Epilepsy Research 133 (2017) 76–82

Contents lists available at ScienceDirect

Epilepsy Research

journal homepage: www.elsevier.com/locate/epilepsyres

Changes in the interictal and early postictal diffusion and perfusion magnetic resonance parameters in familial spontaneous epileptic cats

Yuji Hamamoto[1], Daisuke Hasegawa[1,*], Shunta Mizoguchi[1], Yoshihiko Yu, Masae Wada, Takayuki Kuwabara, Aki Fujiwara-Igarashi, Michio Fujita

Department of Clinical Veterinary Medicine Nippon Veterinary and Life Science University, 1-7-1 Kyounan-chou, Musashino, Tokyo 180-8602, Japan

ARTICLE INFO

Keywords:
Diffusion tensor imaging
Diffusion-weighted imaging
Familial spontaneous epileptic cats
Genetic epilepsy
Mesial temporal lobe epilepsy
Perfusion-weighted imaging

ABSTRACT

Objective: The familial spontaneous epileptic cat (FSEC) is thought to be a good genetic model of mesial temporal lobe epilepsy. In the current study, cerebral diffusion and perfusion magnetic resonance imaging (MRI) were used to confirm the functional deficit zone in the FSEC and evaluate the effect of a single seizure on different brain regions.

Methods: Six FSECs and six healthy control cats were used in this study. MRI was performed in the interictal state (resting state for control) and postictal state immediately after the vestibular stimulation-induced generalized epileptic seizure (control cats received the same stimulation as the FSECs). The apparent diffusion coefficient (ADC), fractional anisotropy and perfusion parameters (i.e., relative regional cerebral blood volume (rCBV), relative regional cerebral blood flow (rCBF), and relative regional mean transit time (rMTT)) were measured in the hippocampus, amygdala, thalamus, and gray and white matter.

Results: In the interictal state, the rCBV and rMTT in the hippocampus was significantly decreased in FSECs, compared to the control. In the postictal state, FSECs had a significantly decreased ADC and an increased rCBV, rCBF, and rMTT in the hippocampus, and an increased rMTT in the amygdala, compared to the interictal state.

Conclusion: This study showed that FSECs had interictal hypoperfusion in the hippocampus, and postictal hypodiffusion and hyperperfusion in the hippocampus and/or amygdala. These findings suggested that the hippocampus and/or amygdala act as the functional deficit and expanded seizure-onset zones in FSECs.

1. Introduction

The epileptogenic zone is the most important concept not only for presurgical evaluation for epilepsy surgery (Rosenow and Lüders, 2001; Lüders et al., 2006), but also for understanding the pathophysiology of epilepsy. The epileptogenic zone is defined as the "area of cortex that is necessary and sufficient for initiating seizures and whose removal (or disconnection) is necessary for the complete abolition of seizure." It consists of the following five abnormal cortical zones: the irritative zone, seizure-onset zone, symptomatogenic zone, structural abnormal zone (epileptogenic lesion), and functional deficit zone. Various examinations, with or without invasive procedures, are required to accurately define the epileptogenic zone in patients with epilepsy.

Familial spontaneous epileptic cats (FSECs) have been reported as a natural genetic animal model of mesial temporal lobe epilepsy (MTLE) (Kuwabara et al., 2010). FSECs show two types of epileptic seizures, i.e., spontaneous limbic seizures, with and without secondary generalization, such as limbic kindling and/or kainate models, and vestibular stimulation-induced generalized seizures, similar to the El mouse. Previous studies on FSECs, using scalp electroencephalography (EEG), indicated that the temporal region acts as the irritative zone (Kuwabara et al., 2010; Hasegawa et al., 2014). Further, intracranial video-EEG and magnetic resonance (MR) volumetry demonstrated that the seizure-onset and symptomatogenic zones are in the hippocampus and/or amygdala (Hasegawa et al., 2014), while the structural abnormal zone is in the hippocampus (Mizoguchi et al., 2014).

