Magnetoencephalographic studies of focal epileptic activity in three patients with epilepsy suggestive of Lennox-Gastaut syndrome

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ABSTRACT – Purpose. To determine the electromagnetic sources of localized epileptic activities using magnetoencephalography (MEG) in three adult patients with epilepsy suggestive of Lennox-Gastaut syndrome (LGS). Methods. MEG and simultaneous electroencephalography (EEG) were recorded from three adult patients using a 204-channel, whole-head MEG system. Equivalent current dipoles (ECDs) were calculated for epileptic spikes on MEG according to the single dipole model. Results. In two patients, MEG showed epileptiform discharges restricted to the unilateral temporal area, corresponding to the EEG spikes. The ECDs calculated from these MEG spikes were clustered in the unilateral temporal lobe. In our third patient, MEG spikes appeared in the right centroparietal area; ECDs were located to the right parietal lobe. Conclusions. The sources of epileptiform discharges that were detected in a restricted area were localized to specific parts of the brain cortex. Despite certain limitations (small number of patients; atypical late-onset epilepsy in one) our study suggests that MEG may prove to be a useful tool for investigating electromagnetic features of localized epileptic discharges in patients with LGS. Based on these preliminary results, further studies performed in patients with typical LGS features are justified.

Key words: magnetoencephalography, epilepsy, Lennox-Gastaut syndrome

Lennox-Gastaut syndrome (LGS) is a distinct clinical entity (Commission on Classification and Terminology of the International League Against Epilepsy, 1989), characterized by refractory seizures and mental retardation. It typically develops in early childhood. The clinical seizure patterns that occur in patients with LGS are usually classified as generalized seizures, i.e., tonic seizures, drop attacks and atypical absences. Early reports showed that interictal electroencephalograms (EEG) had diffuse, slow spike-waves (SSW) around 2-2.5 Hz (Chevrie and Aicardi, 1982, Gastaut et al. 1966, Markand, 1977). However, subsequent studies revealed that interictal
epileptic activities that occur in restricted areas also ap-
pear in LGS patients (Fitzgerald et al. 1992, Hughes and
Patil, 2002, Ohtsuka et al. 1990). Magnetoencephalography (MEG) is a powerful tool for
determining the source of localized epileptic activities. Its
excellent spatial resolution is higher than that of conven-
tional EEG. Several researchers have reported that MEG is
useful for localizing the sources of bilaterally-spread activ-
ities (Yu et al. 2004). In this study, we recorded MEG and
EEG simultaneously in three adult patients with epilepsy
suggestive of LGS. We investigated whether the epileptic
activities revealed by MEG had a localized source.

Patients and methods

Patients

From among the seven adult patients with epilepsy sug-
gestive of LGS who visited the Department of Psychiatry
and Neurology in Hokkaido University Hospital during
1999-2004, three patients were selected. They were able
to consent to MEG recording and required no anesthesia at
recording.

Patient 1

A 31-year-old man with no family history of epilepsy, born
after an uncomplicated pregnancy. Early development was
normal until he experienced his first seizure at age five
years. Tonic seizures, myoclonus and atypical absences
occurred daily; his mental status slowly deteriorated. He
was diagnosed as LGS because his EEG showed diffuse
SSW. Medical therapy, including administration of val-
proate, clonazepam, and phenobarbital, proved unsatis-
factory. He presented at our hospital at age 28 years, with
daily occurrence of tonic seizures. Routine, awake EEG
showed a slow background rhythm with frequent, diffuse
SSW. Diffuse 10-Hz fast activities were also observed
during sleep. In addition to these abnormalities, sporadic
spikes were apparent in the right temporal area during
wakefulness (figure 1A). These spikes were not followed
by diffuse SSW. Video-EEG monitoring confirmed daily
tonic seizures, and the ictal discharges showed diffuse
15-Hz rhythmic activity. Other types of seizure, including
partial seizures, were not observed. Magnetic resonance
imaging (MRI) yielded no abnormal findings.

