Six missense mutations were located in the S5–S6 pore regions of domain 2 or 3 in the sodium channel α1-subunit. The substitution of arginine with cysteine at codon 1638 was located in the S4 segment of domain 4. These mutations were located on important regions which play a role to generate action potentials. The part of extracellular loop which links S5 and S6 segments dips down into the membrane to form the ion pore. Some positively charged arginine residues in the S4 segment are known to be essential for the S4 segment to act as the voltage sensor, and the importance was verified by the experiment in which each of the arginine residues in the S4 segment was replaced in turn by a cysteine [22]. In addition to most missense mutations on the regions which have an important function in the electrophysiological properties of the channel [19], we found a missense mutation at codon 1899 of an intracellular C terminal region. The region may also have a basic role in spite of a distal region on the molecule, because this amino acid is highly conserved in α-subunit gene family shown in Fig. 2. In fact, patients 23 and 24 who have the mutation in C terminal region showed slight mental impairment and absence of ataxia, suggesting that location of the mutation may influence the phenotype. In the patients 8 and 17 who also showed slight mental impairment and absence of ataxia, missense mutations of phenylalanine to cysteine and of valine to methionine were detected, respectively. Both phenylalanine and cysteine belong to an uncharged amino acid group, and both valine and methionine are also members of a non-polar and hydrophobic amino acid group. The severity of clinical manifestation might depend on the amino acid produced by missense mutation in the SCN1A gene. It is very important to investigate whether the missense mutations are gain-of-function mutants, if the truncated protein functions as a dominant negative mutant, if the remaining normal gene shows haploid insufficiency in the channel protein level, or if the remaining normal gene is a functional gene in these patients.

Spampanato et al. [23] reported functional analysis of two missense mutations of the SCN1A gene in the patients with GEFS+, in which one mutation showed hyperexcitability and the other showed hypoexcitability of the sodium channel. Their results suggested that either an increase or a decrease in sodium channel activity could result in seizures. Usage of the mutations we detected may be helpful for further analysis of the mechanism.

In only 5 patients with SME, we could not find any mutations in the SCN1A gene. One of the possible reasons is that there are some mutations in the neuronal cells of brain but not in the blood cells. Another is that an expression of the SCN1A gene is decreased or none in the neuronal cells by the mechanisms such as aberrant regulation of the promoter in the SCN1A gene. However, the possibility is still remaining because the brain tissues could not be acquired from the patients with epilepsy.

We could not find the SCN1A mutations in the parents of the patients we studied. One of critical causes of SME may be de novo mutation of the SCN1A gene occurred in the course of meiosis in the germ cells of the parents. The high rate of a family history of convulsive disorders and the presence of sibling cases [20] indicate also a possibility that some mutations of other genes may be associated with the occurrence of SME. To clarify these unsolved issues, a functional analysis of the SCN1A gene and a search for new target genes in SME are required.

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The Relationship between Paroxysmal Kinesigenic Choreoathetosis and Epilepsy

Abstract

Purpose: To clarify the relationship between paroxysmal kinesigenic choreoathetosis (PKC) and epilepsy, we investigated the clinical and electroencephalographic (EEG) findings of patients with familial PKC and epilepsy, as well as sporadic cases with both PKC and epilepsy.
Patients and Methods: Patients consisted of 12 familial cases from seven families and three sporadic cases. The period of follow-up ranged from 17 months to 33 years, 7 months (average: 16 years, 8 months). During the follow-up, a total of 163 EEGs (11 EEGs per subject) were studied, including interictal and ictal EEGs.
Results: Transient epileptic discharges were found in ten of the 15 patients (66.7%) during the clinical course. As for focus, centro-midtemporal and frontal spikes were most often observed. The ictal EEG of an afebrile convulsion in one patient showed a partial seizure with secondary generalization which originated from the frontal area.
Conclusions: It appears that patients who suffer from both PKC and epilepsy have a functional abnormality of the cerebral cortex, particularly in the perirolandic and frontal regions.

Key words
Paroxysmal Kinesigenic Choreoathetosis · Epilepsy · Cortical Hyperexcitability · Cortico-Striato-Pallido-Thalamic Loop

Introduction

It has been long debated whether paroxysmal kinesigenic choreoathetosis (PKC) is a type of reflex epilepsy or an extrapyramidal disorder.

Recently, a common genetic basis of paroxysmal dyskinesia and epilepsy was shown using linkage analysis. Szepetowski et al [23] first revealed an association of paroxysmal choreoathetosis with infantile convulsions in four French families, and designated it as ICCA syndrome. Guerrini et al [9] reported on autosomal recessive rolandic epilepsy with paroxysmal exercise-induced dystonia and writer's cramp (RE-PED-WC) whose locus was mapped to chromosome 16p12 – 11.2. They suggested the existence of a group of diseases which exhibit functional abnormalities in the cerebral cortex and the basal ganglia.

In addition, a PKC locus was recently mapped to the pericentromeric region of chromosome 16 in eight Japanese families [24] and in an African-American family [4]. A second PKC locus was identified on the long arm of chromosome 16 in an Indian family [25]. These regions of ICCA syndrome, RE-PED-WC and PKC loci overlap one another.

The differences and similarities of the clinical symptoms of these disorders are now being intensely debated.

In order to clarify the relationship between PKC and epilepsy, we investigated the clinical and electroencephalographic (EEG) findings of patients with familial PKC and epilepsy, as well as sporadic cases with both PKC and epilepsy.

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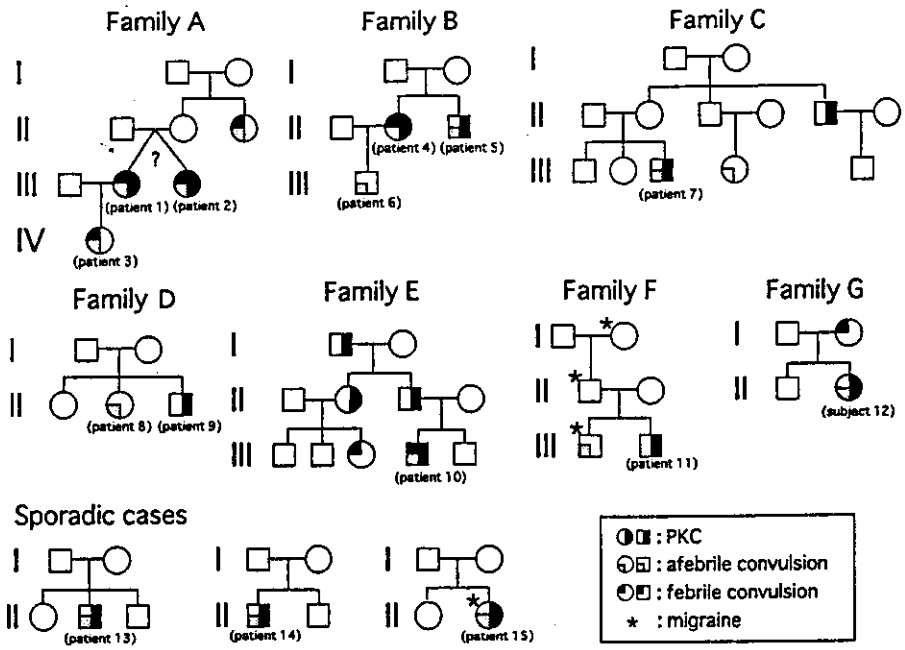

Fig. 1 Pedigrees of the families with PKC and convulsions.

Patients and Methods

Patients were drawn from individuals who were seen at the Okayama University Hospital from 1967 to 2000. They consisted of 12 familial cases from seven families, and three individuals without a family history of PKC or epilepsy. Three sporadic cases were affected by both PKC and epilepsy (Fig. 1).

The age at initial examination ranged from three months to 15 years, 11 months. The period of follow-up ranged from 17 months to 33 years, 7 months (average: 16 years, 8 months). During the follow-up, in principle, EEGs were performed once every 1–2 years on an outpatient basis. Interictal EEGs included waking and sleeping EEGs and photic stimulation. Hyperventilation was performed whenever possible. Three patients were admitted to our hospital during infancy due to frequent convulsions.

