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Original Article

Application of MSI in MRI-negative focal cortical dysplasia patients with epilepsy

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Abstract: Background: Focal cortical dysplasia (FCD) is the most common cause of intractable epilepsy in children and adolescent. Purpose: To evaluate the application value of magnetic source imaging (MSI) in treatment of magnetic resonance imaging (MRI)-negative FCD patients with epilepsy. Methods: MSI characteristics of 17 cases of MRI-negative focal cortical dysplasia patients with epilepsy were retrospectively analyzed. All patients were treated by surgery. Results: In 17 patients, there were 3 cases of FCD Ia, 7 cases of FCDIb, 3 cases of FCDIIa and 4 cases of FCDIIb. FCD was located at temporal lobe in 8 cases, occipital lobe in 3 cases, frontal lobe in 2 cases and two lobes in 4 cases. In follow-up, 14 patients obtained satisfied curative effect. 1 patient was improved significantly and 2 patients were fine. The concordance between MSI and electrocorticogram in localizing epileptogenic foci was 65%. Conclusion: MSI is a new prospective noninvasive functional neuroimaging technique for identifying and delineating epileptogenic foci in MRI-negative FCD patients.

Keywords: Focal cortical dysplasia, magnetic resonance imaging, epilepsy, magnetic source imaging

Introduction

Focal cortical dysplasia (FCD) is the most common cause of intractable epilepsy in children and adolescent [1]. As the neuropathology of these conditions has been better clarified, the nomenclature has undergone numerous revisions. Their recognition has grown with the use of neuroimaging, and recent advances in imaging technology will further improve detection. Clinical, electroencephalographic, and imaging findings are often diagnostic. Treatment for developmental and behavioral disability remains largely symptomatic, and epilepsy medications are often ineffective. Epilepsy surgery, however, can be successful in selected patients [2].

Surface electroencephalogram (EEG) studies demonstrated spike activity over the affected regions in most cases. However, because of volume conduction and the lack of source analysis, the origin of interictal onset could not be related exactly to the lesion. Magnetoencephalography (MEG) is the measurement of extracranial magnetic fields produced by electrical currents, mostly intracellular, within the brain. These magnetic fields are extremely weak, on the order of one billionth that of the earth, and can be measured only by superconducting quantum interference devices (squids). MEG source localization can help to obtain in vivo information on the epileptogenicity of different types of cortical malformations. It is potentially more accurate than EEG localization techniques because magnetic fields are not attenuated or distorted by the skull and scalp, which allows cerebral sources to be modeled more simply. MEG spike and seizure sources are routinely co-registered with the patient's brain magnetic resonance imaging (MRI) for clinical interpretation. This has been called magnetic source imaging [3]. Otsubo et al [4] reported on a series of 12 pediatric patients who underwent epilepsy surgery, including six patients with cortical dysplasia. In MEG single-spike analysis, most of them showed dipole clusters within the lesion, reflecting intrinsic epileptogenicity. Another MEG study in four patients with FCD confirmed the hypothesis of intrinsic epileptogenicity with dipole localizations within the lesions [5]. Ishii et al [6] recom-

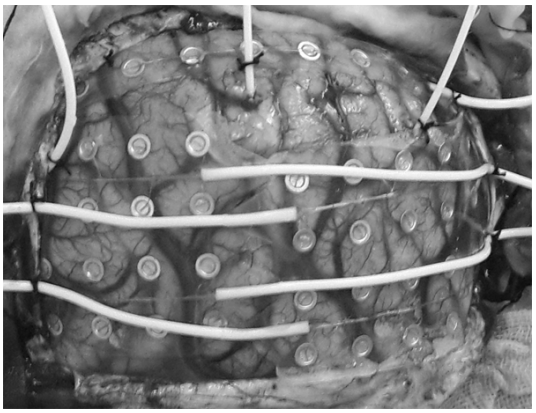

Figure 1. Representative ECoG operation in one patient (female, 32 years old). Results showed spikes in left frontal lobe.

mend Synthetic Aperture Magnetometry-kurtosis (SAM (*g*2)), a spatially filtered source localization technique in MEG, and MEG interictal spike source localization in patients with epileptogenic FCD. SAM (*g*2) analysis showed overlapping of interictal MEG spike sources with the ictal onset zone (IOZ) on electrocorticogram (ECoG) in all three children. The key of successful neurosurgical treatment is localizing the epileptic foci precisely [7]. But the MRI of 17-50% FCD patients confirmed by surgery was negative, even though reviewed by experienced radiologist [7-9]. And few data are available for simultaneous MEG and ECoG recordings in epilepsy caused by FCD.

