Epilepsy Research 138 (2017) 1–4

Contents lists available at ScienceDirect

Epilepsy Research

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

Short communication

Noninvasive detection of focal brain hyperthermia related to continuous epileptic activities using proton MR spectroscopy

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ARTICLE INFO

Keywords:
Focal epilepsy
Magnetic resonance spectroscopy
Brain temperature
Focal hyperthermia

ABSTRACT

Recent studies using rat models suggested that epileptic discharges (EDs) can induce focal brain hyperthermia, but such ED-related hyperthermia has not been confirmed in humans. We examined hyperthermia of the focus of epilepsy using noninvasive proton magnetic resonance spectroscopy (^{1}H-MRS) thermometry. We recruited six pediatric patients with refractory daily seizures, continuous interictal epileptic discharges, and concordant focus lesions on MRI who had undergone comprehensive presurgical exams. ^{1}H-MRS thermometry calculated the temperatures of the presumed epileptogenic lesions, and we examined the contralateral counterparts in each patient as controls. As a result, the mean temperature of the epileptogenic foci (36.81 °C) was significantly higher than that of the controls (36.01 °C). The mean difference was 0.81 °C (95%CI: 0.22–1.39, $p = 0.017$). ^{1}H-MRS thermometry may have the ability to noninvasively detect focal brain hyperthermia related to continuous EDs in human subjects, and to contribute to a better understanding and focus detection of epilepsy.

1. Introduction

The relationship between epilepsy and the temperature of the brain was first discussed at least 50 years ago (Baldwin and Frost, 1956). According to recent studies of rats, epileptic discharges (EDs) can induce focal brain hyperthermia (Tokiwa et al., 2013), and focal brain hyperthermia can induce EDs (Wang et al., 2011). It was also suggested that focal brain cooling can attenuate EDs and that such cooling could possibly become a new treatment for drug-resistant epilepsy (Fujii et al., 2012). However, ED-related hyperthermia has poorly been confirmed in human subjects.

Regional parenchymal temperatures can be noninvasively measured by proton magnetic resonance spectroscopy (^{1}H-MRS) with the determination of the water and *N*-acetyl aspartate (NAA) peaks, which are respectively affected and unaffected by temperature (Cady et al., 1995). We hypothesized that this ^{1}H MRS thermometry could detect ED-related hyperthermia *in vivo* in the brains of humans with refractory epilepsy, and that this use of ^{1}H MRS thermometry may lead to the prediction of the effects of brain cooling treatment as well as a better understanding of the pathophysiology of focal epilepsies. The aim of the present study was to verify the ability of a noninvasive ^{1}H MRS thermometry technique to detect hyperthermia of epileptogenic foci in patients with continuous epileptic activities.

2. Materials and methods

2.1. Patients

We recruited patients who were diagnosed with refractory focal epilepsy and underwent a comprehensive presurgical evaluation, including video-EEG monitoring, conventional MRI, interictal ^{18}F FDG-PET, and ictal/interictal ^{99}mTc-ECD SPECT at our Epilepsy Center between May 2015 and April 2016. The inclusion criteria for study participation were as follows: (1) at least daily seizures, (2) continuous

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http://dx.doi.org/10.1016/j.eplepsyres.2017.10.001
Received 4 October 2016; Received in revised form 3 September 2017; Accepted 1 October 2017
Available online 06 October 2017
0920-1211/

Table 1
Clinical demographics and MRS thermometry results.

Patient:	1	2	3	4	5	6
Sex	F	M	M	M	F	M
Age at MRS	0y 3m	1y 3m	6y 7m	10y 7m	1y 3m	2y 7m
Age at onset	2m	0d	3d	2y 3m	4m	3m
Seizure type	epileptic spasm	focal motor	epileptic spasm	focal sensory	epileptic spasm	focal motor
Seizure freq.	5–10/d	5–15/d	5–10/d	1–4/d	1–2/d	1–8/d
Etiology	HME	HME	HME	FCD	FCD	TSC
Location on MRI	Rt. Hemispheric	Lt. Hemispheric	Rt. Hemispheric	Rt. Parietal	Rt. Frontal	Lt. Frontal
Interictal scalp EEG	Bil. supp-burst (Rt. dominant)	Lt. hemispheric slows	Bil. diffuse spikes (Rt. dominant)	Rt. centro-parietal sharps	Rt. centro-parietal slows	Lt. frontal spikes
Operation	hemispherotomy	hemispherotomy	callosotomy	lesionectomy	N/A	lesionectomy
Pathology	Dysplasia	Dysplasia	N/A	FCD IIb	N/A	Cortical Tuber
Outcome	Free	Free	Reduction	Free	N/A	Free
Follow-up period	3m	6m	1m	9m	N/A	1m
Focus temp.	36.96	37.65	36.18	36.29	37.62	36.18
Contra temp.	36.29	36.96	36.24	34.83	36.93	34.80
Body temp.	37.1	36.1	37.1	36.8	35.9	36.6

d: day, FCD: focal cortical dysplasia, HME: hemimegalencephaly, Lt: left, m: month, N/A: not available, Rt: right, supp-burst: suppression burst, TSC: tuberous sclerosis complex, y: year.