Seven patients underwent ictal video-EMG-EEG polygraphic recordings of PKC attacks during hospitalization. A total of 163 of EEGs (11 EEGs per subject) were recorded, including both interictal and ictal EEGs.

Neuroimaging studies were conducted on all but one patient (patient 8). Computed tomography (CT) was performed in four patients, magnetic resonance imaging (MRI) in six, and CT plus MRI in one. In addition, MR angiography (MRA) and single-photon emission CT (SPECT) were performed in one patient. Left middle cerebral arteriography was performed in another. The 15 patients were evaluated retrospectively with respect to clinical course and chronological changes in EEG findings.

Results

Clinical characteristics of convulsions

Thirteen of 15 patients had febrile and/or afebrile convulsions. Febrile, afebrile and febrile plus afebrile convulsions were present in one, eight and four patients, respectively. Age at initial seizure ranged from three months to 13 years, six months. Seizure frequency ranged from several times to about ten times throughout the clinical course. In four of these 13 patients (30.8%), seizure frequency was several times per day in infancy. Seizures disappeared by the age of two years in seven patients (53.8%). The oldest age of seizure remission was 14 years.

Seizure types included generalized tonic-clonic seizures in 12 patients and complex partial seizures in one patient. Two of the 13 patients (patients 12 and 15) also had PKC attacks which were immediately followed by a generalized tonic-clonic seizure. Patient 12 had choreoathetosis and muscle weakness on the right side of the body which were triggered by sudden movements. Some of these PKC attacks were immediately followed by cloudiness of consciousness and secondarily generalized tonic-clonic convulsion. Patient 15 had right upper limb dystonia which was also triggered by sudden movements. Sometimes PKC attacks gradually proceeded to the right jerky movement, cloudiness of consciousness and generalized tonic-clonic convulsions.

Clinical characteristics of PKC attacks

PKC attacks were seen in 12 of 15 patients. Age at onset ranged from three to ten years. Brief episodes of dystonic, choreic and athetoid movements were triggered by sudden voluntary movements in all patients. Precipitants included not only sudden movements, but also mental stress in three patients and coffe intake in one patient.

PKC attacks involved the bilateral extremities in three patients only one side of the body in four, the right upper extremity i one, and only one side of the body of which laterality change from time to time in four patients.

The duration of PKC attacks varied from several seconds to abou one minute. The frequency of PKC attacks ranged from severa times per week to about 50 times per day.

Table 1 Interictal EEG findings

Background activities	*No. of cases*	*(%)*
Normal	7	(46.7)
Hypersynchronous alpha rhythm	3	(20.0)
Slow posterior waves of youth	2	(13.3)
Occiptial 3–4 c/s rhythm	3	(20.0)
Epileptic discharges		
No epileptic discharge	5	(33.3)
C-mT spikes	5	(33.3)
C-mT + frontal spikes	1	(6.7)
C-mT + frontal spikes + diffuse sp-w	1	(6.7)
C-mT spikes + diffuse sp-w	2	(13.3)
diffuse sp-w	1	(6.7)

C-mT: centro-midtemporal, sp-w: spike-and-waves

With regard to prodromal symptoms, one patient (patient 13) felt discomfort in the lower extremity prior to the appearance of choreoathetosis or dystonia. Six patients (patients 1, 2, 4, 5, 11 and 12) complained of muscle weakness in the lower extremity or on one side of the body. Four patients (patients 4, 5, 11 and 12) were not able to maintain an upright posture due to muscle weakness, which was triggered by sudden movements.

EEG findings

Interictal EEGs

Background activities and epileptic discharges are shown in Table 1. Hypersynchronous alpha rhythms, slow posterior waves of youth and paroxysmal bursts of occipital 3–4 Hz rhythm [7] were blocked by opening the eyes. Hypersynchronous alpha rhythms were observed from five to 22 years of age, slow posterior waves of youth from seven to 11 years of age and paroxysmal burst of occipital 3–4 Hz rhythm from five to 17 years of age.

EEGs showed epileptic discharges in ten of the 15 patients (66.7%). These epileptic discharges appeared only transiently. In addition, they were seen in only 29 (17.8%) of 163 EEG records. As for the focus, centro-midtemporal spikes were most often observed. These spikes increased during sleep. However, the waveform differed from typical rolandic spikes (Fig. 2).

Ictal EEGs of convulsion and PKC attack:

An ictal EEG of an afebrile convulsion in infancy was recorded in one patient (patient 7). It was a partial seizure with secondary generalization which originated from the frontal region (Fig. 3).

There were no epileptic changes in eight ictal EEGs of PKC attacks in four patients (patients 4, 5, 9 and 13).

Clinical course and prognosis

A summary of chronological changes in EEG findings and clinical course is presented in Fig. 4. Of the 13 patients having afebrile or febrile convulsions, phenobarbital was effective in stopping convulsions in seven patients, phenobarbital/valproate in two patients, phenobarbital/phenytoin in one patient, and carbamazepine (CBZ) in one patient. Two patients who received no antiepileptic drugs (AEDs) showed spontaneous remission after several febrile or afebrile convulsions. In general, the response to AEDs was favorable and there were no refractory cases.

CBZ was administered to all patients with PKC. CBZ dosage was 100–600 mg per day (blood concentration ranged from 1.1 to 9.4 µg/ml). PKC attacks were easily controlled with regular CBZ medication. However, attacks returned sporadically upon cessation of CBZ administration. In patients having both convulsions and PKC attacks (patients 12 and 15), both were suppressed by CBZ administration.

At the end of the follow-up, nine patients had not experienced PKC attacks for at least one year on CBZ medication. Two patients had occasional PKC attacks when they forgot to take CBZ (patients 10 and 12). Another patient experienced a recurrence of PKC attacks when she decided to stop CBZ due to pregnancy (pa-

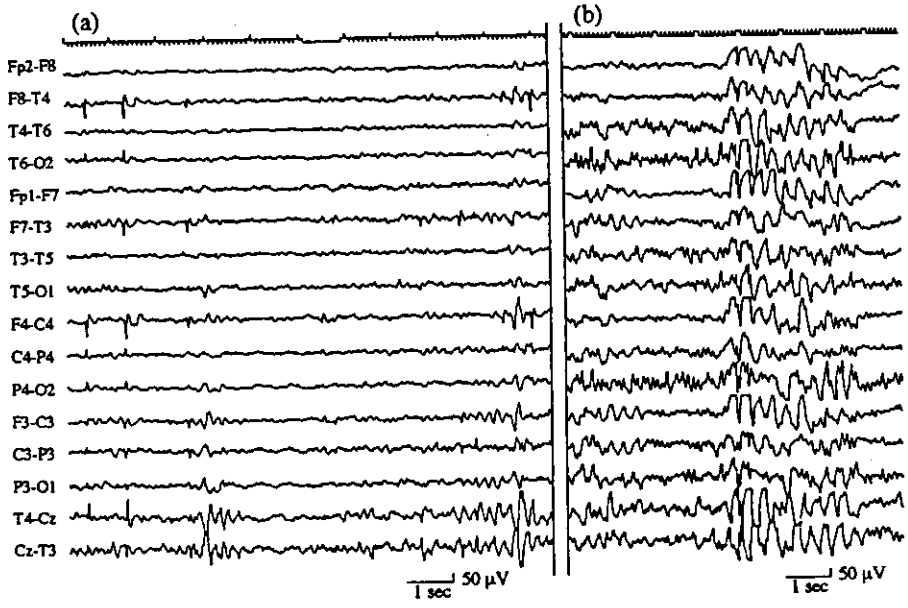

Fig. 2a and b Epileptic discharges on interictal EEGs. a Centro-midtemporal spikes in subject 14 at age seven years. b Diffuse spike-and-wave complex in subject 12 at age 10 years.