In this study, we analyzed the magnetic source imaging (MSI) characteristics of MRI-negative FCD patients retrospectively and evaluate the value of MSI in them. The concordance between MSI and ECoG in localizing epileptogenic foci was also investigated.

Materials and methods

Clinical data of patients

From 83 patients with FCD confirmed by surgery from December 2005 to December 2010, 17 cases of MRI-negative patients with epilepsy were enrolled in this study. Their MSI characteristics were retrospectively analyzed. There were 14 males and 3 females, with age of 13-43 years old (mean 23 years). All of MR images were reviewed and analyzed in consensus by two experienced radiologists. The types of seizure were as follows: generalized tonic-clonic seizure, 13 cases; partial followed by generalized seizure, 2 cases; complex partial seizure, 2 cases. The patients had seizure at least 1-2 times every month. All patients were treated by medicine, but the seizure could not be controlled.

MRI

MR images superimposed with MEG were acquired by using a 1.5 T MRI system (Signa horrizon, GE Healthcare, New Jersey, USA). Spoiled gradient recalled (SPGR) sequence was used. The MR images consisted of 124 sequential sagittal slices of 1.5 mm thickness, no space, Flip angle 30°, with a resolution of 256×192 points on a field of view of 300×300 mm. TR=30 ms, TE=17 ms. 9 patients received conventional MRI examination on a 3.0 Tesla MRI system (Signa excite), axial T1 fluid attenuated inversion recovery (FLAIR): TR 2633 ms TE 23.3 ms TI; T2-weighted images: TR 5000 ms, TE118.8 ms; T2FLAIR: TR 9602 ms, TE 116 ms, TI 2400 ms; Slice thickness 5 mm. The other 8 patients had conventional MRI examination on that 1.5 Tesla MRI system, axial T1-weighted images: TR 480 ms TE 12 ms; T2-weighted images: TR 3400 ms, TE 98 ms; Fluid attenuated inversion recovery (FLAIR): TR 8002 ms, TE 105 ms, TI 2000 ms; slice thickness 5 mm.

MEG data acquisition and analysis

All patients were performed in magnetically shielded room with 306-channels whole-head biomagnetometer (VectorView 306 whole-head biomagnetometer, Neuromag, Helsinki, Finland). The signals of the brain were filtered with a bandpass at 0.03~300 Hz on line and digitized 1000 Hz. A 40 min period of spontaneous MEG raw data was recorded. The brain activity with dipolar field patterns was modeled with equivalent current dipoles (ECDs). The shape of the brain was modeled by boundary element model (BEM). The ECD locations were superimposed on the patient's head MRI with the aid of anatomic reference points in MEG and MRI examination, which is defined as MSI [10, 11]. The data were off-line analyzed with the bandpass 1-60 Hz, so as to prohibit the change of low frequency and the environment noise of high frequency.