interictal epileptic discharges (> 1 epileptic discharge per 2–3 s) on video-EEG monitoring prior to the ^{1}H MRS scan, and (3) a concordant lesion on conventional MRI. The exclusion criteria were: (1) widespread focus lesions on MRI to the contralateral hemisphere, (2) the existence of encephalitis, meningitis, or ischemic encephalopathy, and (3) a history of neurosurgery.

All six of the recruited patients were children (Table 1): three with hemimegalencephaly, two with focal cortical dysplasia, and one with tuberous sclerosis. We obtained written informed consent for their participation in the study from their parents, and the study was approved by the Institutional Review Board at Japan's National Center of Neurology and Psychiatry Hospital.

2.2. ^{1}H MRS acquisition

The ^{1}H MRS scan for all patients was performed on a 3.0-T MR system with a 32-channel coil (Philips Medical Systems Achieva, Best, The Netherlands), following conventional presurgical MRI sequences which were prioritized clinically and ethically. The volumes of interest (VOIs) were located in the presumed epileptogenic lesions (Fig. 1, red squares), and the contralateral counterparts as controls (Fig. 1, green squares). In the patients with hemispheric lesions (Nos. 1–3), the VOIs of the focus side were located in the areas concordant with other clinical information such as that obtained by video-EEG monitoring and seizure semiology. The single patient with tuberous sclerosis (No. 6) had several cortical tubers revealed by MRI, but the presumed epileptogenic lesion was well-limited in the left precentral tuber (Fig. 1F) based on the findings of ictal EEG and seizure semiology.

Single-voxel ^{1}H MRS spectra were acquired from a VOI ($15 \times 15 \times 15\ mm^3$). A point-resolved spectroscopy sequence was used. The acquisition was performed in the sagittal plane (repetition time/echo time 5000/35 ms; 1024 points per spectrum; spectral width 2000 Hz). Before the scan, with the exception of the oldest child (No. 4), the patients were each sedated with a thiopental injection because they were unable to remain still during the scan.

2.3. Brain temperature estimation

We used the water and NAA peaks on the ^{1}H MRS results to determine the brain temperatures. By using the following equation by Cady et al. (1995), we were able to obtain the temperatures corresponding to the water and NAA peaks:

$$T = 286.9 – 94*(\delta_{H2O} – \delta_{NAA}) \quad (1)$$

Here, T is the temperature (°C), and δ_{H2O} and δ_{NAA} are the resonance frequencies expressed in ppm. We estimated δ_{H2O} and δ_{NAA} using LCmodel software (L.A. Systems, Tokyo; http://www.las.jp/products/s16_lcmodel/) (Provencher, 1993). Examples of LCmodel estimation and ^{1}H MRS thermometry are provided in our previous paper (Sumida et al., 2016). We also measured the tympanic temperature in each patient prior to the scan with an infrared thermometer (Omron Healthcare, Kyoto, Japan).

2.4. Statistical analysis

We compared the temperatures of the focus sides with those of the contralateral sides by paired t-test using SPSS software (ver. 23.0, SPSS Japan, Tokyo). A p-value < 0.05 was considered significant. We also performed post hoc power analysis using G*Power software 3.1.9.2 (Faul et al., 2007).

3. Results

3.1. Clinical data

The patients' clinical data are shown in Table 1. The surgery was performed several days after the ^{1}H MRS scan in five of the six patients. Only patient No. 5 did not undergo surgery, because seizure reduction was obtained by medication changes and incidental infectious gastroenteritis. Her etiology is thus based on only the visual assessment of conventional MRI results.

3.2. ^{1}H MRS thermometry

The estimated temperatures are also presented in Table 1. The mean temperature of the epileptogenic foci (36.81 °C) was significantly higher than that of the controls (36.01 °C). The mean difference was 0.81 °C (95%CI: 0.22–1.39, $p = 0.017$). The post hoc power analysis calculated 0.81 as the power value with relatively high correlation coefficient ($r = 0.83$).

4. Discussion

With this first-time application of ^{1}H MRS thermometry, the results of the present study demonstrated significant focal hyperthermia at the epileptogenic foci in patients with continuous epileptic activities. We thus speculate that ^{1}H MRS thermometry can detect ED-related hyperthermia noninvasively in human subjects.

A recent study using a rat model showed that penicillin-induced EDs elevated the focal brain temperature, and the mean increase was