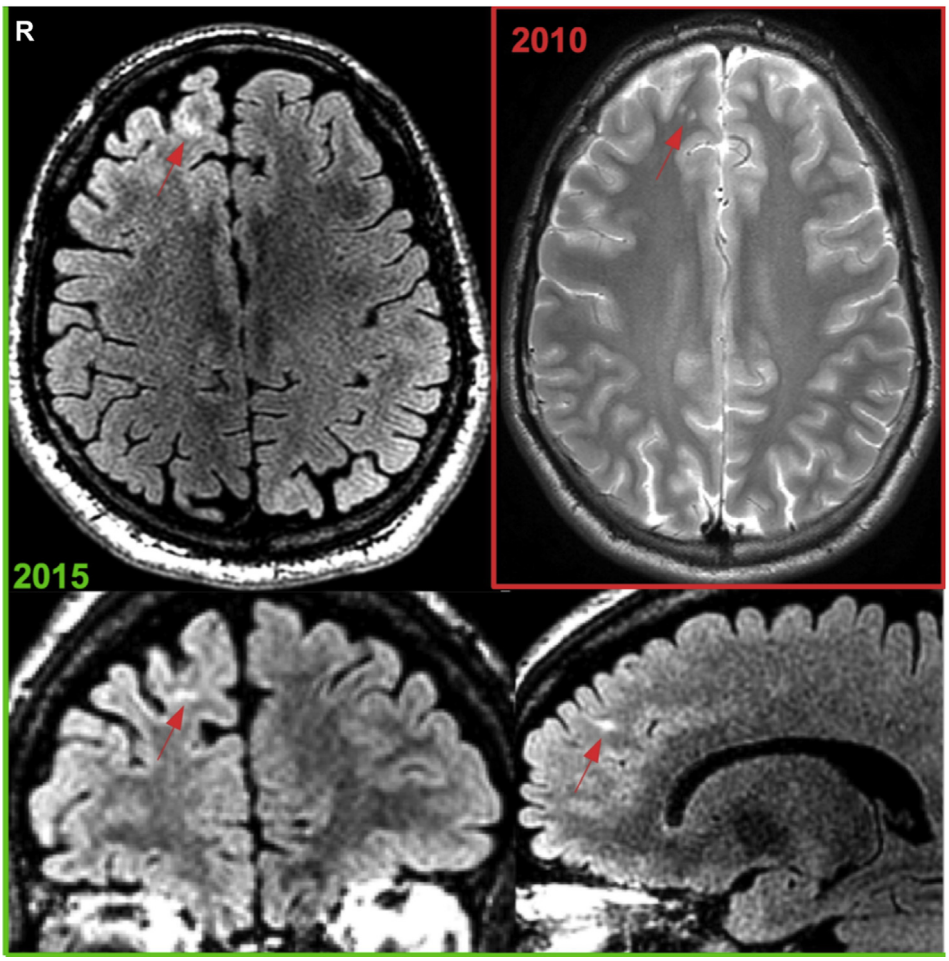

Figure 9 Patient 65: FCD / gliosis in right superior frontal gyrus. Diagnosis was made based on the 3D T2-FLAIR image of 2015 (green image borders). The abnormality was not reported on the previous 2D axial T2-w image (red image borders) where only one slice showed the small abnormality. R = right.

data quality (motion artefacts and low SNR), human factors (lesion not reported), and loss of information through incomplete documentation (wording: "small hippocampus" instead of "hippocampal sclerosis").