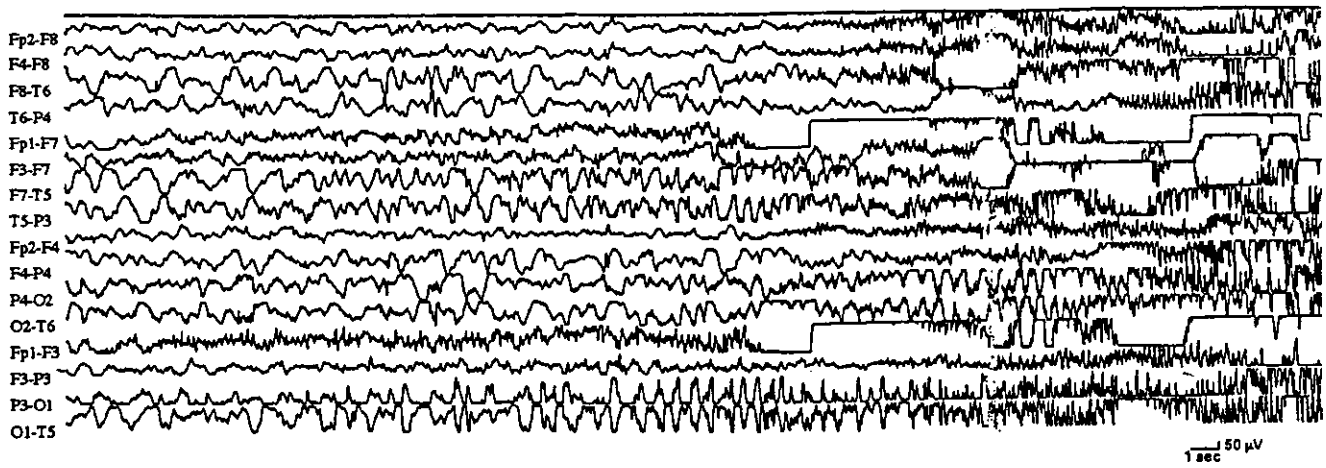

Fig. 3 The ictal EEG of an afebrile generalized tonic-clonic convulsion was seen in a three-month-old boy (subject 7). It reveals 4 – 5 Hz rhythmic spikes in the left frontal region are subsequently replaced by diffuse irregular spike-and-wave complexes. The total duration of the seizure was 110 seconds.

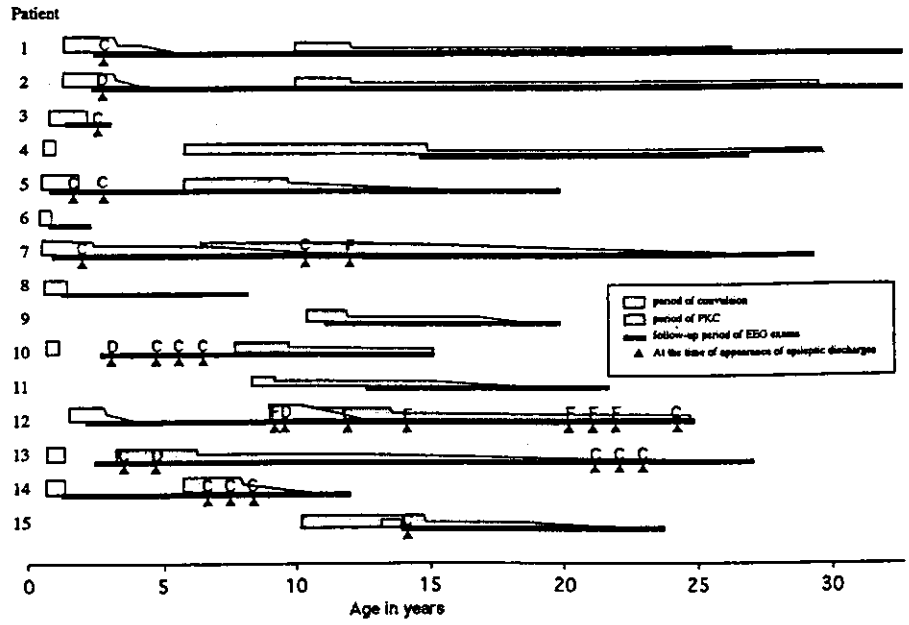

Fig. 4 Chronological change in EEG findings and clinical course. C: centro-mid-temporal spikes, F: frontal spikes, D: diffuse spike-and-wave.

tient 4). These three patients still had PKC attacks but learned to abort these attacks at the onset of the aura by stopping all voluntary movement.

Neuroimaging study

CT and MRI showed no abnormalities in our patients. Likewise, angiography, MRA and SPECT showed no abnormalities.

Other neurological manifestations

Patient 15 complained of migraines. Three family members from family F also had migraines. The brother of the patient 11 had several afebrile seizures at six months of age. At age 20, he began to have migraines with aura which were associated with ictal hemiparesis, followed by frequent vomiting and confusion lasting approximately 24 hours.

Discussion

Although the coexistence of epilepsy and PKC in the same individual or family is not rare, the characteristics of the epilepsy which occur along with PKC have not yet been fully elucidated. Nor have any long-term follow-up studies been performed on these patients. Szepetowski et al [23] reported that partial seizures or secondarily generalized convulsions occur from three to 12 months in ICCA syndrome. However, other authors reported that some patients in whom convulsions began in infancy continued to have infrequent seizures up to early adolescence or adulthood [15,22].

Our patients share clinical features with those syndromes which have been mapped to the pericentromeric region of chromosome 16.

To the best of our knowledge, there have been no reports on ictal EEGs of convulsions in a patient with PKC. Moreover, long-term follow-up studies of EEGs have not yet been carried out. We recorded an ictal EEG of an afebrile convulsion in infancy and discovered that it was a partial seizure with secondary generalization originating from the frontal lobe.

Interictal EEGs showed frontal and centro-midtemporal spikes in most of our patients. Therefore, it is likely that seizures are partial seizures of the frontal and perirolandic regions with secondary generalization in other patients who had interictal spikes in the same regions.

Epileptic discharges were observed even during the period of PKC after remission of epilepsy in our patients. Consequently, it is thought that during the period of PKC, a functional abnormality of the cerebral cortex, particularly in the frontal and perirolandic regions, continued and influenced the occurrence of PKC attacks. According to most previous studies, epileptic discharges were not found in patients with PKC [2,10,12,14]. It is possible that the epileptic discharges might have been overlooked in these studies since, in our series, epileptic discharges were seen in only 17.8% of all EEG records.

The PKC attacks of our patients showed many typical features of PKC: short duration of involuntary movement triggered by sudden movement, high frequency of attacks, and favorable response to CBZ. On the other hand, a significant number of patients showed muscle weakness triggered by voluntary movement, and inability to maintain an upright posture. Muscle weaknesses have sometimes been described as a symptom of PKC [2,14,17]. Fukuda et al reported a family with an atonic variant of PKC [8].

Four patients in whom ictal EEG-EMGs were recorded during PKC attacks revealed no changes. Many previous reports showed no EEG changes during PKC attacks [2,21] except for a few reports, in which central-dominant diffuse 12–15 Hz rhythms [18], bifrontal high-voltage slow waves at 2–4 Hz with mixed hypersynchronous alpha rhythms [13] and diffuse 5 Hz spikes [11] were reported. These changes were thought to be of subcortical origin [11].

It is necessary to understand the mechanisms of normal voluntary movement in order to comprehend mechanisms of involuntary movement. The motor circuit comprises the cerebral cortex (including the supplementary motor area, motor cortex and premotor cortex), putamen, internal and external segment of the globus pallidus, substantia nigra pars reticulata, subthalamic nucleus and thalamus [1]. There are two pathways in the motor circuit. The direct pathway functions as a positive feedback loop and generates increased cerebral cortex activity, while the indirect pathway acts as a negative feedback loop and controls its own activity. In the cortico-striato-pallido-thalamic loop, the direct pathway is considered to be relatively dominant in hyperkinetic disorders such as Huntington's chorea [6].

With regard to the mechanism in the occurrence of PKC, symptomatic patients of PKC with organic brain abnormalities have been reported. These lesions include demyelination of the putamen and thalamus in multiple sclerosis [20], calcification of the basal ganglia in hypoparathyroidism [3], infarction of the thalamus [5] and brain injury in the frontal lobe [19]. These data indicate that a pathological lesion in the frontal lobe, basal ganglia or thalamus can cause PKC attacks.

