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Histopathology of 3 Tesla MRI-negative extratemporal focal epilepsies

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ABSTRACT

Background: Information about the histopathology in 3 Tesla MRI negative extratemporal epilepsies is relatively limited. Most common histopathological findings in earlier (mixed 1.5 or 3 Tesla) MRI-negative series are focal cortical dysplasia (FCD), gliosis or normal findings. These series mostly use the older Palmini criteria for classification and grading. We focus on histopathology of only 3 Tesla MRI-negative extratemporal epilepsies according to the current ILAE criteria and investigate potential correlation to seizure outcome 1 year postoperatively.

Materials and methods: Sixteen substrates of 3 Tesla MRI-negative extratemporal epilepsies were examined in two steps. Standard stains and immunohistochemical reactions and Palmini criteria were used prospectively during the initial examination. Retrospectively, all specimens were re-examined and re-evaluated. Phospho-6 and calretinin stains and ILAE criteria were used during the review examination.

Results: Initial examination revealed 5 FCDs Palmini 1b, two 1a, five 2a and 4 cases of gliosis. The review examination according to ILAE criteria revealed 6 FCDs type IIa, 2 FCDs Ib and 7 mild malformations of cortical development (mMCD) type II. None of our cases was labelled as isolated gliosis after the review examination. The incidence of FCD, after the review examination per ILAE criteria, was reduced to 56%; versus 75% per Palmini.

Conclusions: In "true" 3 Tesla MRI-negative extratemporal epilepsies, incidence of FCD may be lower than in earlier MRI-negative series that included weaker MRI-field. Furthermore, consistent review examination may confirm the diagnosis of mMCD type II as substrate in cases diagnosed as "gliosis" or "normal" in the past.

1. Introduction

Patients with pharmacologically intractable epilepsy and negative (non-lesional) magnetic resonance imaging (MRI) are among the most challenging to treat [1–3]. The absence of a delineated lesion on MRI or a specific histopathological lesion (non-lesional epilepsy) is associated with worse seizure outcome [3]. However, in the current literature, the term non-lesional epilepsy is used to refer to either negative MRI or pathology, although MRI is the starting point that determines the further diagnostic and treatment strategy, whereas pathology is the ending point. Information about the histopathology in MRI negative extratemporal epilepsy is relative limited. The most common histopathological findings in surgical series are focal cortical dysplasia (FCD) [2,4–6], gliosis [7,8] or even normal findings [9–11]. These series use 1.5 or 3 Tesla MRI for the selection of MRI-negative cases. Recently, a consensus for the histopathological classification and grading of FCDs (international league against epilepsy; ILAE) has been proposed [12,13]. This grading system has not been taken into consideration in case series that had been published earlier. Therefore, the

Abbreviations: MRI, magnetic resonance imaging; FCD, focal cortical dysplasia; HS, hippocampal sclerosis; ILAE, international league against epilepsy; H&E, hematoxylin & eosin; NF, neurofilament; KB, Klüver-Barrera; SP, synaptophysin; Map2, microtubule associated protein 2; CD, cluster of differentiation; HLA-DR, human leukocyte antigen-D related; GFAP, glial fibrillary acidic protein; PS6, phospho-S6; NeuN, neuronal nuclear antigen; FLAIR, fluid attenuation inversion recovery; EEG, electroencephalography; mMCD, mild malformation of cortical development; mTOR, mechanistic target of rapamycin.

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available information often lacks grading or refers to the older grading system of Palmini [14].

Within this study, we focus on the histopathological findings of extratemporal resection specimens in epilepsy patients with non-lesional 3 Tesla MRI according to an epilepsy specific protocol. We review all resection specimens from 3 Tesla MRI-negative cases, according to the up-to-date neuropathology techniques [15] and use the ILAE-classification system.

Aim of this study is (1) to add knowledge on the pathology of 3 Tesla MRI-negative extratemporal epilepsies, (2) to clarify the prevalence of FCD according to the ILAE classification system and compare it with the old Palmini classification within this patients' subgroup and to (3) prove if there is any association between histopathology and seizure outcome in MRI-negative extratemporal epilepsy.