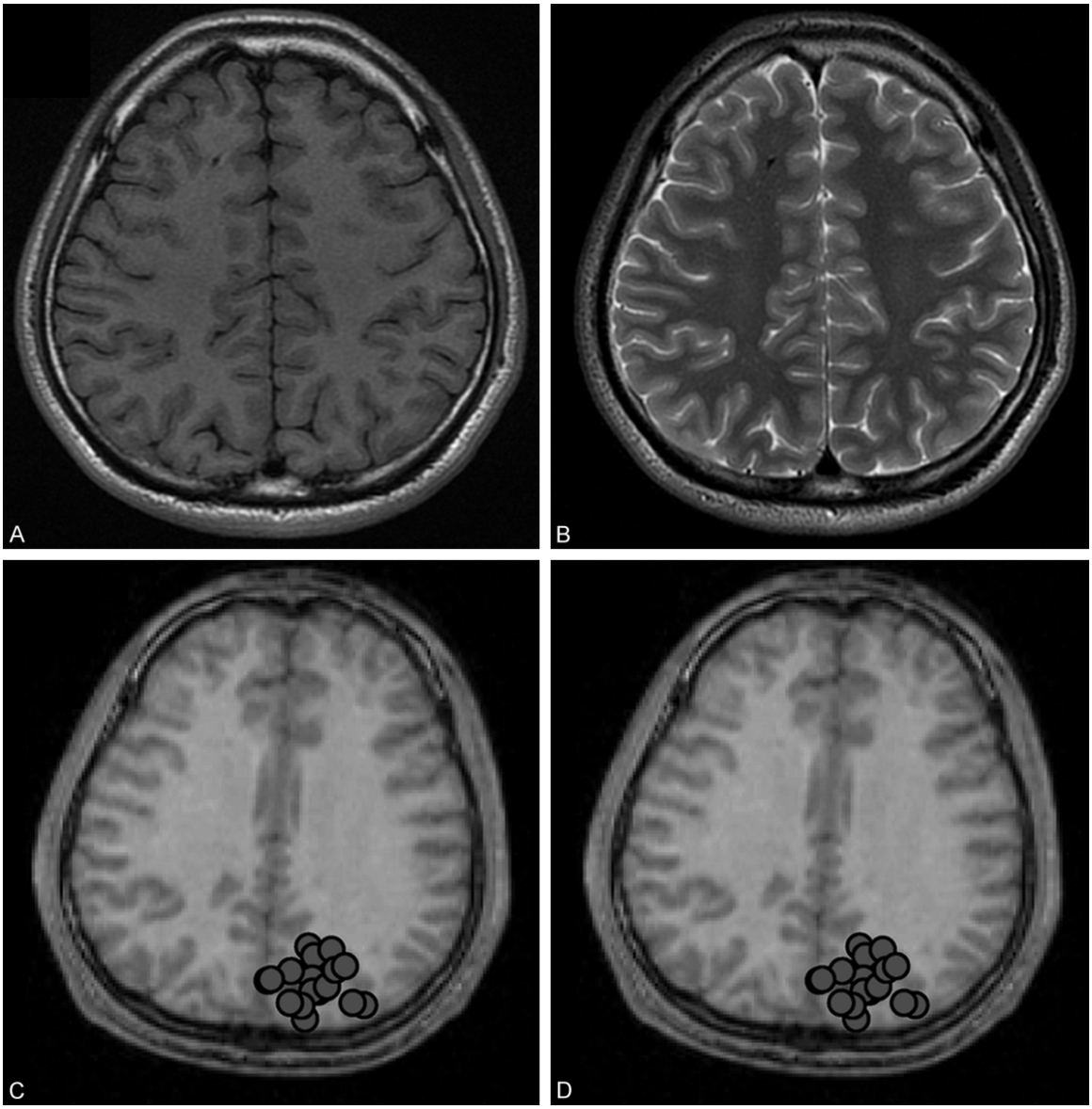

Figure 2. Male, 19 years old. The epileptic history was 8 years. The clinical manifestation was tic of limbs, loss of consciousness and aconuresis sometimes. The patient had seizure once several days. A and B. T1WI and T2WI was normal. C and D. Axial and sagittal MSI showed that the interictal spikes were located at left parieto-occipital lobe. ECoG showed those were at left occipital lobe. The epileptic foci located at left occipital lobe were resected. The seizure was free after surgery. The pathological result was FCDIb.

Evaluation standard after surgery

ECoG was performed, and the representative ECoG operation was shown in **Figure 1**. All patients performed the surgery. If the epileptogenic foci was at anterior temporal lobe, the anterior temporal lobe and hippocampus would be resected; at other lobes, the epileptogenic foci resection or thermo-coagulation would be performed. The follow-up time ranges from 13 to 48 months. The surgical results were evaluated according to Engel standard of effect.

Results

In 17 patients, there were 3 cases of FCD Ia, 7 cases of FCD Ib (**Figure 2A-D**), 3 cases of FCD IIa, 4 cases of FCD IIb (**Figure 3A-D**). Hippocampal sclerosis and micro grey matter heterotopia were also found in 3 cases. FCD was located at temporal lobe in 8 cases, occipital