The results presented here indicate that one important factor why lesions had previously escaped the attention of the reporting neuroradiologist may be the choice of sequence with lesions being more conspicuous on dedicated epilepsy protocols.[10–13] According to Duncan *et al.* 2016,[12] Duncan 1997[22] and ILAE 1997,[10] 3D whole-brain T1W and T2W and 2D FLAIR imaging should be included in an effective epilepsy-dedicated protocol. Additionally, apart from the specific choice of the sequence itself, lesion conspicuity may be influenced by data quality, section thickness, angulation, and resolution. Expert neuroradiologist reassessment using epilepsy-dedicated MRI can detect HS with sensitivity and specificity of >90%.[11,23] Two images not routinely acquired in the evaluation of patients with epilepsy at the authors' centre proved useful for the detection of FCDs/gliosis (3D T2-FLAIR) and encephalocoeles (3D T2W). Tschampa *et al.*[24] indicated previously that 2D/3D T2-FLAIR sequences are equally useful for detecting FCDs visually, while Friedman[13] stated that the whole-brain coronal 3D T2W sequence can be helpful in detecting encephalocoele and may be superior over T1W sequences.[25] Encephalocoeles may be an under-appreciated aetiology of temporal lobe epilepsy.[26] Additionally, an isotropic voxel size may increase the diagnostic yield as it can cover multiple locations within the brain and may identify small lesions, such as encephalocoeles or gliosis. It has been previously reported that image artefacts, such as subject motion, can affect lesion conspicuity.[14] As a rule, when patients moved excessively during the recently applied epilepsy research dedicated protocol, MRI was reacquired in order to avoid motion artefacts. High lesion conspicuity on good-quality MRI is the core characteristic for the neuroradiologist to be able to confidently report an abnormality. For patients who remain "non-lesional", it may be apt to also acquire 3D T2-FLAIR and 3D T2W data as these sequences can increase the lesion pick-up-rate, are easily implemented, and can be performed at low cost concerning acquisition times. As a direct result of this translational study using research-dedicated MRI, clinicians at The Walton Centre NHS Foundation Trust have now started to request 3D T2-FLAIR images for patients with refractory focal epilepsy and previous inconclusive MRI.

Please cite this article in press as: Kreilkamp BAK, et al., Neuroradiological findings in patients with "non-lesional" focal epilepsy revealed by research protocol, Clinical Radiology (2018), https://doi.org/10.1016/j.crad.2018.08.013

