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**The presence of short and sharp MEG spikes implies focal cortical
dysplasia**

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Abstract

Purpose: This study focused on the characteristic needle-like epileptic spikes of short duration and steep shape seen on magnetoencephalography (MEG) in patients diagnosed with focal cortical dysplasia (FCD) morphologically. We aimed to validate the analysis of MEG spike morphology as a noninvasive method of identifying the presence and location of FCD.

Methods: MEG was collected by 204-channel helmet-shaped gradiometers. We analyzed MEG spike sources for 282 patients with symptomatic localization-related epilepsy. MEG showed clustered equivalent current dipoles when superimposed on their three-dimensional-magnetic resonance images (MRI) in 85 patients. Fifty-seven patients were excluded from our study, because they had destructive brain lesions or an insufficient number of spikes for statistical analysis. Twenty-eight patients (18 males, 10 females; aged 1-34 years) were finally matched to our inclusion criteria, and were categorized into three groups: FCD (7 patients), non-FCD (10 patients), and non-lesion (11 patients), based on the MRI findings. We measured the duration, amplitude, and tilt manually for at least 15 spikes per patient, and compared the three groups using a one-way analysis of variance, followed by the Tukey test when statistically significant ($p < 0.05$). In 17 patients with visible MRI lesions, we investigated the correlation between the depth of the lesion and the tilt using the Pearson product moment correlation.

Results: The average spike duration was significantly shorter in the FCD and non-lesion groups than in the non-FCD group ($p < 0.05$). The average amplitude was not significantly different between the three groups. The average spike tilt was significantly steeper in the FCD group than in the non-FCD group ($p = 0.0058$). There

was no significant difference between FCD and non-lesion patients in both duration and tilt. Our additional study revealed a significant negative correlation between the depth of the lesion and the average tilt ($p = 0.0009$).

Significance: MEG epileptiform discharges of short duration and steep tilt characterize FCD, especially when located at the superficial neocortical gyrus. We speculate that this particular spike morphology results from the intrinsic epileptogenicity of FCD. Morphological analysis of MEG spikes can evaluate the etiology of epileptogenic lesions and detect a strong, localized epileptogenic focus such as that typically observed in FCD.

Keywords: focal cortical dysplasia, epilepsy, magnetoencephalography, spike morphology, waveform analysis

Abbreviations: ECD, equivalent current dipole; ECoG, electrocorticography; FCD, focal cortical dysplasia; MEG, magnetoencephalography; MRI, magnetic resonance imaging; MTLE, medial temporal lobe epilepsy; EEG, electroencephalography; SEM, standard error of the mean.

1. Introduction

Focal cortical dysplasia (FCD) occurs during fetal neuronal migration, and is characterized by abnormal cortical organization with or without cellular abnormalities. FCD may also progress pathologically to become intractable focal epilepsy (Taylor et al., 1971). According to the classification by Palmini et al. (2004), FCD type IA is pathologically characterized by the presence of neocortical dyslamination, and FCD type IB is typified by the presence of abnormal hypertrophic pyramidal-like cells. FCD type II is distinguished from type I by the presence of dysmorphic neurons in the gray and/or white matter (FCD type IIA), while FCD type IIB has the additional presence of balloons cells.

Recently, surgical resection strategies have provided favorable outcomes in patients with intractable epilepsy and FCD (Alexandre et al., 2006; Cohen-Gadol et al., 2004; Hong et al., 2000; Kloss et al., 2002; Krai et al., 2003). Although progressive resolution of magnetic resonance imaging (MRI) contributes to the pre-surgical diagnosis of FCD, MRI sometimes misses the presence of FCD, particularly in those patients with type I or IIA histology. Magnetoencephalography (MEG) is a relatively modern diagnostic tool used to identify the location of epileptogenic foci in patients with epilepsy, while equivalent current dipole (ECD) source analysis is a conventional procedure used to define the localized epileptogenic zone in patients with intractable epilepsy (Iida et al., 2005; Otsubo et al., 2001; Stefan et al., 2003). MEG ECD localizations are well correlated to the MRI findings of FCD (Bast et al., 2004; Ishibashi et al., 2002; Morioka et al., 1999), as FCD has an intrinsic epileptogenic potential (Palmini et al., 1995). However MEG spike sources sometimes show an aberrant epileptogenic area with localized epileptic currents in patients without

definite MRI findings. These findings might imply the presence of MRI-invisible epileptogenic lesions, such as FCD type I or IIA. The huge advantage of MEG analysis is that it is a noninvasive neuroimaging tool with high spatial and temporal resolution. So MEG is especially powerful for advanced clinical investigation in epileptic children.