Lombroso reported the existence of ictal discharges during PKC attacks arising focally from the supplementary sensory-motor cortex and ipsilateral caudate nucleus using depth and subdural electrodes [16]. In our study, some patients experienced PKC attacks immediately followed by a clouding of consciousness and a convulsion. Some of our patients aborted a PKC attack at the onset of the aura by stopping all voluntary movements. These findings support the contention that PKC attacks are caused by a disturbance in the cortico-striato-pallido-thalamic loop.

Based on the findings in the ictal EEG of an afebrile convulsion during infancy and the existence of the frontal and centro-midtemporal spikes, we conclude that the patients who suffer from both PKC and epilepsy have the cortical hyperexcitability particularly in the frontal and perirolandic regions. A functional abnormality of the cortex in the cortico-striato-pallido-thalamic loop influence the occurrence of PKC attacks.

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Benefit of Simultaneous Recording of EEG and MEG in Dipole Localization

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Summary: *Purpose:* In this study, we tried to show that EEG and magnetoencephalography (MEG) are clinically complementary to each other and that a combination of both technologies is useful for the precise diagnosis of epileptic focus.

Methods: We recorded EEGs and MEGs simultaneously and analyzed dipoles in seven patients with intractable localization-related epilepsy. MEG dipoles were analyzed by using a BTI Magnes 148-channel magnetometer. EEG dipoles were analyzed by using a realistically shaped four-layered head model (scalp–skull–fluid–brain) built from 2.0-mm slice magnetic resonance imaging (MRI) images.

Results: (a) In two of seven patients, MEG could not detect any epileptiform discharges, whereas EEG showed clear spikes. However, dipoles estimated from the MEG data corresponding to the early phase of EEG spikes clustered at a location close to that of the EEG-detected dipole. (b) In two of seven patients, EEG showed only intermittent high-voltage slow waves (HVSs) without definite spikes. However, MEG showed clear epileptiform discharges preceding these EEG-detected HVSs. Dipoles estimated for these EEG-detected HVSs were located at a location close to that of the MEG-detected dipoles. (c) Based on the agreement of the results of these two techniques, surgical resection was performed in one patient with good results.

Conclusions: Dipole modeling of epileptiform activity by MEG and EEG sometimes provides information not obtainable with either modality used alone. **Key Words:** MEG—EEG—Localization-related epilepsy—Dipole.

The dipole localization method has been widely used for noninvasive localization of spike foci (1–3). After the development of magnetoencephalography (MEG), most comparative studies of MEG and EEG have focused on comparing the localization accuracy of MEG and EEG dipoles (4,5). We addressed the way in which dipole localization with a combination of MEG and EEG supplements the information obtainable by either technique alone. We try to show that EEG and MEG are clinically complementary to each other, and that a combination of both technologies is useful for the precise diagnosis of epilepsy patients.

PATIENTS AND METHODS

Subjects were drawn from all the outpatients and inpatients of Okayama University Hospital who were being considered for antiepileptic surgery between July 2000 and June 2001. We obtained consent from the parents of seven of these patients to perform MEG investigation at the Okayama Ryogo Center. The patients consisted of six boys and one girl (average age, 15 years and 1 month; range, 5 years and 7 months to 19 years and 2 months). All the patients had intractable localization-related epilepsy.

We recorded EEGs and MEGs simultaneously. MEGs were recorded with a 148-channel whole-head magnetometer (BTI Magnes, San Diego, CA, U.S.A.) with simultaneous 21-channel EEG recording by using the international 10-20 system with additional electrodes at Fpz and Oz referenced to the ears. The MEG and EEG sampling rates were 678.17 and 500 Hz. The MEG signal was filtered in real time with a highpass of 200 Hz and a lowpass of 0.1 Hz. EEG was filtered with 0.5–100 Hz. Common reference points (nasion, inion, and ear holes) were used for MEG, EEG, and magnetic resonance imaging (MRI) for coregistration of the data.

Both EEG and MEG outputs were monitored on real-time displays. The data epochs were visually selected by using both the MEG and EEG waveforms. We marked

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0.5- to 1-s segments that contained epileptiform spikes and were free of artifact and selected 10 to 20 of these segments to be analyzed.

MEG dipoles were calculated based on data from 37 channels selected over the region of interest. MEG dipoles were analyzed by the single-dipole model with the BTI program. In the calculations, the head was modeled as a sphere with a radius that best fit the local skull curvature at the probe positions. The skull shape was derived from a three-dimensional (3D) digitalization of the surface of the patient's scalp before the recording session.

According to the Homma's dipole theory (6), EEG dipoles were analyzed by using a realistically shaped four-layered head model (scalp–skull–fluid–brain) built from 2.0-mm slice MRI images (Real-Neurotechnology Co., Toyama, Japan). Both MEG and EEG dipoles were estimated every 2 ms, and the locations of dipoles exhibiting >0.98 correlation were displayed. The MEG dipole localizations were coregistered with MRI (1.5 Tesla, GE Co.) of the patient's brain automatically. We compared the EEG dipole localizations on MRI by visual inspection. When either EEG or MEG could not detect any clear epileptic discharges, the dipole analyses were performed at the corresponding points to the epileptic discharges found with the other technique. That is to say, EEG spikes were used to determine the MEG epoch for analyzing in cases without MEG spikes and vice versa.

We received consent to perform surgery on one of the patients mentioned in this series (case 3, described later).

RESULTS

In two of the seven patients, the EEG showed clear spikes where MEG could not detect any clear epileptiform discharges. The following is an example of such a case.

Case 1

An 18-year-old man had complex partial seizures with visual symptoms. His EEG showed focal spikes at the right occipital electrode. MEG could not detect a dipolar field at a single section corresponding to the early phase of the EEG spikes. Therefore, averaging techniques were applied to 38 MEG segments, by using EEG spikes as markers, and this produced a clear dipolar field on averaged MEGs. Dipoles estimated for this dipolar field were located in the mesial occipital lobe, which corresponded well with his clinical features (Fig. 1).

In another case, dipoles estimated from the MEG data corresponding to the early phase of the EEG spikes clustered at a location close to that of the EEG dipole (both dipoles were located in the right mesial temporal lobe). These results corresponded well with his clinical and neuroimaging data.

In two of the seven patients, EEG showed only intermittent high-voltage slow waves (HVSs) without definite spikes. MEG showed clear spikes preceding these EEG-detected HVSs. Dipoles estimated for the ascending phase of these EEG-detected HVSs were located close to the dipoles estimated by MEG. The following case is representative of these two cases.

Case 2

A 16-year-old boy had complex partial seizures with motor signs predominantly in his left arm, and secondarily generalized seizures. Interictal single-photon emission computed tomography (SPECT) revealed a hypoperfusion area in both his frontal and temporal lobes, whereas MRI revealed no abnormal lesions. His EEG showed bilateral HVS bursts in the frontal area. MEG showed clear epileptiform discharges preceding these EEG-detected HVS bursts. EEG dipoles estimated for the peak of these HVS bursts were located at the bottom of the frontal lobe, far from the MEG-estimated dipole locations. However, dipoles estimated for the ascending phase of these EEG-detected HVS bursts were located close to the location of the MEG-estimated dipoles (in the same or the neighboring gyri as the MEG-estimated dipoles; Fig. 2).

Three patients showed clear epileptic spikes on both EEG and MEG. In these cases, EEG and MEG dipoles corresponded well to each other. The following is an example of such a case.

