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3 Tesla MRI-negative focal epilepsies: Presurgical evaluation, postoperative outcome and predictive factors

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ABSTRACT

Objective: To investigate presurgical diagnostic modalities, clinical and seizure outcome as well as predictive factors after resective epilepsy surgery in *3 Tesla* MRI-negative focal epilepsies.

Patients and methods: This retrospective study comprises 26 patients (11 males/15 females, mean age 34 ± 12 years, range 13–50 years) with *3 Tesla* MRI-negative focal epilepsies who underwent resective epilepsy surgery. Non-invasive and invasive presurgical diagnostic modalities, type and localization of resection, clinical and epileptological outcome with a minimum follow-up of 1 year (range 1–11 years, mean 2.5 ± 2.3 years) after surgery as well as outcome predictors were evaluated.

Results: All patients underwent invasive video-EEG monitoring after implantation of intracerebral depth and/or subdural electrodes. Ten patients received temporal and 16 extratemporal or multilobar (n = 4) resections. There was no perioperative death or permanent morbidity. Overall, 12 of 26 patients (46%) were completely seizure-free (Engel IA) and 65% had a favorable outcome (Engel I–II). In particular, seizure-free ratio was 40% in the temporal and 50% in the extratemporal group. In the temporal group, long duration of epilepsy correlated with poor seizure outcome, whereas congruent unilateral FDG-PET hypometabolism correlated with a favorable outcome.

Conclusions: In almost two thirds of temporal and extratemporal epilepsies defined as "non-lesional" by *3 Tesla* MRI criteria, a favorable postoperative seizure outcome (Engel I–II) can be achieved with accurate multimodal presurgical evaluation including intracranial EEG recordings. In the temporal group, most favorable results were obtained when FDG-PET displayed congruent unilateral hypometabolism.

1. Introduction

In patients with pharmacoresistant focal epilepsies, surgical resection of the epileptogenic zone has proven to be an effective treatment option. Multimodal presurgical evaluation including magnetic resonance imaging (MRI), video-EEG monitoring, and neuropsychological testing aims at the identification and accurate delineation of the epileptogenic zone. In particular, the detection of a structural lesion on MRI provides an important clue of the individual seizure onset area and may guide the placement of intracerebral depth or subdural electrodes if intracranial EEG recordings are needed. The term "MRI-negative" refers to patients in whom presurgical MRI fails to demonstrate a potentially epileptogenic structural abnormality [1]. In contrast, the term "non-lesional", as used in current literature, may imply the absence of such abnormality either on MRI or in histopathology [2]. It has been shown that seizure outcome of resective epilepsy surgery is better in lesional than in non-lesional focal epilepsies [2].

The absence of a lesion on MRI is one of the main reasons to refuse surgery in pharmacoresistant focal epilepsy [1,3]. Despite of technological advances and use of *3 Tesla* magnetic field, MRI-negative cases

Abbreviations: EEG, electroencephalography; MRI, magnetic resonance imaging; MST, multiple subpial transections; fMRI, functional magnetic resonance imaging; FDG-PET, fluorodeoxyglucose positron emission tomography; SPECT, single photon emission computed tomography; SEEG, stereoelectroencephalography; ATL, anterior temporal lobectomy; AHE, amygdalohippocampectomy; sAHE, selective AHE; iEcoG, intraoperative electrocorticography; SFG, superior frontal gyrus; PMC, primary motor cortex; SMA, supplementary motor area; TPR, temporal pole resection; HS, hippocampal sclerosis; FCD, focal cortical dysplasia; LEAT, long-term epilepsy associated tumor; FLAIR, Fluid Attenuated Inversion Recovery; MPRAGE, Magnetization Prepared Rapid Gradient Echo

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still represent 20–40% of surgical candidates in epilepsy centers, and the successful treatment of those patients remains challenging [1,4,5]. Moreover, MRI negative series reported so far include *1.5 Tesla* imaging, but *3 Tesla* MRI can be expected to show even subtle lesions. Thus, it could be expected that patients diagnosed MRI-negative by more strict criteria (i.e. 3 *Tesla* MRI and epilepsy specific protocol) would be even more difficult to treat. Here we present our surgical series of *3 Tesla* MRI-negative patients suffering from pharmacoresistant focal epilepsy with a special emphasis on presurgical evaluation and postoperative outcome.

2. Patients and methods

The present study has been approved by the local ethics committee. The ethics committee did not demand written consent from patients, since all data had been collected prospectively for treatment purposes and were reviewed retrospectively for this study. No additional data were collected retrospectively for research purpose. The study is registered at the German Clinical Trials Register (DRKS00010013). It is a retrospective single institution case series of consecutive patients.

We retrospectively searched the patient databases of our academic epilepsy center from 2004 (after the installation of a *3 Tesla* MRI scanner) to 2015. Patients with pharmacoresistant focal epilepsy who fulfilled the following criteria were included: (1) negative (non-lesional) *3 Tesla* MRI according to the specific epilepsy protocol as described below, (2) resective epilepsy surgery, and (3) minimum postoperative follow-up of 1 year.