This study analyzed the shape and characteristic morphology of MEG spikes in epileptic patients with FCD to define the etiology of the epilepsy and diagnose FCD directly from the MEG spike morphology.

2. Methods

MEG was performed in 427 patients at Hokkaido University Hospital from May 1996 to March 2012. MEG analyses were conducted for the diagnosis of epileptic syndrome as well as for pre-surgical evaluation. We reviewed MEG data of 282 patients with symptomatic localization-related epilepsy.

MEG was detected by 204-channel helmet-shaped gradiometers (Vector View System, Elekta AB., Stockholm, Sweden) and MEG spike sources were analyzed by dipole-fit software (xfit, Neuromag Oy, Helsinki, Finland). We recorded the MEG data at a sampling rate of 600 Hz, and then the data were band-pass filtered between 1 and 30 Hz to visualize and select the epileptic MEG spikes. Spike sources were demonstrated as ECDs and superimposed onto the subjective three-dimensional-MRI. We used the goodness of fit value to estimate how well the measured MEG currents correlated to the estimation from a pre-defined ideal brain model. Significant ECDs were represented when they showed > 70% goodness of fit and between 100 and 700 nAm dipole moments.

The distribution of ECDs was classified as clustered if more than 70% of the ECDs were located in neighboring Brodmann's areas (Ito et al., 2014). Clustered ECDs were found in 85 patients. From this data set, we excluded 13 patients having destructive brain lesions. Forty-four patients with insufficient epileptic spikes for analysis in MEG recordings (< 15) were also excluded.

Twenty-eight patients (18 males, 10 females; aged 1-34 years, mean age 17.3 years) were finally matched to our inclusion criteria (Fig.1), and were categorized into three groups: FCD group (n = 7, aged 1-34 years, mean age 14.4 years); non-FCD group (n = 10, aged 13-34 years, mean age 18.9 years); and non-lesion group (n = 11,

aged 8-31 years, mean age 17.5 years), according to the MRI findings (Table 1). In the FCD group, two patients were diagnosed pathologically with FCD type IIA or type IA. In the non-FCD group, seven of ten patients were diagnosed with medial temporal lobe epilepsy (MTLE) with hippocampal sclerosis, and the other three patients had cavernous hemangioma, glioma, and amygdala enlargement, respectively. Ten patients diagnosed as FCD by MRI findings did not match our inclusion criteria, because MEG did not show clustered dipoles, and most (7 out of 10) were less than 5 years (aged 1-13 years, mean age 5.1 years).

Representative clustered MEG spikes were selected to analyze the spike morphology. We used the spike duration, amplitude, and the spike tilt as morphological parameters. The duration was defined as the period between the onset and the end of each trough of the spike source around the peaks. As the parameter reflecting the sharpness of the spike, tilt was defined as the amplitude between the spike onset and the peak, divided by the period between the onset and the peak. We measured the duration, amplitude, and tilt manually for at least 15 spikes for each patient, and calculated the average and standard error of the mean for each parameter. These averages were compared statistically among the three groups using a one-way analysis of variance, followed by the Tukey-Kramer honestly significant difference test when statistically significant ($p < 0.05$). The cut-off value for each parameter for differentiating FCD from non-FCD was also evaluated by a receiver operating characteristic (ROC) curve, when statistically significant.

Furthermore we analyzed the depth of the lesions in order to measure its influence on spike morphology. In the 17 patients from the FCD and non-FCD groups with visible MRI lesions, we measured the depth of the lesion from the surface of the

scalp with OsiriX (OsiriX Foundation, CA, USA), a type of Digital Imaging Communications in Medicine viewer software. Depth was measured from three directions (axial, coronal, and sagittal), and the shortest one was taken. In addition, we investigated the correlation between the depth of the lesion and the average tilt of the MEG spikes using the Pearson product moment correlation.

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3. Results

3.1. Morphological analysis

The average spike duration was 66.6 ± 3.7 ms for the FCD group, 95.2 ± 3.0 ms for the non-FCD group, and 79.2 ± 4.9 ms for the non-lesion group. The spike duration in the FCD and non-lesion groups was significantly shorter than in the non-FCD group ($p = 0.0003$, $p = 0.0202$, respectively), while there was no difference between the FCD and non-lesion groups (Fig. 2A). The cut-off value determined from the ROC curve for differentiating FCD from non-FCD was 80.9 ms (sensitivity, 1.0; specificity, 1.0).