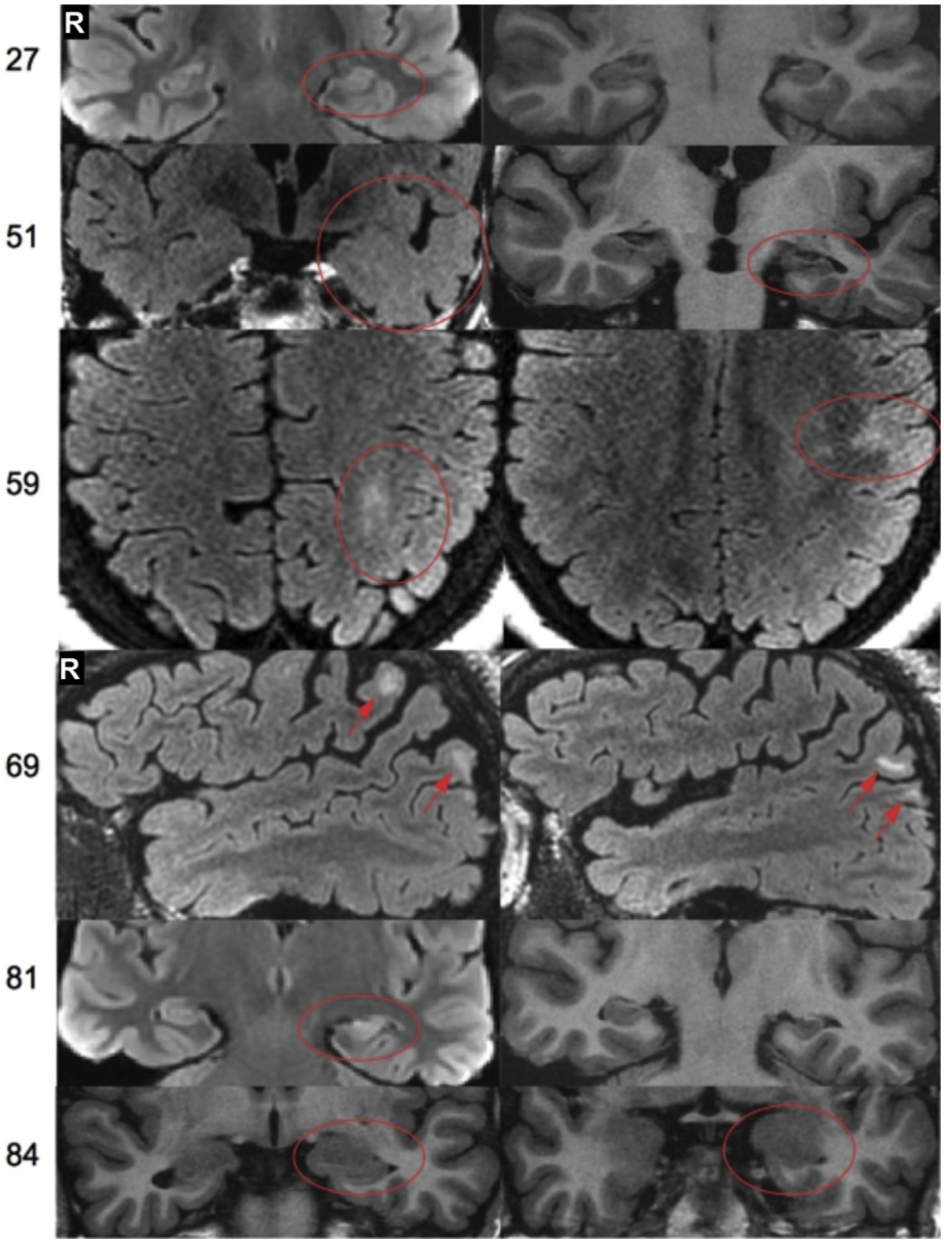

Figure 10 Formerly 'non-lesional' cases showing lesions using the epilepsy dedicated research protocol. Numbers refer to patient IDs. Please refer to Table 2 for details on each lesion identified. R = right.

Regarding human factors, the lesion most frequently left unreported was HS (nine cases), which was also reported in a previous study.[11] These authors reported that HS was overlooked in 86% of cases when the MRI was read by general radiologists relative to expert neuroradiologists. In this sample, FCDs accounted for the second most frequent lesions left unreported (four cases). These results correspond to those found by Stevens[27] where routine MRI failed to show HS in all cases and FCDs in 20% of all cases. Multiple sites of gliosis and a single unilateral amygdala enlargement were identified in two different patients on their most recent epilepsy-dedicated research MRI conducted in the context of this study. Unfortunately, the previous MRI was not available in these cases. Zubkov *et al.*[28] described a patient with a hypothalamic hamartoma (HH) who did not benefit from right temporal lobectomy as his HH (possibly also involved in the epileptogenic network) was overlooked. He then had the HH removed and consequently suffered severe memory problems (amnesia). This case illustrates the need to assess for dual (or even multiple) pathology in treatment of pharmacoresistant epilepsy prior to surgery. The review presented here has shown several patients with multiple lesion sites; therefore, it is important that neuroradiologists are aware of the satisfaction-of-search effect[29] and continue radiological assessment even when epilepsy-related lesions have already been identified. Importantly, based on the present results, a differential checklist has been devised for radiologists when assessing the presence

Please cite this article in press as: Kreilkamp BAK, et al., Neuroradiological findings in patients with "non-lesional" focal epilepsy revealed by research protocol, Clinical Radiology (2018), https://doi.org/10.1016/j.crad.2018.08.013

Table 3
Lesions found in the most recent MRI and retrospective comparison to previous MRI and reports.

ID	22	24	25	38	66	56	61	65
Lesion	Right HS & Small-vessel-disease	Right HS & right cerebello-pontine angle cystic lesion - epidermoid	Bilateral HS	Left HS	Left HS	Right HS and right parahippocampal FCD	Left temporal encephalocoele	FCD/gliosis in right superior frontal gyrus
MRI	Epilepsy protocol at OC	Epilepsy protocol at OC	Epilepsy protocol at OC	Epilepsy protocol at OC	Epilepsy protocol at OC	Standard protocol at other hospital	Epilepsy protocol at OC	Epilepsy protocol at OC
Reason	*Low SNR*	*Motion artefacts* and human factor: documentation	Human factor: documentation	Human factor: not reported	Human factor: not reported	*Angulation not orthogonal to the long axis of the hippocampus*	*2D MRI only (large slice thickness, ~5 mm)*	*2D MRI only (large slice thickness, ~5 mm)*
Figure	2	3	4	5	6	7	8	9