2.1. Patient population

Twenty-six patients (11 males/15 females) fulfilled the inclusion criteria. Mean age at the time of surgery was 34 ± 12 years (range 13-50 years). Ten patients received temporal and 16 extratemporal resections, including 4 multilobar resections. Patients' records including diagnostic modalities were reviewed retrospectively. Clinical and epileptological outcome (according to the Engel classification [6]) were evaluated with a minimum follow-up of 1 year after surgery (range 1–11 years, mean 2.5 ± 2.3 years).

2.2. Presurgical evaluation

All patients were submitted to presurgical assessment undergoing a standard protocol comprising clinical, neuroradiological, electroencephalographic and neuropsychological data. In each patient, MRI, ictal and interictal video-EEG monitoring and neuropsychological testing were performed. Moreover, fMRI for language lateralization was done in all cases. Additional tests, if needed, included Wada-test (n = 2), SPECT (n = 5) and PET (n = 24) scan.

2.3. MRI specifications and review

MRI protocols for patients with focal epilepsy syndromes have repeatedly been published and slightly modified over the years [7,8]. Key sequences include coronal T2-weighted fast spin echo and FLAIR sequences with thin (~2–3 mm) slices perpendicular to long axis of the hippocampus [9]. Subtle cortical signal abnormalities are best appreciated with FLAIR sequences. For morphometric analyses a 3D T1-weighted MPRAGE sequence is needed. The specific MRI protocol applied in our academic epilepsy center is given in Table 1.

We retrospectively reviewed all MRIs that had been labelled "negative" or "non-lesional" during presurgical work-up for any lesions that might have been overseen initially. The criterion for MRI to be classified as "negative" (non-lesional, i.e. without any specific potentially epileptogenic structural abnormality) was the judgment of an experienced neuroradiologist (H.U.) after thorough review with experienced epileptologists. In 2 patients a temporal encephalocele was identified during the revision process. These patients were excluded from the study.

Table 1
MRI protocol for patients with focal epilepsy syndromes [7].

No.	Acquisition time	Sequence	Orientation/slice thickness	Diagnostic yield
1	~7 min	3D T1-w FFE or MPRAGE	sag/ 1 × 1 × 1 mm	– multiplanar reformation – voxel-based morphometry
2	~4–5 min	2D T2-w TSE	ax/3–5 mm	– exact angulation
3	~7–10 min	3D FLAIR SPACE	sag/ 1 × 1 × 1 mm	– FCD – HS
	altern. 5 min	2D FLAIR-TSE and	ax/2–3 mm	
	altern. 5 min	2D FLAIR-TSE	cor/2–3 mm	
4	~6 min	2D T2-w TSE	cor/2–3 mm	– HS
5	~3 min	SWI or 2D-FFE	ax/1.5–5 mm	– cavernoma, hemosiderin
(6)	~5 min	3D T1-w FFE or MPRAGE + contrast	sag/ 1 × 1 × 1 mm	– tumor (LEAT)

2.4. FDG-PET and SPECT

FDG-PET was done in 9 out of 10 temporal and 15 out of 16 extratemporal cases in search for hypometabolic brain areas. Lateralized hypometabolism was found in 5 temporal and 7 extratemporal cases. Interictal and ictal single photon emission computed tomography (SPECT) was done only in 5 cases and was non-localizing in all of them (normal in 2 cases, incongruently lateralizing in another 2 cases, congruently lateralizating in 1 case).

2.5. Invasive EEG recordings

Based on semiology, interictal and ictal surface EEG, FDG-PET and/or SPECT findings and neuropsychological assessment, an anatomo-electro-clinical hypothesis of the individual seizure onset zone was defined. Due to the lack of a potentially epileptogenic structural lesion on MRI, or due to ambiguous or discordant results of non-invasive preoperative diagnostics and for cortical mapping, invasive video-EEG monitoring with intracranial electrodes was indicated and performed in all patients. In cases with a hypothesis of superficial cortical seizure origin or indication for brain mapping subdural electrodes were preferred. For exploration of mesial structures (e.g hippocampus, insular cortex or cingular gyrus) multiple depth electrodes were used. In particular, 10 patients (38%; 5 extratemporal, 5 temporal) received multiple intracerebral depth electrodes for SEEG. In 8 patients subdural grid and strip electrodes (31%, all extratemporal) were implanted, and 8 patients had a combination of subdural and intracerebral depth electrodes (31%, 3 extratemporal, 5 temporal). Electrode contacts that were primarily involved in the intracranial seizure pattern defined the epileptogenic zone. In addition, the irritative zone (defined by interictal epileptiform discharges), seizure propagation and localization of eloquent areas determined the extent of resection on an individual basis.

2.6. Statistical analysis

Results were expressed as mean values with standard deviation. Statistical comparison for categorical values between groups was accomplished using the two-tailed Fisher exact test. Differences in mean numerical values were compared using the two-tailed *t*-test. GraphPad Prism version 6 for Mac (GraphPad Software Inc., La Jolla, USA) was used as statistical software and for data processing. P-values < 0.05 were considered to be statistically significant.