The average spike amplitude was not significantly different among the three groups (FCD, 824.6 ± 96.8 fT/cm; non-FCD, 598.9 ± 34.5 fT/cm; non-lesion, 684.8 ± 71.8 fT/cm).

The average spike tilt was 27.5 ± 4.0 fT/cm/ms for the FCD group, 15.1 ± 1.2 fT/cm/ms for the non-FCD group, and 19.5 ± 2.2 fT/cm/ms for the non-lesion group. The tilt in the FCD group was steeper than that in the non-FCD group ($p = 0.0058$). ROC curve analysis revealed the tilt cut-off value for differentiating FCD from non-FCD was 18.9 fT/cm/ms (sensitivity, 1.0; specificity, 0.9). There was no difference between the FCD and non-lesion groups, or between the non-FCD and non-lesion groups (Fig. 2B).

Data from all patients were plotted on a scatter graph showing duration and tilt (Fig. 2C), which allowed visualization of the morphological differences between the three groups.

In 17 patients with visible MRI lesions, there was a negative correlation between depth of the lesion and tilt ($F_{1,16} = 17.19$, $p = 0.0009$; Fig. 3).

3.2. Representative cases

Patient 2: FCD group (Fig. 4)

This patient was a 14-year-old boy with parietal lobe epilepsy. His initial seizure occurred at the age of eight years, and was described as a right-sided hemiconvulsion with somatosensory auras in the right upper and lower limbs. Electroencephalography (EEG) demonstrated intermittent spikes for the C3, P3, and Cz electrodes, while MEG showed repetitive spikes, and ECDs were clustered at the left post-central gyrus (Brodmann's area 1, 2, 3). Although his previous MRI had not indicated any apparent abnormalities, his subsequent MRI was reviewed carefully taking into account the MEG findings. The MR T2-weighted image showed a slightly high signal where the ECDs were clustered and in the subcortical white matter. The patient underwent partial resection to avoid total sensory palsy. Thereafter, his convulsive seizures ceased and he has only experienced simple partial seizures with abnormal sensation in the right arm. Pathologically, the FCD was classified as type IIA. We analyzed the morphology of the clustered MEG spikes according to our definition and found an average duration of 59.5 ms and an average tilt of 22.3 ft/cm/ms.

Patient 10: non-FCD group (Fig. 4)

This representative case was a 13-year-old girl who was diagnosed with medial temporal lobe epilepsy with left hippocampal sclerosis. Her initial seizure occurred at 11 years of age and was described as a complex partial seizure with oral and limb automatism. EEG demonstrated sporadic spikes for the F7 and T3 electrodes, while MEG showed epileptic spikes in the left temporal area, and ECDs were clustered in a horizontal direction in the anterior part of the inferior temporal gyrus (Brodmann's

area 20). She underwent selective amygdalohippocampectomy and has since been seizure-free. Analysis of the MEG spikes revealed an average duration of 89.3 ms, and an average tilt of 12.7 fT/cm/ms.

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4. Discussion

Previous MEG studies in epileptic patients have focused mainly on the source location and orientation of the epileptic current (Ebersole and Pacia, 1996; Fukao et al., 2010; Ishitobi et al., 2005; Kakisaka et al., 2009; Oishi et al., 2006; Park et al., 2004; Stefan et al., 2000), with the results correlating well with the epileptogenic focus that was validated by the operative outcome or electrocorticography (ECoG) findings. Accordingly, MEG is currently recognized as an indispensable neuroimaging tool for epileptic surgery.

In our current study, we concentrated on the shape of epileptic spikes in MEG recordings, based on the findings of unique needle-like spikes in patients with active epileptogenic foci, such as those with FCD. Ishii et al. (2008) also focused on the morphology of MEG spikes and applied the Synthetic Aperture Magnetometry-kurtosis (SAM(g2)) method to pinpoint the epileptogenic zone in patients with FCD. SAM(g2) is a spatially-filtered source localization MEG technique designed to provide an automated analysis of 'spikiness' by using the excess kurtosis statistic (Kirsch et al., 2006). They used this procedure to compare the interictal MEG-SAM(g2) analysis with corresponding ECoG results, and found that the area of highest kurtosis value on MEG-SAM(g2) was localized within the ictal onset zone, thus histopathologically confirming FCD. Their findings overlap with the morphological characteristics of FCD spikes in our current study.

We have confirmed that MEG spikes of FCD patients had significantly shorter spike duration and steeper tilt than those of non-FCD patients. We suspect that these morphological characteristics would be related to the involvement and synchronization of restricted cortices. FCD has intrinsic epileptogenicity and its spike sources must be

derived from within these foci, so the epileptic current should be generated in a narrow area in the cerebral cortex.