Case 3

A 19-year-old man had complex partial seizures with vocalization followed by ballistic movement of his arms and legs. Ictal SPECT revealed a hyperperfusion area in the bottom of the left mesial frontal lobe, and MRI revealed cortical dysplasia in that area. Both EEG and MEG showed clear epileptic spikes in the bilateral frontal lobes. EEG also showed bilateral HVS bursts in the frontal area. MEG showed clear epileptiform discharges preceding these EEG-detected HVS bursts. Both dipoles estimated for the ascending phase of these EEG-detected HVS bursts and EEG epileptic spikes were located in the bottom of the left frontal mesial lobe, close to the location of the MEG-estimated dipoles (Fig. 3). Conversely, dipole analysis also was performed for other high-voltage discharges observed on MEG but not accompanied by EEG discharges. The resulting dipoles were located far from the epileptogenic area indicated by the other imaging techniques. In this case, EEG would not have accurately detected the dipole location without the information provided by MEG, and MEG would not have accurately detected the dipole location without the information provided by EEG. Thus, in this case, EEG and MEG played complementary roles in dipole analysis. Based on further data obtained by subdural and deep electrodes, surgery was performed on the patient's left

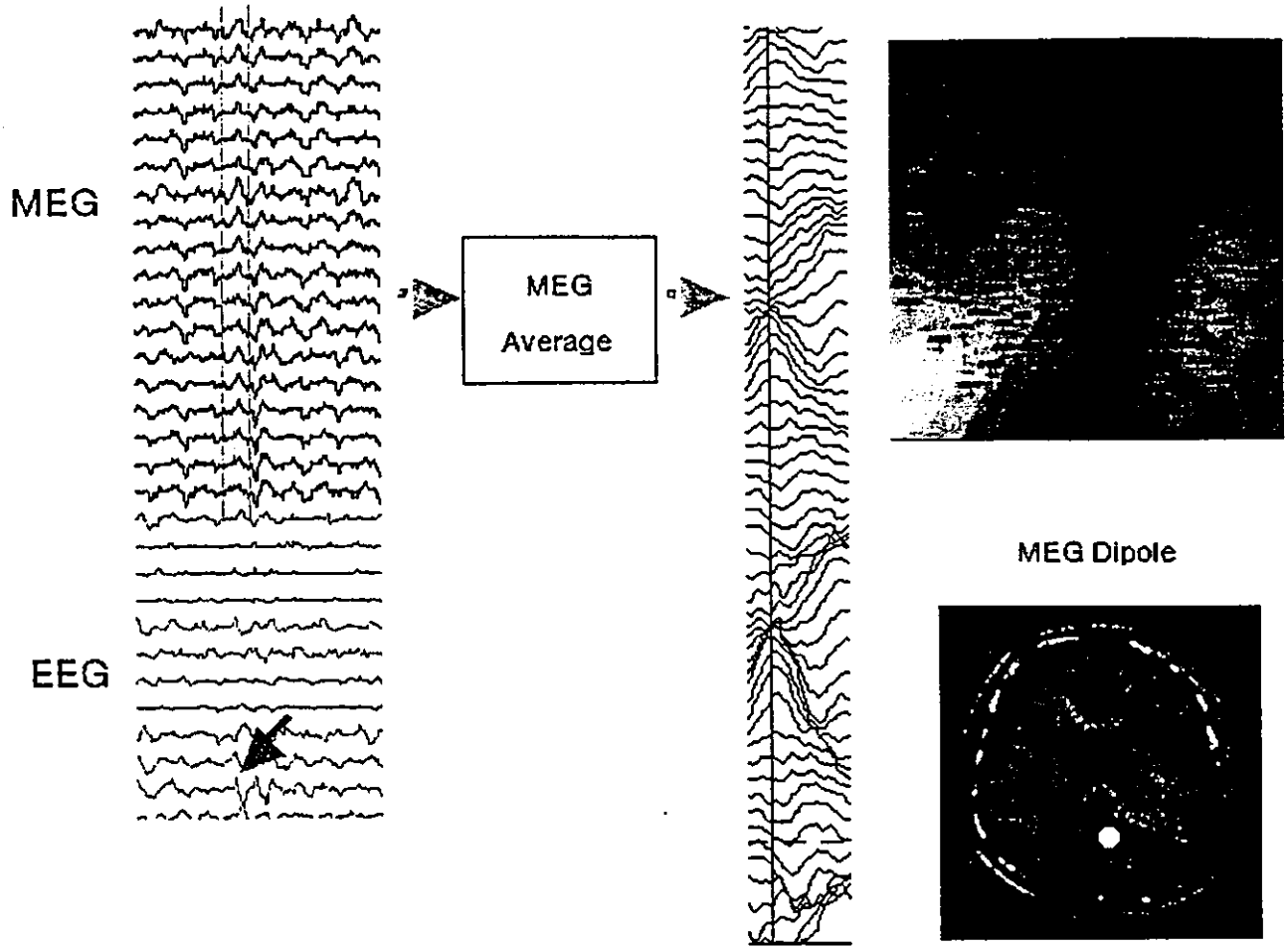

FIG. 1. EEG spike in the right occipital area (arrow, lower left). In the middle of the figure is the averaged magnetoencephalogram (MEG), which was produced by averaging 38 segments of the MEG. This yielded an apparent spike. Upper right, the topography of the averaged MEG. Lower right, the MEG dipole.

mesial frontal area at Nara Medical University. At the time of writing, the patient has been seizure free for 6 months.

DISCUSSION

When it was first introduced, EEG dipole analysis held great promise as a noninvasive method for presurgical epilepsy evaluation (1–3). However, EEG has now been overshadowed by the newer MEG technology. One reason for this is that MEG has better localization accuracy than EEG, because the signal is not distorted by concentric heterogeneities in conductivity.

The complementary nature of MEG and EEG has been described in the past 10 years (7–10). The authors of these articles pointed out that these techniques are complementary for the following reasons: (a) EEG reflects all intracranial currents, whereas MEG is sensitive mainly to tangential sources (i.e., activity of the fissural cortex); and (b) the magnetic field from sources near the center of the head falls off more quickly than the corresponding electric field; as a consequence, MEG is less sensitive to deep sources than is EEG.

In two of our seven cases, MEG could not detect any clear epileptiform discharges, whereas EEG showed clear spikes. In these cases, EEG spikes were useful for determining which MEG epoch to analyze. In case 1, the averaging procedure reduced background noise and produced the dipolar field in MEG. It would have been impossible to know which sections to analyze and average without the EEG information.

In contrast, in another two of our seven cases, EEG showed only intermittent high-voltage slow waves (HVSs) without definite spikes, whereas MEG showed clear spikes preceding these EEG-detected HVSs. Dipoles estimated for the ascending phase of these EEG-detected HVSs were located at a location close to that of the MEG dipoles.

Nakasato et al. (11) found that EEG sometimes inaccurately detected dipoles in an area deep in the base of the skull, significantly displaced from where MEG indi-