In diagnostic imaging, the functional deficit zone can be generally defined using interictal single photon emission computed tomography

Abbreviations: ADC, apparent diffusion coefficient; DSC, dynamic susceptibility contrast; DWI, diffusion-weighted imaging; EEG, electroencephalography; FA, fractional anisotropy; FSECs, familial spontaneous epileptic cats; IV, Intravenous; MR(I), magnetic resonance (imaging); MTLE, mesial temporal lobe epilepsy; PET, positron emission tomography; PWI, perfusion-weighted imaging; (r)CBF, (relative regional) cerebral blood flow; (r)CBV, (relative regional) cerebral blood volume; (r)MTT, (relative regional) mean transit time; ROI, region of interest; SPECT, single photon emission computed tomography; T2WI, T2-weighted imaging

* Corresponding author.
E-mail address: disk-hsgw@nvlu.ac.jp (D. Hasegawa).

[1] The first three authors contributed equally.

http://dx.doi.org/10.1016/j.eplepsyres.2017.04.015
Received 21 February 2017; Received in revised form 13 April 2017; Accepted 20 April 2017
Available online 23 April 2017

(SPECT) and interictal positron emission tomography (PET) (Lüders et al., 2006). Additionally, seizure-onset zone can be defined by ictal SPECT. Advanced magnetic resonance imaging (MRI), including diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI), and perfusion-weighted imaging (PWI) have also been used to determine the functional deficit zone and detect changes in microstructure and microdynamics (Hajnal et al., 1991). Although SPECT and PET are established in accurately evaluating cerebral function, MRI is superior to PET and SPECT, in terms of spatial resolution and non-invasiveness (i.e., it does not require the use of a radioisotope). Recently, we also investigated the utility of DWI, DTI, and PWI in interictal isoflurane-anesthetized FSECs. Hyperdiffusion and hypoperfusion were detected in the amygdala and hippocampus, respectively, which were suspected to be the functional deficit zone (Mizoguchi et al., 2017).

The aim of the current study was to investigate changes in the interictal and early postictal cerebral diffusion and perfusion due to a single seizure, and to establish the functional deficit zone in FSECs. This study could prove the reproducibility and utility of diffusion and perfusion MRI, for detecting abnormal cortical zones in animal models and human patients.

2. Materials and methods

2.1. Ethics

The current study, including the maintenance of the FSEC colony, was approved by the Animal Care and Use Committee of Nippon Veterinary and Life Science University (accession nos.25k-4, 26k-29, 27k-10; representative researcher is D.H.).

2.2. Animals preparation

A total of 12 cats were enrolled in the study. Each cat, in both the FSEC and healthy control groups, had normal physiological, neurological, and blood examinations (complete blood count and serum biochemistry test), as well as urinalysis. The six cats in the FSEC group (five males and one female) had repeatable vestibular stimulation-induced generalized seizures (Kuwabara et al., 2010). The median age of the FSEC group was 36.5 months (range 17–74 months) and the median body weight was 4.1 kg (range 2.8–5.6 kg). The six healthy cats in the control group (three males and three females) did not have a familial relationship to the FSECs that were used. The median age and body weight of control group were 47 months (range 41–47 months) and 3.3 kg (range 2.4–4.0 kg), respectively.

2.3. Study design

For the FSEC group, MRI was performed in the interictal and postictal states. Interictal scans were performed when FSECs had been seizure-free for at least 10 weeks. Postictal scans were performed immediately after a vestibular stimulation-induced generalized seizure. The vestibular stimulation encompassed swinging the cage to the left and right (1 reciprocation/s, the duration time = 2 min/set, interval = 30 s, up to 3 sets) and then rotating it (1 spin/s, the duration time = 1 min/set, interval = 30 s, up to 5 sets), until generalized seizure onset.

All the healthy cats in the control group underwent MRI without vestibular stimulation (corresponding to the interictal state of FSCE group) and 10 min after the vestibular stimulation (which corresponded to the postictal state of FSEC group). The duration of the vestibular stimulation for the control group was 3 sets of the swinging, followed by 5 sets of rotating, since a seizure was induced in all FSECs within this stimulating duration (see Results).