A magnetic field is influenced by distance according to Biot and Savart law, and decreases in amplitude as the distance between the spike source and the detector increases (Barkley & Baumgartner, 2003; de Jongh et al, 2005). MEG showed higher sensitivity to epileptic discharges in neocortical area than to discharges in deep tissues in previous studies of simultaneous MEG and ECoG recordings (Mikuni et al, 1997; Oishi et al, 2002). On simultaneous MEG and intracranial depth electrode EEG recording, MEG spikes with medial temporal focus were significantly lower in amplitude than that with neocortical focus, however, the amplitude of substrate intracranial EEG spikes was similar (Santiuste et al, 2008). In our study the average amplitude was not significantly different among the three groups, while there was a significant difference in the average tilt (amplitude/duration ratio) between the FCD and non-FCD groups. These findings suggest spike tilt is a more sensitive parameter reflecting steepness of spikes than amplitude alone. Our additional study demonstrated that the tilt was well correlated to the depth of the lesion. The short and steep spike shape tends to be exhibited in patients with FCD at the superficial neocortical gyrus.

This study showed no apparent difference in the shape of MEG spikes between FCD and non-lesion patients, with short duration MEG spikes recorded in both groups. MRI does not always show the presence of FCD, especially FCD type I and IIA, which are also major causes of intractable localization-related epilepsy for which surgery leads to seizure control (Fauser et al., 2004; Krsek et al., 2009; Widjaja et al., 2008). Therefore, it is possible that our findings show the presence of FCD that was undetected by MRI among the non-lesion group. However, our study has a critical

limitation – because none of the non-lesion group patients came to surgery, we could not confirm MRI-invisible FCD by pathologic findings from the surgical specimens. Our clinical goal is to noninvasively evaluate epileptogenic lesions in candidates for epilepsy surgery, and to define the presence of FCD even in cases where the MRI lesions are subtle, since the outcome of surgery in these patients is not necessarily unfavorable (Alacrón et al., 2006; Chapman et al., 2005; Cukiert et al., 2001). Indeed, among our patients, some FCD lesions were identified on MRI only after carefully reviewing where the ECDs of MEG were clustered. However, an abnormal MRI is one of the predictors of seizure freedom in the surgical management of FCD, so epilepsy surgery for patients with no MRI-evident lesion is still challenging, and careful interpretation of MEG results is needed even when ECDs are well clustered. Occasionally, clustered ECDs might have other origins, and reflect propagated epileptic current, such like in patients with MTLE. We therefore propose that a detailed analysis of MEG spike morphology could enable a more accurate detection of true epileptogenic lesions, such as those typically seen in FCD. MEG is one of the unique tools for the functional analysis to the organic lesion on cerebral cortex non-invasively. Conventional researches of MEG study for the symptomatic epileptogenic lesion have mentioned the clustering of epileptic spike sources. Our current view for the epileptic focus has demonstrated another aspect of MEG analysis for symptomatic epilepsy.

5. Conclusions

In conclusion, morphological analysis of MEG spikes has the advantage of noninvasively evaluating the etiology of epileptogenic lesions. This approach is

helpful for detecting a strong, localized epileptogenic focus such as that typically observed in FCD, even if the MRI findings are subtle.

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6. Acknowledgements

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7. Conflicts of Interest

None of the authors have any conflicts of interest to disclose.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Figure captions

Figure 1

Flowchart of inclusion criteria for analysis. Diagnoses other than symptomatic localization-related epilepsy (SLRE) are as follows and were initially excluded from our database: idiopathic generalized epilepsy (n = 20), idiopathic localization-related epilepsy (n = 25), symptomatic generalized epilepsy (n=25), unclassified (n = 41) and non-epilepsy (n = 34). Cases with clustered equivalent current dipoles (ECDs) but having destructive brain lesions were also excluded as follows: infarction (n = 6), post-lobectomy (n = 3), broad white matter lesion (n = 2) and post-encephalopathy (n = 1). Fully matched cases (n = 28) were divided into three groups according to the magnetic resonance image (MRI) findings as shown in the bottom panels. MEG, magnetoencephalography; FCD, focal cortical dysplasia.

