論　文　内　容　要　旨

Secondary epileptogenesis on gradient magnetic-field topography correlates with seizure outcomes after vagus nerve stimulation

（傾斜磁場トポグラフィーでの二次性てんかん原性は迷走神経刺激装置植込術後の発作転帰と関連する）

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Objective: In current epilepsy surgery, vagus nerve stimulation (VNS) is an option for a subset of patients with refractory epilepsy. Although VNS has been established in clinical practice, we do not yet have a clear understanding of the specific mechanism of action behind VNS treatment of pharmaco-resistant seizures. Conventional equivalent current dipole analysis of magnetoencephalography (MEG) shows efficiency for focal resection in patients with pharmaco-resistant focal onset seizures. However, most patients who require VNS are not candidates for focal resection, because of their generalized onset seizures or unknown onset seizures. Gradient magnetic-field topography (GMFT) has been developed to avoid solving the mathematically complex problems for a unique solution for the epileptic foci. GMFT can visualize the dynamic changes in brain magnetic fields from the epileptic source on a three-dimensional brain surface. Corpus callosotomy (CC) is a palliative surgical procedure used to treat generalized seizures in patients with pharmaco-resistant epilepsy. In our present study, we also evaluated patients for whom CC did not improve seizure control and further VNS was required. The intra-and inter-hemispheric spreading of multiple spikes before and after VNS was first measured by MEG to identify the occurrence and time difference of spike spreading in the brain cortex using GMFT. We studied GMFT for pre- and post-VNS MEG in patients who required VNS for their pharmaco-resistant epilepsy. We evaluated the dynamic changes in MEG spike spreading over the unilateral and bilateral hemispheres by GMFT. We hypothesized that spike spreading on GMFT could predict the seizure outcomes of VNS; thus, bilateral spreading is a potential biomarker of seizure control by VNS.

Methods: We retrospectively reviewed the clinical records and MEG findings in patients who underwent VNS implantation and MEG pre-/post- (>6 months) VNS at Hiroshima University Hospital between March 2011 and January 2016. If patients had drop attacks, we preferentially performed CC before VNS. A Neuromag System (a whole-head 306-channel type, Elekta- Neuromag, Helsinki, Finland) digitally generated the MEG data at 600.615 Hz. Each MEG recording consisted of 3 epochs of 10 min with a simultaneous electrocardiogram, electro-oculogram, and international 10–20 system electroencephalography (EEG) recording. The patients rested with closed eyes while seated. We generated GMFT with 10 ms steps for 100 ms before and after the peak of selected MEG spikes from a planar gradiometer. We defined areas with spikes over 300 fT/cm as being an activated zone on GMFT. Based on the spike spreading area, we classified them into 2 categories: unilaterally-spreading spikes (USS), defined as the spread of epileptic activity confined within one hemisphere; and bilaterally-spreading spikes (BSS), which are epileptic activity propagating to the contralateral hemisphere. For each patient, we calculated the proportion of bilaterally spreading spikes (PBS) by dividing the BSS by the BSS plus USS

for each patient. We also measured the interhemispheric time difference (ITD) from the time of spike onset with activated GMFT spreading to the contralateral hemispheric spikes. The seizure reduction rate was calculated from the average number of seizures during the 3 months before the last follow-up. We applied the VNS-specific outcome scale proposed by McHugh et al. Patients were classified as responders if they had a ≥50% total seizure reduction rate (group A) and as nonresponders if they had a <50% total seizure reduction rate (group B). We used a Fisher exact test, Shapiro–Wilk normality test, paired *t* test, Wilcoxon signed rank test, Welch 2 sample *t* test, or Wilcoxon rank sum test. We set the level of significance at $p < 0.05$. We applied receiver operating characteristic (ROC) curve analysis to evaluate the relationship between the sensitivity and specificity of PBS pre-VNS for seizure outcomes.

Results: We analyzed MEG before VNS and clinical profiles in 15 patients (8 female). CC had been performed in 5 patients, None of the analysis based on seizure type reached statistical significance. Nine patients were categorized as VNS responders in group A. The remaining 6 patients were categorized as VNS nonresponders in group B. There was no significant difference in clinical profiles between the group of responders and nonresponders. There were significant decreases in the number of MEG spikes from pre-VNS to post-VNS among the 15 patients (median 34 and 23, $p = 0.042$). There was a significant decrease in the number of MEG spikes in group A (median 32 and 18.5, $p = 0.023$). The number of BSS of group A decreased significantly (median 22 and 5, $p = 0.03$). The preoperative PBS was significantly different ($p = 0.013$) between groups A (median 0.78; range 0–0.89) and B (median 0.01; range 0–0.5). The ROC curve analysis of the proportion of bilateral spreading before VNS and seizure outcomes between groups A and B showed that the proportion of bilateral spreading before VNS was significantly related to good seizure outcomes after VNS. The ITD post-VNS reached a significant difference in 5 patients with CC (median, 15.0 ms; range, 14–17 ms) and 10 patients without CC (median, 22.0 ms; range, 17–33 ms; $p < 0.01$).

Conclusion: The most valuable thing GMFT established was demonstrating the inter- and intrahemispheric spreading of spikes. The secondary epileptogenesis spread from the primary epileptogenesis could be dependent or independent from the primary. Frequent interictal MEG spikes propagating bilaterally on GMFT may reflect a favorable seizure outcome after VNS. GMFT can evaluate the epileptic spikes responding to VNS over the bilateral hemispheres on MEG before and after VNS, which may target the dependent secondary epileptogenesis to control generalized seizures in a subset of patients with pharmaco-resistant epilepsy. In the analysis of MEG before and after VNS implantation, GMFT successfully determined epileptic activity spreading in both hemispheres. High preoperative PBS may serve as a favorable postoperative outcome factor.