Patient 2

A 27-year-old woman with no family history of epilepsy
experienced atypical absences at age 11 years. She was
suspected of having LGS based on EEG showing diffuse
SSW and mental retardation. She was treated with val-
proate, carbamazepine, phenobarbital, and zonisamide,
but her seizures were not controlled. In addition to atypi-
cal absences, tonic seizures occurred from the age of 15.
She was referred to our hospital at age 25 years, with daily
occurrence of tonic seizures. Interictal EEG showed diffuse
SSW and 10-Hz fast discharges during sleep. Moreover,
EEG showed occasional spikes in the right centroparietal
area during wakefulness (figure 1B). They were not asso-
ciated with diffuse SSW. Video-EEG monitoring showed
that tonic seizures with diffuse 15-Hz rhythmic activities
appeared many times daily. No other types of seizure were
observed. Brain MRI scans revealed mild cerebral atrophy,
but no structural lesions were observed.

Patient 3

A 25-year-old woman with no family history of epilepsy
experienced infantile spasms at the age of four months.
She was thought to have West syndrome based on her
EEG, which showed hypsarrhythmia; she was treated
mainly with adrenocorticotropic hormone. The spasms
disappeared at the age of three years. However, tonic
seizures and atonic seizures occurred from the age of
seven, and atypical absences were apparent at the age of
11. Interictal EEG showed diffuse SSW bursts. She was
diagnosed with LGS, preceded by West syndrome. Several
antiepileptic drugs were ineffective at controlling her sei-
zures. She presented at our hospital at age 24 with daily
occurrence of tonic and atonic seizures. Interictal EEG
showed diffuse SSW that were slightly dominant in the
right side, and diffuse 15-Hz fast activities during sleep. In
addition, sporadic spikes in the left temporal area during
wakefulness were also observed (figure 1C). They were
independent of diffuse SSW. Video-EEG monitoring
showed tonic seizures with diffuse 15-20 Hz rhythmic
activity and atonic seizures with diffuse 20-30 Hz rhyth-
ic activity. Mental retardation was apparent. There were
no abnormal MRI findings.

Simultaneous MEG and EEG recording

The MEG was recorded for 30 min with a 204-channel,
whole-head gradiometer system (Neuromag. Helsinki,
Finland) in a magnetically shielded room. An EEG was
obtained simultaneously using scalp electrodes according
to the international 10-20 system. The MEG sampling rate
was 600 Hz, and MEG data were filtered digitally at a
bandpass width of 0.5-40 Hz for data analysis. For mag-
netic source localization, ECDs were calculated accord-
ing to a single dipole model. Those ECDs with a goodness-
of-fit value greater than 80% and a dipole moment from 50
nAm to 600 nAm were considered adequate sources.
These ECDs were superimposed on the patients’ MRI.

Results

The MEG recordings of patient 1 showed 40 spike dis-
charges restricted to the right temporal area corresponding
to the EEG spikes localized to the same area (figure 2A). In
the right temporal lobe, 20 adequate ECDs calculated
from these MEG spikes were clustered (figure 3A).
Figure 1. Interictal EEG of each patient. The sampling rate was 256 Hz; the bandpass width was 0.5-70 Hz.

A) Patient 1: Sporadic spikes were detected in the right temporal area.
B) Patient 2: Occasional spikes were apparent predominantly in the right centroparietal area.
C) Patient 3: Sporadic spikes were detected in the left temporal area.
In patient 2, seven MEG spikes were detected clearly in the right centroparietal area, corresponding to the EEG spikes in the same area (figure 2B). Five adequate ECDs were obtained from these spikes, which were detected in the right parietal lobe (figure 3B). In patient 3, the MEG showed 45 spike discharges restricted to the left temporal area; they corresponded to the EEG spikes localized to that area (figure 2C). In the left temporal lobe, 25 adequate ECDs obtained from MEG spikes were clustered (figure 3C).

In all three patients, MEG spikes corresponding to diffuse SSW were recorded. These MEG spikes appeared bilaterally and diffusely within the sensor array of the whole-head sensors. Although we analyzed more than 30 diffuse SSW in each patient, the dipole moments were quite large: sometimes over 1000 nAm, and its goodness-of-fit value was always less than 50%. Therefore, no ECDs calculated from these spikes met our criteria for adequate sources.