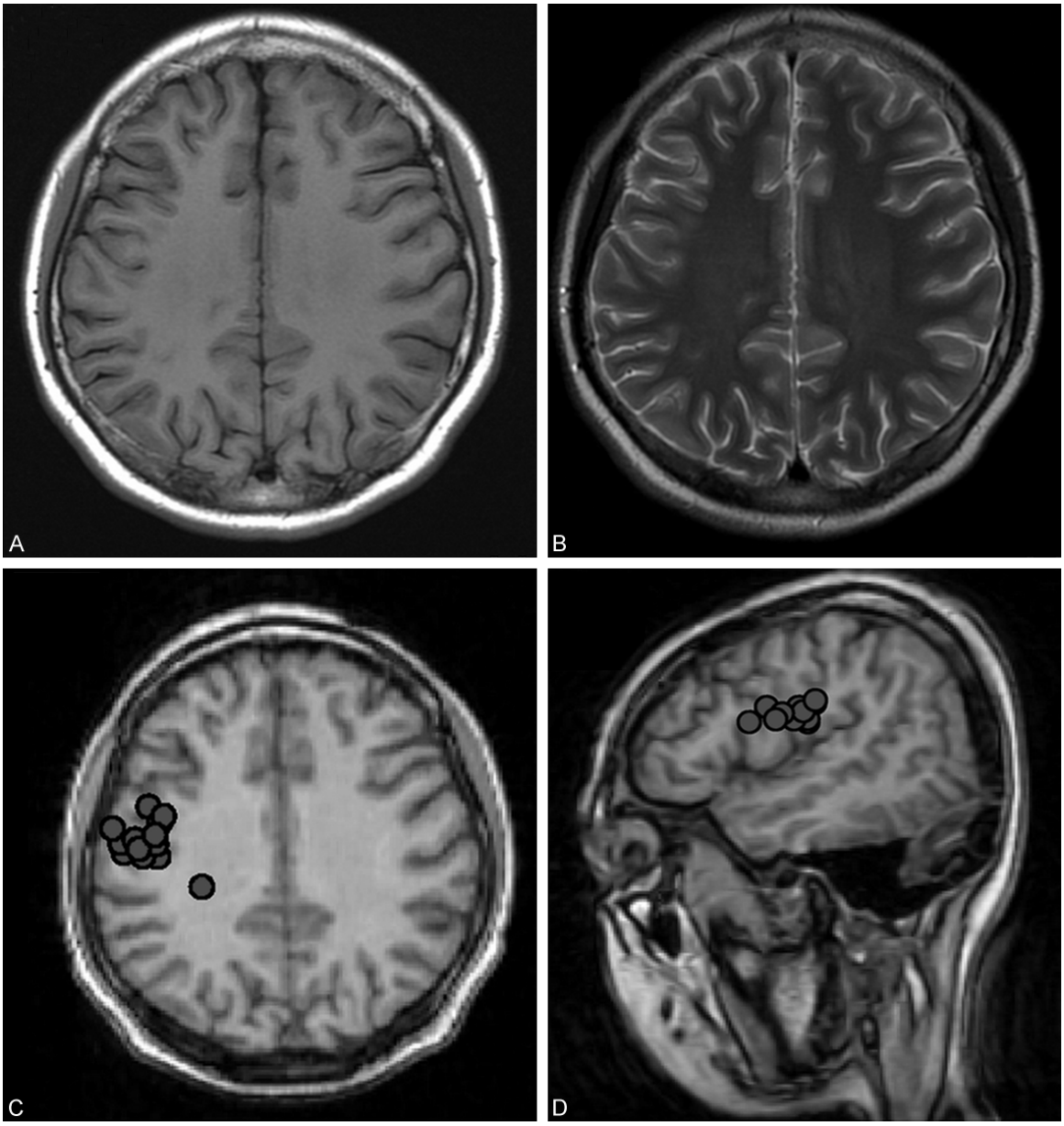

Figure 3. Female, 16 years old. She had seizure first time at 3 years old. The clinical manifestation was eyes on, jerk of left angle of mouth, head, eyes and body turning left. These symptoms lasted one minutes before remission. The patient had seizure several times every day. A and B. T1WI and T2WI was normal. C and D. Axial and sagittal MSI showed that the interictal spikes were located at right central zone. The epileptic foci located at left fronto-parietal lobe were resected. The patient had seizure occasionally 1-2 times one year after surgery. The pathological result was FCDIIb.

lobe in 3 cases, frontal lobe in 2 cases and two lobes in 4 cases. According to Engel standard of curative effect, 14 patients received satisfied curative effect (Engel I). 1 patient was improved significantly (Engel II), and 2 patients were fine (Engel III). The concordance between MSI and ECoG in localizing epileptogenic foci was 65% (11/17). The location of MSI and ECoG, type of surgery and pathological results were shown in **Table 1**.

Discussion

Taylor et al [1] first reported and proposed the term "focal cortical dysplasia" (FCD) in 1971. FCD is the common cause of refractory epilepsy

Table 1. Location of MSI, ECoG surgery type and pathological results

Case	MSI	ECoG	Surgery type	Pathological results
1	Right FT	Right FT	RT+H resection, F thermo-coagulation	FCDIb
2	Left T	Left FT	LFT+H resection	FCDIIa
3	Right T	Right T	RT+H resection	FCDIa
4	Left TO	Left TO	LTO+H resection	FCDIIa
5	Right TPO	Right O	RO resection	FCDIb
6	Left T	Left T	LT+H resection	FCDIb
7	Right T	Right T	RT+H resection	FCDIa
8	Left T	Left TF	LT+H resection, LF thermo-coagulation	FCDIIb
9	Left FP	Left T	LT+H resection	FCDIb
10	Left PO	Left PO	LO resection	FCDIIb
11	Left FTP	Left FTP	LFT+H resection	FCDIa
12	Left F	Left F	LF resection	FCDIIa
13	Bilateral F Right P	Right FT	RF resection	FCDIIb
14	Right FP	Right FP	RFP resection	FCDIIb, GMH
15	Right FT	Right FT	RT+H resection	FCDIb, GMH, HS
16	Left FT	Left FT	LFT+H resection	FCDIb, GMH, HS
17	Left PO	Left O	LO resection	FCDIb