2.4. MRI protocol

All MR images were obtained with a 3.0-Tesla unit (Signa® HDtx 3.0 T, GE Healthcare, Tokyo, Japan). An 8 ch human knee array radio frequency coil was used. All the cats were fasted for 12 h prior to the MRI and were infused with 5 mg/kg/h lactate ringer solution during scanning. The cats were anesthetized with propofol (7 mg/kg, IV) for tracheal intubation and were then maintained with sevoflurane (2.5%) and oxygen. The cats were mechanically ventilated with a respiratory rate of 12 breaths/min during MRI. The heart rate was continuously monitored with an MR peripheral gate system and the body temperature was maintained at 36–38 °C using warm-water bags placed around the body. The cats were in the prone position with their heads placed in the coil.

DWI was obtained using spin echo-echo planar imaging periodically rotated overlapping parallel lines with enhanced reconstruction (TR/TE = 8000/87.4 ms, FOV = 15 × 15, slice thickness = 3.0 mm, matrix = 256 × 256, NEX = 1, motion probing gradient = 3 axis, and b value = 1000 s/mm^2).

DTI was obtained using spin echo-echo planar imaging (TR/TE = 8000/85 ms, FOV = 15 × 15, slice thickness = 3.0 mm, matrix = 128 × 128, NEX = 2, motion probing gradient = 15 axis, and b value = 1000 s/mm^2).

Dynamic susceptibility contrast (DSC) enhanced PWI was obtained using gradient echo-echo planar imaging (TR/TE = 2000/32 ms, FOV = 15 × 15, slice thickness = 3.0 mm, matrix = 256 × 192, NEX = 1, time-resolution = 2 s/phase, number of phase = 50 time points/slice, total slices = 20, slices of images = 1000, and total imaging time = 100 s). The images were acquired with the concurrent IV administration of 0.2 mL/kg (0.1 mmol/kg) gadodiamide using an automatic injector (the injection rate was 1 mL/s).

Finally, a conventional T2-weighted image (T2WI) was acquired as an anatomical reference. T2WI was obtained by fast spin echo (TR/TE = 7000/85 ms, FOV = 15 × 15, slice thickness = 3.0 mm, matrix = 384 × 288, and NEX = 1). All images were acquired in the transverse plane.

2.5. Diffusion and perfusion parameters

Diffusion parameters (i.e., apparent diffusion coefficient (ADC) from DWI and fractional anisotropy (FA) from DTI) and perfusion parameters (i.e., relative regional cerebral blood volume (rCBV), relative regional cerebral blood flow (rCBF), and relative regional mean transit time (rMTT) from PWI) were calculated and mapped using the internal software of the MRI unit (Functool, GE Healthcare, Tokyo, Japan). Each parameter was measured on each map; circular region of interests (ROIs) were defined in the bilateral hippocampus, amygdala, thalamus, and gray matter and subcortical white matter of the parietal cortex. A trained, expert veterinary neuroradiologist (D.H.) positioned the ROIs, in reference with the atlas of cat brain (Sinder and Niemer, 1961). The size of the ROI was 5 mm^2 for the hippocampus, gray matter, and subcortical white matter, and 10 mm^2 for the amygdala and thalamus.

2.6. Statistical analysis

Commercial software (Statcel3, OMS, Saitama, Japan) was used for the statistical analyses of all measurements. All measurements were made from the left and right sides of each subject in each group. Due to the wide variation of perfusion parameters among individuals, the ipsilateral subcortical white matter ratio of each region was calculated for the statistical analysis in each perfusion parameter. Comparisons of all parameters in each region between the FSEC and control group in the interictal state (inter-stimulation) were performed using a Mann–Whitney *U* test. Further, in both the FSEC and control groups, all the parameters of each region were compared between the interictal (inter-stimulation) and postictal (post-stimulation) using a Wilcoxon