Epilepsy protocol: The initial epilepsy protocol at our centre (OC) involved only higher resolution in-plane 2D sequences for patients with presumed seizures (no 3D images).
Epilepsy-dedicated research protocol: 2D coronal FLAIR MRI with high in-plane resolution (~0.5 mm), 3D T1W/T2W/T2FLAIR imaging. 3D sequences were reserved for pre-surgical work-up, for instance (1) MRI-negative image with indication of a strong EEG localisation and (2) presumed lesions in patients with MRI-positive findings for further evaluation and characterisation. Technical reasons for previous MRI-negative report are shown in italics.
OC, The Walton Centre NHS Foundation Trust; HS, hippocampal sclerosis.

of a lesion: (1) medial temporal lobe on coronal T1-FLAIR/T2-FLAIR (especially for patients with complex partial seizures) to investigate for HS; (2) cortical thickening and blurring of grey–white matter margin on T1W image for FCD; (3) floor of the middle cranial fossa on T2W images for encephalocoeles; and (4) subtle cortical and subcortical white matter hyperintensity on T2-FLAIR image for gliosis.

Another important point relates to the communication between neuroradiologists and clinicians. A recent study on patients with frontotemporal dementia has found that diagnostic information may be reported inappropriately (with a limited factual description and incomplete misleading interpretation of MRI) unless MRI images are jointly reviewed and discussed by neurologists and neuroradiologists.[30] In the present study, the apparent hesitation in officially diagnosing hippocampal volume loss on MRI as HS has resulted in two patients being misclassified as non-lesional. Therefore, clinicians may benefit from an equidistant rating scale where it is possible for the neuroradiologist to indicate how confident they are in reporting an abnormality and to state reasons for why their confidence is very high/high/medium/low or very low (e.g., due to slice angulation/motion artefacts). A similar rating scale has been used by some centres to record the degree of atrophy in patients,[30–32] the likelihood of presence of FCD[33] and artefacts.[14] A confidence rating scale may facilitate reacquisition with appropriate and individualised sequence parameters if necessary, but certainly this should be subject to further research.

Even though the true-positive rate of 33% within this investigation of a realistic clinical setting is large and potentially clinically significant for individual patients, one limitation remains the fact that results are based on a small sample size. Another limitation of this dataset is that it does not allow the direct comparison of individual sequence acquisition parameters or of MRI hardware. The type of MRI sequences and the data quality varied for all initial clinical MRI studies, which were not part of the more recently applied epilepsy-dedicated protocol and acquired at different time points. As in the example of an initial negative report based on MRI with poor quality and lesion conspicuity, the lesion may not have been appreciated due to artefacts, human factors or both (i.e., retrospectively the lesion is discernible on the initial MRI even when taking the artefacts into account). This also reflected the opinion of the consultant neurologist and neuroradiologists who retrospectively re-evaluated the initial MRI images: in almost all cases the reasons for leaving an abnormality unreported remain multifactorial. Consequently, this made it difficult to attribute a single reason to leaving a lesion unreported. A prospective study where MRI is evaluated by an expert neuroradiologist in a blinded fashion (e.g., one with motion artefacts, one without in the same patient, etc.) may resolve some of these open questions. Nevertheless, this retrospective study of previous MRI in a realistic clinical setting was capable of shedding light on the factors that may influence everyday clinical practice. An acknowledgement of these being multifactorial may facilitate a deeper understanding and re-evaluation of current MRI protocols, neuroradiological assessment, and communication between clinicians.

In conclusion, it is important for all clinicians to undertake detailed assessment of MRI images and discuss difficult patient cases in MDT meetings. Ultimately, consideration of all the interdependent factors mentioned in this review have important implications for (i) treatment options for the individual patient, especially regarding epilepsy surgery performed on newly identified epileptogenic lesions; and (ii) study populations that may have been confounded by undetected lesions in patient samples if sequences were not dedicated to depicting epilepsy lesions and MRI was not reassessed by an expert neuroradiologist. These factors may influence everyday clinical practice and research into lesional/"non-lesional" epilepsy. As some lesions may be too subtle to appreciate on MRI, even via expert neuroradiological assessment, it is important to develop automated lesion analysis tools, which allow reliable whole-brain quantitative comparison of a

Please cite this article in press as: Kreilkamp BAK, et al., Neuroradiological findings in patients with "non-lesional" focal epilepsy revealed by research protocol, Clinical Radiology (2018), https://doi.org/10.1016/j.crad.2018.08.013

single patient's MRI with those acquired from healthy controls.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

This research was funded by a University of Liverpool PhD Scholarship 2014–2017 awarded to BAKK and the Epilepsy Action Postgraduate Study Bursary 2014–2015 awarded to BAKK.