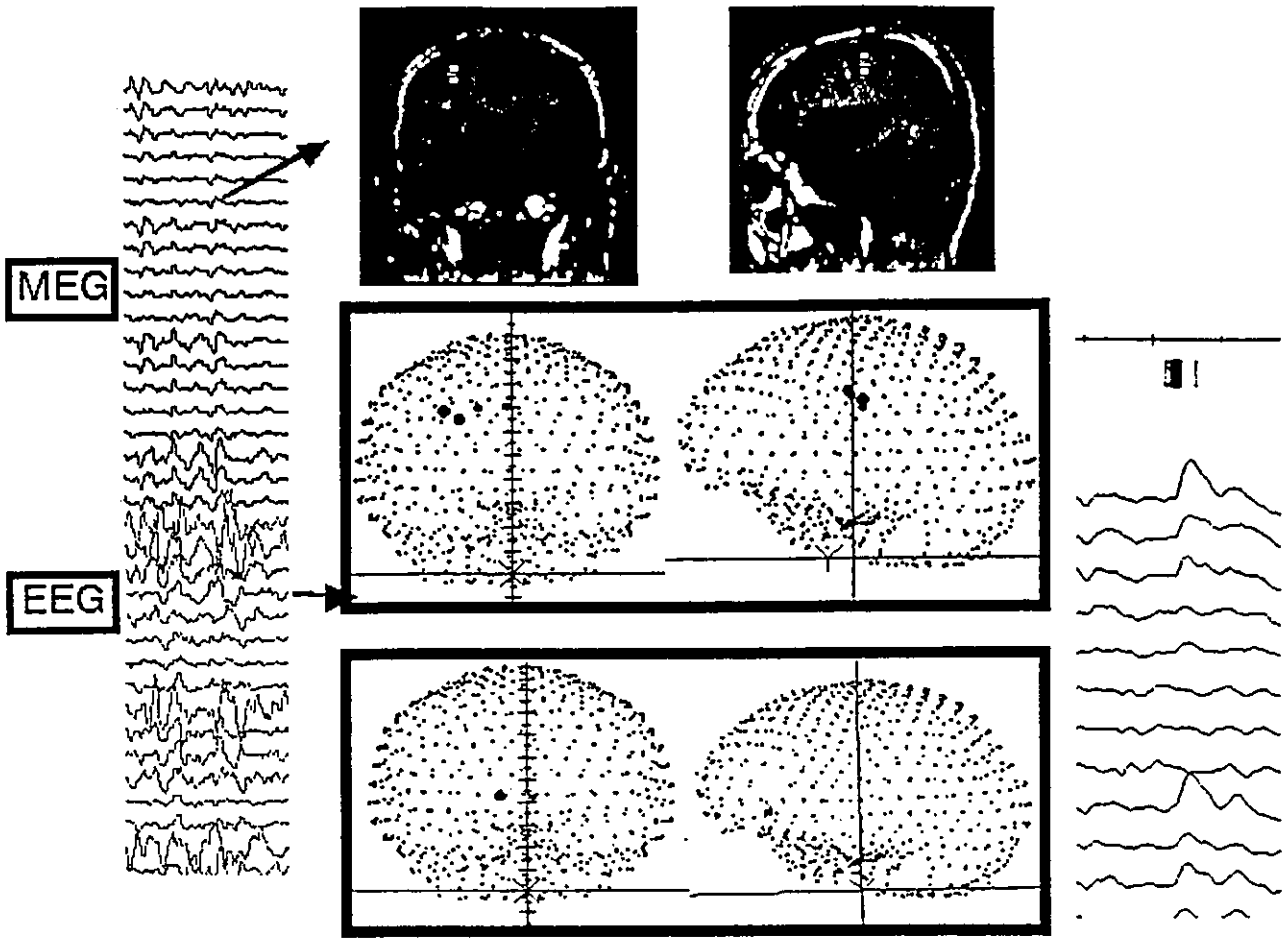

FIG. 2. The upper portion of the figure shows magnetoencephalography (MEG) dipoles. The middle shows EEG dipoles estimated at the ascending phase of the high-voltage slow waves (HVSs). The lower shows EEG dipoles estimated at the peak of the HVSs. The lower right portion of the figure shows EEG-detected HVSs. The colored area was investigated for EEG dipoles.

cated these lesions to be. The reason for this disparity could be the wide spread of the radial EEG pattern, where one polarity covers the entire upper hemisphere in the spherical EEG model. In our cases, the HVS peaks might have been the result of widespread electrical activity. Thus the EEG dipoles at the peaks of the HVSs were located at the bottom of the frontal lobe.

Some authors found that MEG peaks preceded the main EEG peak by 9–40 ms in some patients (12,13). Therefore they emphasized the importance of modeling the early phases of EEG spikes when localizing interictal epileptic zones. Epileptic spikes commonly propagate, and both magnetic and electric fields change over the course of the spike. Minami et al. (13) explained this propagation based on findings that MEG and EEG spikes propagate in a similar manner to somatosensory-evoked magnetic field (SEF). Ochi et al. (10) also showed how differences between the orientation of EEG and MEG dipoles could explain time differences between the two dipoles. Because magnetic fields can lead or lag EEG fields, depending on the orientation of the initial source cortex and that of the cortex to which the spike propagates, it is important to model the early fields, which more closely reflect the actual spike origin.

In our case 2, the epileptogenic focus would have been incorrectly estimated if dipole analyses were performed only at the peak of these HVSs without the information provided by MEG. In addition, we sometimes encountered patients who showed no definite epileptic spikes but only paroxysmal HVSs on EEGs. The results indicated by EEG dipoles of these HVSs, which corresponded well to MEG spike dipoles, suggest that these HVSs point to the true location of the epileptogenic zone.

Conclusion

In at least five of our cases, the combination of MEG and EEG dipole analysis provided information that would not have been obtained by use of either modality individually. In one case, combined use led to successful localization for surgery.

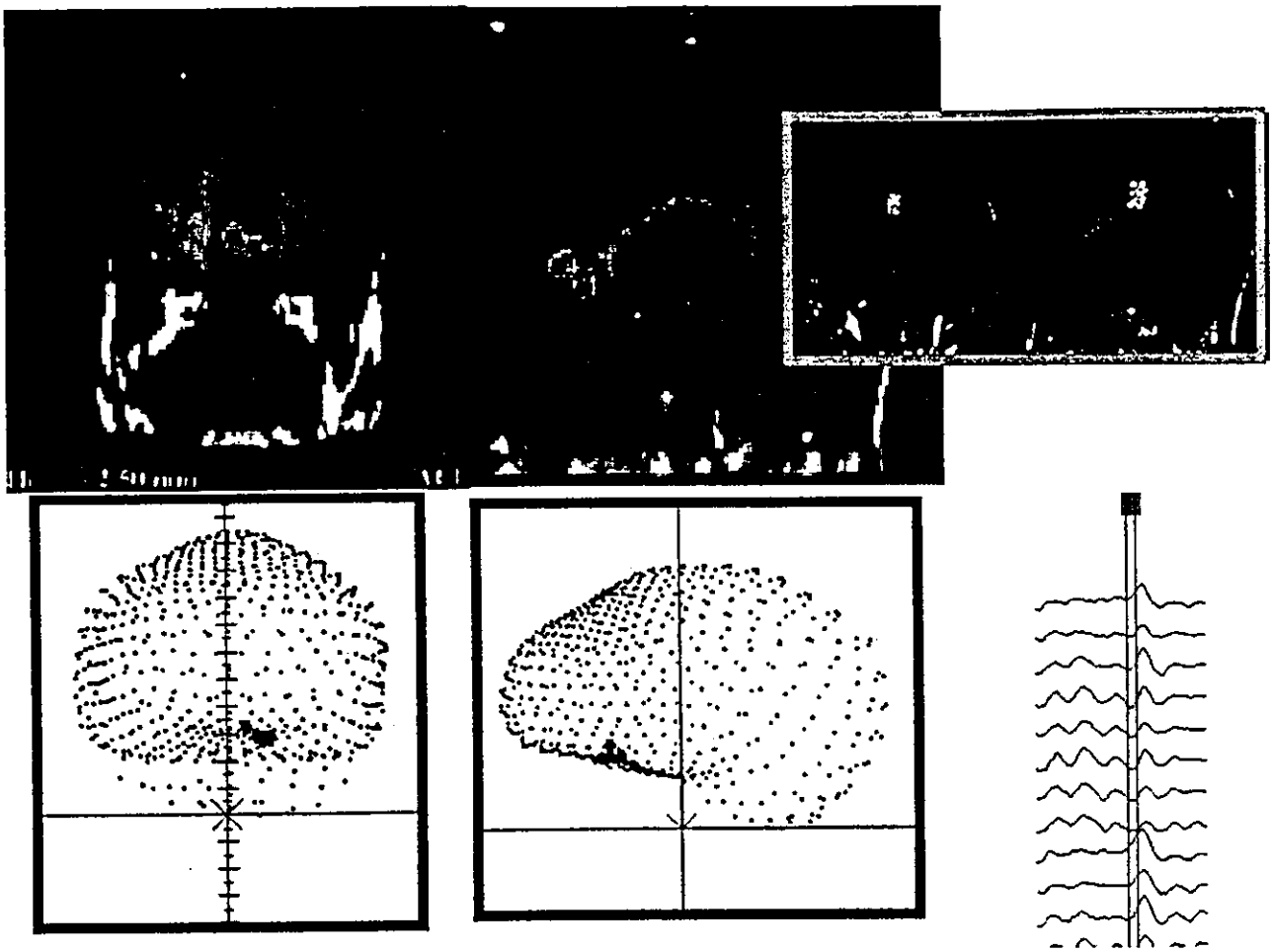

FIG. 3. The upper portion of the figure shows magnetoencephalography (MEG) dipoles estimated for MEG spikes corresponding to EEG spikes. The lower shows EEG dipoles estimated at the ascending phase of the high-voltage slow waves (HVSs). Upper right, MEG dipoles estimated for high-voltage discharges on MEG, not associated with EEG spikes. Lower right, EEG-detected HVSs. The colored area was investigated for EEG dipoles.