MSI: magnetic source imaging; ECoG: electrocorticogram; T: temporal lobe; P: parietal lobe; F: frontal lobe; O: occipital lobe; H: hippocampus; GMH: grey matter heterotopia: HS: hippocampal sclerosis; FCD: focal cortical dysplasia.

and about 76% patients with FCD had refractory epilepsy [1]. The seizure is caused by FCD in 25% adult and 50% child [8]. The percentage of follow-up seizure free after surgery was 45-75% [6], surgical excision of the lesion and epileptic foci could get good results.

Palmini et al [12] divided the FCD into FCDI and FCDII, with each being separated into two subgroups (Ia, Ib and IIa, IIb, respectively) in 2004. This categorization is adopted generally and supported by International League Against Epilepsy (ILAE). And recently, according to clinical, imaging and neuron-pathological characteristics, ILAE proposed a new classification in 2011 [13]. The FCD was divided into three groups: FCDI, FCDII and FCDIII. FCDI (Ia, Ib) and FCDII (IIa, IIb) was same with those proposed by Palmini. FCDIII represented cortical abnormality accompanied with hippocampal sclerosis (IIIa), tumor (IIIb), vascular malformation (IIIc) or other acquired lesions (IIId). There were 3 FCD patients accompanied with hippocampal sclerosis and micro grey matter heterotopia in this study. Because grey matter heterotopias was not included in the new classification, we adopted the categorization proposed by Palmini in 2004.

Some studies showed that the MRI of 17-50% FCD patients confirmed by surgery was negative, even though reviewed by experienced radiologist [7-9, 14]. Wang et al [15] found the most common pathologies in MRI-negative patients was FCD. In our study, 17 FCD patients with negative MRI were found out from 83 cases of FCD confirmed by surgery, and the percentage was 20.5%. This was similar with the literature. It was very important to localize the epileptic foci precisely in MRI-negative FCD patients before surgery. ECoG is still the gold standard in localizing epileptic foci, but it is invasive and cannot be applied routinely. EEG was the common used noninvasive electrophysiological means, but it might have large error, even bigger than 1 cm [10]. MSI is a noninvasive method for integrating information on brain electrophysiology obtained by MEG with information on brain anatomy structure gained by MRI. It has millimeter and millisecond precision [10, 11]. It has been already applied for localizing the epileptic foci before surgery in epileptic patients [7, 11, 16]. Widjaja et al [7] localized the epileptic foci in 27 FCD patients by integrating MEG and MRI into MSI. The MRI was positive in 22 cases and the epileptic foci was localized successfully by MSI in 26 patients. Surgical excision of the FCD cortex and epileptic foci get good results. Bast et al [17] recorded interictal EEG and MEG simultaneously in nine children and adolescents. In all cases, the analysis of

averaged spikes showed a localization of onset- and peak-related sources within the visible lesion for both EEG and MEG. Of the single spikes, 91% localized within the lesion with MEG, and 93% with EEG. In three patients operated on, the resected area included the onset zones of averaged EEG and MEG spike activity. These patients had excellent postoperative outcome and became seizure free.

The epileptic foci were localized by MSI presurgery and ECoG intra-surgery in all patients and resected as far as possible. Neurosurgery physician placed the cortical electrodes according to MSI result and had surgical excision according to the localization by ECoG. The concordance between MSI and ECoG in localizing epileptogenic foci was 65% (11/17). In the follow-up, 14 patients received satisfied curative effect (Engel I); 1 patient was improved significantly (Engel II) and 2 patients were fine (Engel III).

Bulk cases statistic data [9] showed that 2% epilepsy was caused by grey matter heterotopia, and 20% of them accompanied with FCD. Even using voxel-based 3D MRI analysis, some grey matter heterotopia would be ignored yet [18]. The MRI of some patients with hippocampal sclerosis would be also negative [19]. In all 17 patients with FCD, hippocampal sclerosis and micro grey matter heterotopia were found in 2 cases simultaneously, one patient had hippocampal sclerosis. All of the MR images were negative.

In conclusion, MSI can identify and localize the interictal spikes and epileptogenic foci in MRI-negative FCD patients non-invasively, help the neurosurgery physician in surgery.

Disclosure of conflict of interest

None.

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