Figure 2

Results of waveform analysis. Data are mean \pm standard error of the mean (SEM). (A) Comparison of magnetoencephalography (MEG) spike durations showed that the average spike durations in the focal cortical dysplasia (FCD) and non-lesion groups were significantly shorter than in the non-FCD group ($*p = 0.0003$, $*p = 0.0202$, respectively), but there was no significant difference between the FCD and non-lesion groups. (B) Comparison of tilt revealed that the average tilt in the FCD group was steeper than that in the non-FCD group ($*p = 0.0058$). There was no difference between the FCD and non-lesion groups, or between the non-FCD and non-lesion groups. (C) A scatter graph between duration (X-axis) and tilt (Y-axis) for all patients allowed visualization of the morphological differences among the three groups. The FCD plots (red dots) were distributed in the middle upper area, representing short duration and steep tilt. In contrast, the non-FCD plots (white dots) tended to be in the right lower area, representing long duration and gentle tilt. The non-lesion plots (blue

dots) were spread over both areas. A horizontal dotted line on the Y-axis indicates the cut-off value (18.9 fT/cm/ms) determined from the ROC curve for differentiating FCD from non-FCD.

Figure 3

Correlation between lesion depth and spike tilt. In 17 patients with a lesion visible via magnetic resonance imaging, there was a negative correlation between the depth of the lesion and the average tilt of magnetoencephalography spikes. ($F_{1,16} = 17.19, p = 0.0009$).

Figure 4

Waveform analysis of magnetoencephalography (MEG) spikes in representative cases. Panels A, B and C show data from a representative patient from the focal cortical dysplasia group (Patient 2), while panels D, E, F show data from, a representative patient from the non-focal cortical dysplasia group (Patient 10). (A) Magnetic resonance image (MRI) (T2-weighted) showing high signal in the left postcentral gyrus and subsequent white matter (yellow arrow). (B) Clustered equivalent current dipoles (ECDs) were located in the left sensory area, within the MRI-detected lesion (red dots). (C) Distribution of the 204-channel MEG spikes, and an enlarged representative spike in the left central area showing a short, steep shape. (D) MRI (fluid-attenuated inversion recovery) showing left hippocampal atrophy (yellow arrow). (E) Clustered ECDs were located in a horizontal direction in the anterior part of the inferior temporal gyrus (red dots), a typical pattern of source localization of MEG in medial temporal lobe epilepsy. (F) Distribution of the 204-channel MEG spikes, and an enlarged representative spike in the left temporal area showing a slightly longer, blunt shape. The waveform analysis parameters (dotted lines) were t

(duration), defined as the period between the onset and the end of each trough of the spike source around the peaks; t_1 , the period between the onset of the spike and the peak; and h , the amplitude between the spike onset and the peak. Tilt was calculated as t_1/h , and reflected spike sharpness.

Table 1. Patient profiles, MRI, MEG, and pathological findings.

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Group	Patient	Sex /Age (y)	Lesion-side /Location	Brodmann's area of clustered ECDs	MRI findings	Pathological findings
FCD	1	Male/6	Left/F	4	FCD	not done
	2	Male/14	Left/P	1, 2, 3	FCD	FCD IIA
	3	Female/34	Right/F	47	FCD	not done
	4	Female/6	Left/P	40	FCD	not done
	5	Male/1	Left/P	19	FCD	not done
	6	Female/23	Left/F	6	FCD	not done
	7	Male/17	Left/F	9,10	FCD	FCD IA
Non- FCD	8	Male/34	Left/T	20	HS	HS
	9	Male/29	Right/F	13, 14, 15, 16	Tumor	CH
	10	Female/13	Left/T	20	HS	HS
	11	Female/16	Right/T	20	HS	HS
	12	Male/14	Right/T	21	HS	HS
	13	Male/20	Left/T	21	HS	HS
	14	Male/14	Right/T	20	HS	HS
	15	Male/16	Left/T	27	HS	HS
	16	Female/16	Right/T	38	AE	not arrived
	17	Male/17	Right/P	1, 2, 3	Tumor	Glioma
Non- lesion	18	Male/8	Left/F	4	normal	not done
	19	Male/8	Left/F	46	normal	not done
	20	Male/9	Right/F	6	normal	not done
	21	Female/16	Left/P	40	normal	not done
	22	Female/19	Right/P	39	normal	not done
	23	Male/17	Right/T	37	normal	not done
	24	Female/23	Left/F	6	normal	not done
	25	Female/12	Left/T	22	normal	not done
	26	Male/31	Left/T	21	normal	not done
	27	Male/21	Right/O	18	normal	not done
	28	Male/29	Left/T	29	normal	not done

MRI, magnetic resonance imaging; MEG, magnetoencephalography; FCD, focal cortical dysplasia; ECDs, equivalent current dipoles; F, frontal; P, parietal; T, temporal; O, occipital; HS, hippocampal sclerosis; CH, cavernous hemangioma; AE, amygdala enlargement.

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