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脳と発達　2002：34；23—29

＝原著論文＝

Pentobarbitalやmidazolamの持続静注から離脱困難な難治性てんかん発作重積に対する非経静脈的phenobarbital大量療法

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要旨　難治性のてんかん発作重積または群発（refractory status epileptics, RSE）に対して，欧米ではphenobarbital（PB）の静注による超大量療法の有効性が報告されている．我々は，midazolam（MDL）やpentobarbital（PTB）の持続静注から離脱困難なRSEに対して，PBの筋注または坐薬による大量投与を行い発作を完全にコントロールし，持続静注から離脱できた．意識レベルや脳波所見は早期に改善した．PB大量投与による呼吸抑制や血圧低下は軽度であったが，γ-GTPが上昇した．

MDLやPTBの持続静注で効果不十分なRSEに対して，PBの静注剤のない日本でも，非経静脈的PB大量療法が，効果，副作用の点から勧められると考えた．

見出し語　難治性けいれん重積，非経静脈的phenobarbital大量療法

はじめに

てんかん発作重積または群発を止めることは，神経学的予後を決める上で，大変重要である．Diazepam（DZP）やphenytoin（PHT）の静注，バルビツール系薬剤の投与でけいれんが止まらない難治性の場合，midazolam（MDL）やpentobarbital（PTB）の持続静注が勧められている[1~5]．しかし，これらの持続静注でもけいれんを完全にコントロールできなかったり，一時けいれんがおさまっても減量によりけいれんが再発し，持続静注から離脱困難な例がある．これらの点滴静注の効果は即効性があり，強力であるが，呼吸抑制，血圧低下などの副作用がおこりやすく[2,3]，呼吸管理や中心静脈確保，昇圧剤使用，burst suppressionパターンにするための頻回の脳波モニタリング等の集中管理が必要である[4,5]．

一方，欧米ではてんかん発作重積に対して，静注によるphenobarbital（PB）の超大量療法の効果が報告されている[6,7]．日本には，PBの静注剤はなく，けいれん重積に対するPBの超大量療法は一般には行われていない．今回，我々は，MDLやPTBで発作が十分コントロールできなかったり，減量に伴いけいれんが再発するため持続静注の離脱が困難なてんかん発作重積または群発例に対して，PBを筋注や坐薬で非経静脈的に大量に使用し，その効果をみた．なお，症例1を除いて，PBを大量に投与することに関して，考えられる副作用を含めて事前に親に説明し，同意を得た（症例1は，両親がおらず，付き添う家族もいなかったため，叔父と弟に対して具体的な説明は事後に行った）．表1に3症例のまとめを示す．

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I　症　　例

症例1　36歳，女性（図1）．

菌状核赤核淡蒼球ルイ体萎縮症．寝たきりで経管栄養を行っている大島分類1の重症心身障害者．てんかん発作は今回の重積まで数カ月に1回位の頻度であり，valproate（VPA）800 mg/日と clonazepam（CZP）6 mg/日でコントロールされていたが，インフルエンザウイルス感染罹患後の平成11年1月25日（第1病日），突然眼球偏位し，口角口唇の振戦，手指のミオクローヌスの後に両上肢の強直間代けいれんの重積状態となった．DZP, PHT, PTB の静注および MDL の点滴静注（0.3 mg/kg/hr）でけいれんが止まらず，挿管後 PTB の点滴静注を 2 mg/kg/hr で

表1　PB 大量療法を行った3症例のまとめ

	症例1	症例2	症例3
年齢・性	36歳・女性	5歳・男児	11カ月・男児
原疾患	DRPLA	脳炎後てんかん	皮質形成異常
発作症状	眼，口の発作 両上肢強直間代	眼，口の発作 左上肢間代	眼，口の発作 無呼吸
重積に対して使用した静注剤	DZP, PHT	DZP, PHT	PHT
MDL の使用量	0.3 mg/kg/hr	0.2 mg/kg/hr	0.4 mg/kg/hr
PTB の使用量	2.0 mg/kg/hr	6.0 mg/kg/hr	未使用
PB 大量療法開始時期	重積開始後5日	重積開始後5カ月	痙攣群発後1日
PB 最大投与量	1200 mg	200 mg	300 mg
（1日量）	25 mg/kg	13 mg/kg	33 mg/kg
投与法	筋注	筋注，坐薬	筋注，坐薬
重積離脱時期	PB 大量後1日	PB 大量後2日	PB 大量後5日
痙攣消失時期	PB 大量後2日	PB 大量後7日	PB 大量後10日
（その時の PB 血中濃度）	（58μg/ml）	（50μg/ml）	（52μg/ml）
PB 最大血中濃度	76μg/ml	84 μ/ml	73μg/ml

DRPLA：菌状核赤核淡蒼球ルイ体萎縮症，MDL: midazolam, PTB: pentobarbital, PB: phenobarbital, DZP: diazepam, PHT: phenytoin

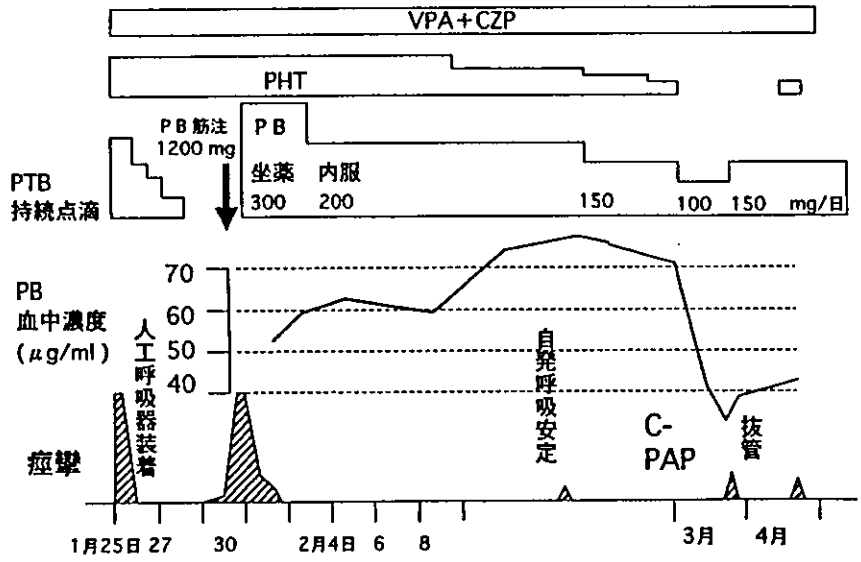

図1　症例1の臨床経過（本文参照）
C-PAP：呼吸器による持続陽圧呼吸

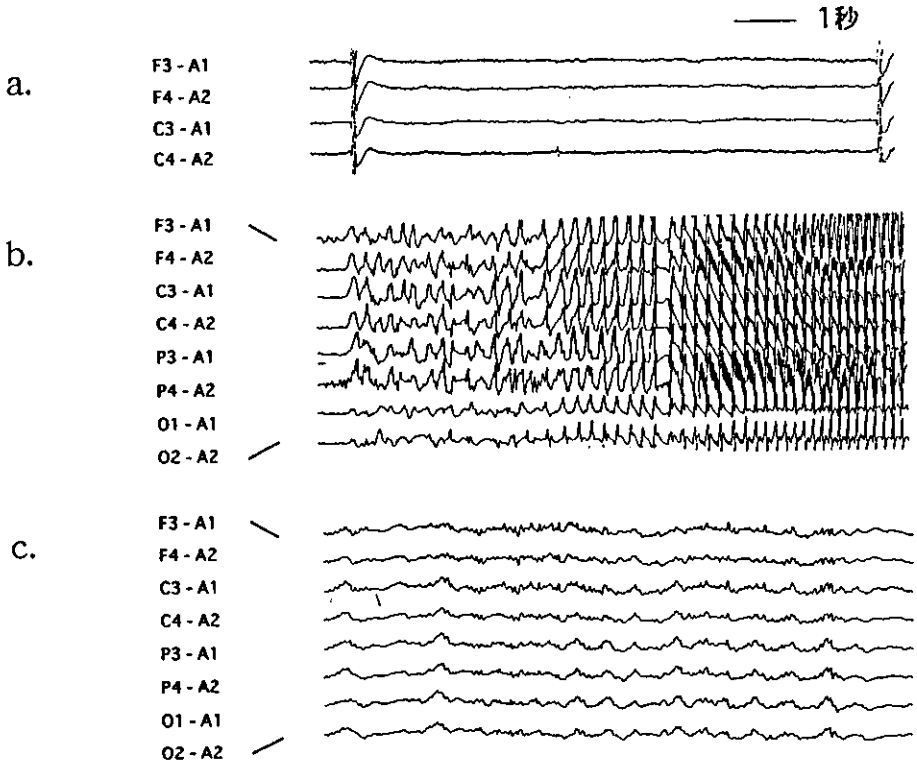

図2　症例1の脳波

a. 重積後PTB持続投与中，発作間欠期．脳波はburst suppressionパターンを示した．
b. PTB中止後1日，発作時．全般性の棘徐波複合が出現した．
c. PB大量投与後（PB血中濃度60 μg/ml），発作間欠期．発作波はほぼ消失し，背景波も改善した．