2. Materials and methods

The local ethics committee approved the study. It is part of the DRKS00010013 study registered at the German Clinical Trials Register.

We retrospectively searched our patients' databases from 2004 (after the installation of a 3 Tesla MRI device) to 2015. Patients with (1) medically refractory extratemporal or multilobar epilepsies and (2) non-lesional 3 Tesla MRI that had undergone (3) resective surgery were included into the study.

2.1. Patients' demographics

A total of 16 patients (6 male, 10 female, mean age at time of surgery 32 ± 13 years, range 13–50 years) with non-lesional 3 Tesla MRI-negative focal epilepsy and extratemporal or multilobar (n = 4) resections were included into the study. Surgery included 10 frontal resections, one occipital, one parietal, two temporo-occipital and two fronto-temporal resections.

2.2. Magnetic resonance imaging

MRI protocols for patients with focal epilepsies have been reported and slightly modified over the years [16,17]. Key sequences include a coronal T2-weighted fast spin echo and FLAIR sequences with thin (~2–3 mm) slices perpendicular to long axis of the hippocampus [18]. Subtle cortical signal abnormalities are best appreciated with FLAIR sequences and for morphometric analyses a 3D T1-weighted MPRAGE sequence is needed. "Newer" 3 Tesla MRI protocols include a 3D FLAIR sequence with 1 mm^3 isotropic voxels enabling multiplanar reformations and thus the detection of small FCDs which could have been overlooked in the past [17]. The MRI protocol used in our academic institution is shown in Table 1. The criteria for an MRI to be classified as negative (non-lesional) were the judgment of neuroradiologist specialized in epilepsy (H.U.) and the consensus of an interdisciplinary epilepsy conference with neuroradiologists, epileptologists and neurosurgeons.

2.3. Histopathological examination

For the present study, all specimens (n = 16) from 16 MRI-negative patients, that had been prospectively histopathologically examined (initial examination), were re-examined and re-evaluated retrospectively (review examination).

In all cases the material was macroscopically evaluated by a physician after its entry into the histopathological laboratory and cut and processed for further histopathological examinations. Cortical tissue were cut orthogonally in approximately 5–10 mm thick slices. After formalin fixation and paraffin embedding, conventional histological stains for hematoxylin and eosin (H&E) and Klüver-Barrera (KB) were performed. Furthermore, additional immunohistochemical reactions were performed for neurofilament (NF), synaptophysin (SP), microtubule associated protein 2 (Map2), neuronal nuclear antigen (NeuN), CD3, CD20, CD34, CD 68/HLA-DR (human leukocyte antigen-D related), glial fibrillary acidic protein (GFAP) and Vimentin. Phospho-S6 (PS6) and calretinin were also performed during the review process retrospectively. All histopathological and immunohistochemical preparations were examined by a neuropathologist for pathological findings.

For the classification and grading of the FCD the criteria according to Palmini [14] had been used prospectively during the initial examination. The criteria of the ILAE classification [12,13] were taken into consideration during the review process.

2.4. Statistical analysis

Results were expressed as mean with standard deviation. Statistical comparison for categorical values (e.g. Engel outcome class) between groups was accomplished using the two-tailed Fisher exact 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 statistical significant.

3. Results

3.1. Pathological findings

A total of 16 cortical specimens were examined. Pathological findings of the initial and review examination as well as seizure outcomes are summarized in Table 2.

Four (25%) of the investigated cortical specimens (n = 16) showed exclusively a discrete to distinct gray-white differentiation disorder as well as a reactive astrogliosis, microgliosis and satellitosis. In these cases, a blurred border between gray and white brain matter was found (KB, SP) with detection of several ectopic immature nerve cells within the subcortical white matter (Map2). These

Table 1
MRI protocol for patients with focal epilepsy syndromes [17].

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 VISTA or 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		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)