References

1. Téllez-Zenteno JF, Hernández Ronquillo L, Moien-Afshari F, *et al*. Surgical outcomes in lesional and non-lesional epilepsy: a systematic review and meta-analysis. *Epilepsy Res* 2010;**89**:310–8.
2. Lerner JT, Salamon N, Hauptman JS, *et al*. Assessment and surgical outcomes for mild type I and severe type II cortical dysplasia: a critical review and the UCLA experience. *Epilepsia* 2009;**50**:1310–35.
3. Mosewich RK, So EL, O'Brien TJ, *et al*. Factors predictive of the outcome of frontal lobe epilepsy surgery. *Epilepsia* 2000;**41**(7):843–9. https://doi.org/10.1111/j.1528-1157.2000.tb00251.x.
4. Jehi LE, Najm I, Bingaman W, *et al*. Surgical outcome and prognostic factors of frontal lobe epilepsy surgery. *Brain* 2007;**130**:574–84.
5. Siegel AM, Cascino GD, Meyer FB, *et al*. Resective reoperation for failed epilepsy surgery: seizure outcome in 64 patients. *Neurology* 2004;**63**:2298–302.
6. Janszky J, Jokeit H, Schulz R, *et al*. EEG predicts surgical outcome in lesional frontal lobe epilepsy. *Neurology* 2000;**54**:1470–6.
7. Berg AT, Vickrey BG, Langfitt JT, *et al*. Multicentre Study of Epilepsy Surgery. The multicentre study of epilepsy surgery: recruitment and selection for surgery. *Epilepsia* 2003;**44**(11):1425–33.
8. Holmes MD, Born DE, Kutsy RL, *et al*. Outcome after surgery in patients with refractory temporal lobe epilepsy and normal MRI. *Seizure* 2000;**9**(6):407–11.
9. Scott CA, Fish DR, Smith SJ, *et al*. Presurgical evaluation of patients with epilepsy and normal MRI: role of scalp video-EEG telemetry. *J Neurol Neurosurg Psychiatr* 1999;**66**(1):69–71.
10. ILAE: Commission on Neuroimaging of the International League Against Epilepsy. Recommendations for neuroimaging of patients with epilepsy. *Epilepsia* 1997;**38**(11):1255–6.
11. Von Oertzen J, Urbach H, Jungbluth S, *et al*. Standard magnetic resonance imaging is inadequate for patients with refractory focal epilepsy. *J Neurol Neurosurg Psychiatr* 2002;**73**(6):643–7. https://doi.org/10.1136/jnnp.73.6.643.
12. Duncan JS, Winston GP, Koepp MJ, *et al*. Brain imaging in the assessment for epilepsy surgery. *Lancet Neurol* 2016;**15**(4):420–33. https://doi.org/10.1016/S1474-4422(15)00383-X.
13. Friedman E. Epilepsy imaging in adults: getting it right. *AJR Am J Roentgenol* 2014;**203**(5):1093–103. https://doi.org/10.2214/AJR.13.12035.
14. Phal PM, Usmanov A, Nesbit GM, *et al*. Qualitative comparison of 3-T and 1.5-T MRI in the evaluation of epilepsy. *AJR Am J Roentgenol* 2008;**191**(3):890–5. https://doi.org/10.2214/AJR.07.3933.
15. Winston GP, Micallef C, Kendell BE, *et al*. The value of repeat neuroimaging for epilepsy at a tertiary referral centre: 16 years of experience. *Epilepsy Res* 2013;**105**(3):349–55. https://doi.org/10.1016/j.eplepsyres.2013.02.022.
16. Wiebe S, Jette N. Epilepsy surgery utilization: who, when, where, and why? *Curr Opin Neurol* 2012;**25**(2):187–93.
17. Wiebe S, Gafni A, Blume WT, *et al*. The economics of surgery for temporal lobe epilepsy. *J Epilepsy* 1996;**9**:144–5.
18. Bell GS, Sinha S, Tisi J, *et al*. Premature mortality in refractory partial epilepsy: does surgical treatment make a difference? *J Neurol Neurosurg Psychiatr* 2010;**81**:716–8.