**Discussion**

In our patients, clinical features (types of seizures and mental retardation) were suggestive of LGS. Diffuse SSW and diffuse fast activities during sleep, which were apparent on EEG, were consistent with findings of previous reports (Chevrie and Aicardi, 1982; Gastaut et al. 1966; Markand, 1977). Furthermore, localized epileptic spikes were also visible on the interictal EEG recordings. The MEG recordings of each patient showed diffuse EEG spikes in a restricted area. The ECDs obtained from these spikes were localized in specific areas of the brain cortex.

Although previous EEG studies have revealed that localized spikes appear in LGS patients (Fitzgerald et al. 1992, Hughes and patil, 2002, Ohtsuka et al. 1990), the role of localized spikes in the pathogenesis of LGS remains unknown. A previous study using intracranial EEG recordings revealed the focal origin of the localized spikes in LGS patients, suggesting that these spikes were secondary foci of LGS (Fisher and Niedermeyer, 1987). In the present study, the origins of the localized spikes were determined non-invasively using MEG source analysis.

The results of our dipole source localization suggest that localized spikes in each patient arose from a specific part of the brain cortex. Previous reports demonstrated that removal of the focal lesion eliminated seizures in some LGS patients (Angelini et al. 1979; Quarato et al. 2002). Therefore, the possibility exists that localized spikes that are apparent in LGS patients are primary foci of LGS, and give rise to secondary bilateral synchrony. However, our patients showed no focal lesions on MRI, no abnormal neurological findings, or partial seizures. Furthermore, dipole analyses failed to obtain any focal component from the diffuse discharges. It is therefore difficult to infer that localized spikes were the primary foci of LGS in our patients.

In Patient 1 and Patient 3, the ECDs were clustered in the unilateral temporal lobes. Previous studies have demonstrated that localized discharges in LGS patients appeared most frequently in temporal areas (Fitzgerald et al. 1992, Hughes and patil, 2002). Several researchers considered that the generalized discharges in LGS formed independent secondary foci in the temporal lobe and are described as “secondary temporalization” (Melo and Niedermeyer, 1991). Furthermore, these localized discharges have been reported to be more frequent in LGS patients followed over the long term (Hughes and patil, 2002, Ohtsuka et al. 1990). Furthermore, the patients in our study had been treated for more than 15 years. Therefore, a kindling mechanism caused by repetitive generalized discharges might be related to the formation of localized epileptic discharges in LGS. From this point of view, although our patients showed no clinical partial seizures at the time of MEG recording, they seem to have a greater likelihood of developing such seizures in the future.

In addition to the above, another possibility pertains to the role of localized spikes in LGS. It is widely held that LGS...
results from complex interrelation of a diffuse or multifocal cortical insult that occurs at a particular time in the developing brain (Markand 2003). Blume suggested that increased cortical excitability underlies the pathogenesis of LGS (Blume, 2001). Furthermore, a long-term follow-up study of LGS showed that approximately one third of patients with LGS eventually developed severe epilepsy with multiple independent spike foci, which is defined as epilepsy with three or more independent spike foci in both hemispheres and generalized seizures (Ohtsuka et al. 1990). Therefore, localized cortical spikes can occur as a result of diffuse damage to the cerebral cortex, indepen-

Figure 3. ECDs calculated from the MEG spikes. A) Patient 1: ECDs are clustered in the right temporal lobe. B) Patient 2: ECDs are localized in the right parietal lobe. C) Patient 3: ECDs are clustered in the left temporal lobe.
dently from diffuse SSW. In Patient 3, localized spikes appeared contralateral to the predominant side of the diffuse SSW, which might support this inference.

In conclusion, MEG may prove to be a useful tool for investigating electromagnetic features of localized epileptic discharges in patients with LGS. The sources of localized spikes were determined adequately using a single dipole model. Our results suggest that localized spikes were formed: 1) secondarily by repetitive diffuse SSW; and 2) as a result of diffusely damaged cerebral cortex, independent of diffuse SSW. However, our study suffers from important limitations, making definite conclusions difficult: the sample of three patients is small; one of our patients presented with a late-onset generalized epilepsy not figuring the typical characteristics of LGS; all three patients were investigated in adulthood. For the above reasons, our results might not be representative of the general LGS population and need to be validated by further studies.

References