19. Seiam AH, Dhaliwal H, Wiebe S. Determinants of quality of life after epilepsy surgery: systematic review and evidence summary. *Epilepsy Behav* 2011;**21**:441–5.
20. Blümcke I, Thom M, Aronica E, *et al*. International consensus classification of hippocampal sclerosis in temporal lobe epilepsy: a task force report from the ILAE commission on diagnostic methods. *Epilepsia* 2013;**54**:1315–29.
21. Wieser HG, Blume WT, Fish D, *et al*. ILAE Commission Report. Proposal for a new classification of outcome with respect to epileptic seizures following epilepsy surgery. *Epilepsia* 2001;**42**:282–6.
22. Duncan JS. Imaging and epilepsy. *Brain* 1997;**120**(2):339–77. https://doi.org/10.1093/brain/120.2.339.
23. Oppenheim C, Dormont D, Biondi A, *et al*. Loss of digitations of the neurology hippocampal head on high-resolution fast spin-echo MR: a sign of mesial temporal sclerosis. *AJNR Am J Neuroradiol* 1998;**19**:457–63.
24. Tschampa HJ, Urbach H, Malter M, *et al*. Magnetic resonance imaging of focal cortical dysplasia: comparison of 3D and 2D fluid attenuated inversion recovery sequences at 3T. *Epilepsy Res* 2015;**116**:8–14. https://doi.org/10.1016/j.eplepsyres.2015.07.004.
25. Toledano R, Jimenez-Huete A, Campo P, *et al*. Small temporal pole encephalocoele: a hidden cause of "normal" MRI temporal lobe epilepsy. *Epilepsia* 2016;**57**(5):841–51.
26. Saavalainen T, Jutila L, Mervaala E, *et al*. Temporal anteroinferior encephalocoele: an underrecognized etiology of temporal lobe epilepsy? *Neurology* 2015;**85**(17):1467–74.
27. Stevens JM. Imaging in epilepsy. *Clin MRI* 1995;**5**:14–23.
28. Zubkov S, Del Bene VA, MacAllister WS, *et al*. Disabling amnestic syndrome following stereotactic laser ablation of a hypothalamic hamartoma in a patient with a prior temporal lobectomy. *Epilepsy Behav Case Rep* 2015;**4**:60–2.
29. Berbaum KS, Franken EA, Dorfman DD, *et al*. Satisfaction of search in diagnostic radiology. *Invest Radiol* 1990;**25**:133–40.
30. Dewer B, Rogers P, Ricketts J, *et al*. The radiological diagnosis of frontotemporal dementia in everyday practice: an audit of reports, review of diagnostic criteria, and proposal for service improvement. *Clin Radiol* 2016;**71**(1):40–7. https://doi.org/10.1016/j.crad.2015.09.008.
31. Kipps CM, Davies RR, Mitchell J, *et al*. Clinical significance of lobar atrophy in frontotemporal dementia: application of an MRI visual rating scale. *Dement Geriatr Cogn Disord* 2007;**23**(5):334e42.
32. Scheltens P, Launer LJ, Barkhof F, *et al*. Visual assessment of medical temporal lobe atrophy on magnetic resonance imaging; interobserver reliability. *Neurology* 1995;**242**:557e60.
33. Wang ZI, Jones SE, Jaisani Z, *et al*. Voxel-based morphometric magnetic resonance imaging (MRI) postprocessing in MRI-negative epilepsies. *Ann Neurol* 2015;**77**(6):1060–75. https://doi.org/10.1002/ana.24407.

Please cite this article in press as: Kreilkamp BAK, et al., Neuroradiological findings in patients with "non-lesional" focal epilepsy revealed by research protocol, Clinical Radiology (2018), https://doi.org/10.1016/j.crad.2018.08.013