行い，けいれんが消失した．自発呼吸が消失したため，人工呼吸管理を行った．翌日，収縮期血圧が80 mmHgとなり，尿量の減少も見られたため，昇圧剤（ドーパミン最大7μg/kg/min）の投与を行った．脳波で，burst suppressionパターン（図2a）が持続したため，PTBを徐々に減量して，第4病日中止した．翌第5病日は昇圧剤を中止できたが，けいれんが再現した．脳波所見は発作間欠期にburst suppressionとなったが，発作時には全般性の棘徐波複合（図2b）が出現した．その後，徐々にけいれんが頻発し，第6病日，約5～10分毎に，口角よりはじまる左上肢の間代けいれんが群発した．PTBを再開すると持続静注が長期化し，呼吸と血圧のコントロールに苦慮することが予想されたので，代わりにPB100～200 mgを筋注で1～2時間ごとに投与した．14時間に計1,200 mg（25 mg/kg/day）を大量投与し，けいれん群発より離脱できた．翌日（第7病日）よりPBは坐薬で300 mg/日投与し，けいれんは間欠的に出現していたが，第8病日より，けいれんが全く消失した．第9病日のPB血中濃度は58 μg/mlであった．翌日より，PBは200 mg/日の内服とした．PB大量投与11日目（第16病日）の脳波では，背景波が改善し，てんかん性突発波は消退した（図2c）．その後，PBの血中濃度は第26病日に76.0μg/mlまで上昇したが，昇圧剤を必要とする血圧低下はなかった．PTB使用時からの呼吸抑制は，PBの血中濃度上昇にもかかわらず，徐々に軽減し，PBの血中濃度が70μg/ml以上でも，自発呼吸が安定した．呼吸器が離脱可能な状態であったが，持続陽圧呼吸で約1カ月間様子をみて抜管した．PBの減量中，時々の発作によりPBを一時的に増量することはあるが，けいれん重積は，起きていない．なおγ-GTPが50～100U/l（正常値：4～43U/l）と軽度上昇した．

症例2　5歳，男児．

脳炎後の難治性てんかん．ねたきりで経管栄養を行っている大島分類1の重症心身障害児．脳炎発症当初の平成10年9月より，けいれん重積または群発が長期間持続しており，前医でDZP, PHT, MDL, lidocaineの静注および様々の抗けいれん薬（PB, VPA, PHT, CZP，抱水クロラール，zonisamide）を使用したが効果なく，呼吸器管理下のPTBの点滴静注（最大6 mg/kg/hr）で重積は頓挫したが，PTBを中止すると再燃し，離脱できなかった．平成11年1月，当科に転院した後も眼球偏位し，左上肢を間代するけいれんが数分ごとに群発した．脳波では，右中心部または頭頂部に先行部をもつ多棘波の2次性全般化が頻発して見られた．PHT静注やMDLの持続点滴（0.2 mg/kg/hr）はある程度効果があったが，発作を完全消失させることはできなかった．同年2月にPBを筋注および坐薬で100～200 mg（6～13 mg/kg/day）を投与した後，3日目にけいれんの頻度が著明に減少した．PB投与7日目のPBの血中濃度は50μg/mlで，8日目にけいれんが消失した．PBの血中濃度はその後さらに上昇し最大84μg/mlまで上昇したが，血圧低下や呼吸抑制はなかった．また，PBが高濃度のうちから覚醒し刺激に対する反応性も改善した．PBの血中濃度の低下に伴い，てんかん発作の再発傾向を認めたが，PBを増量し60μg/mlを超えると，けいれんが抑制された．PB開始後まもなくよりγ-GTPの高値（321～720U/l）を認め，PBの影響が考えられた．大量投与から離脱するために，臭化カリウムを併用したが，十分な効果が得られていない．

症例3　11カ月，男児．

右前頭葉皮質形成異常．定類なく追視がはっきり

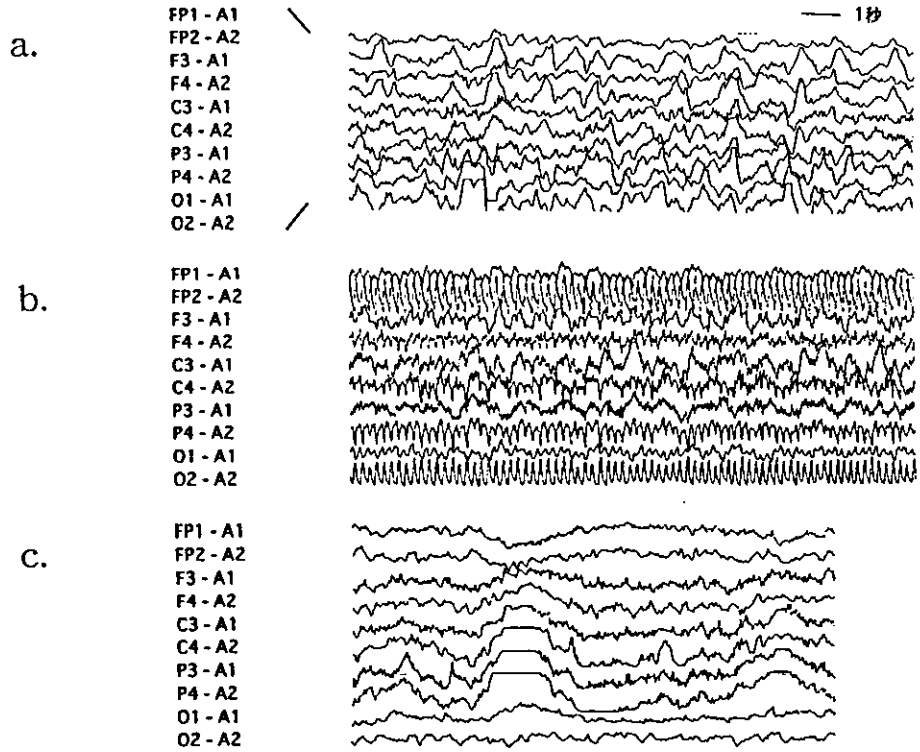

図3　症例3の脳波

a．重積前，発作間欠期．右前頭部優位に，高振幅徐波が目立つ．

b．重積中，PB大量投与後（PB血中濃度23 μg/ml）．右側に多棘波が持続した．

c．PB大量投与後（PB血中濃度52 μg/ml），発作消失時．脳波上のてんかん性放電もほぼ消失した．背景波も，重積前aに比べて，徐波傾向が消失するなど改善した．

しない大島分類1の重症心身障害児．難治性のてんかん発作は臭化カリウムでコントロールされていたが，平成12年2月，眼球偏位，動作停止し，無呼吸となる発作が30分に1回以上の頻度で群発した．MDLの持続点滴（最大0.4 mg/kg/hr）で，発作の頻度が減少したが，数時間に1回の頻度で発作が持続するため，PB 8 mg/kg/dayの内服を開始した．2日目，PBを坐薬や筋注も含めて計19 mg/kg/day投与した後，けいれんの重症度が軽減し，5日目，PB 300 mg（33 mg/kg/day）を主に坐薬で投与した翌日，けいれんが著減したが，その時のPB血中濃度は52 μg/mlであった．11日目（PBの血中濃度は同じ），けいれんが全く消失した．脳波では，重積前に見られた左右差を伴う高振幅徐波や棘波が消退した（図3）．その後，PBの血中濃度は73μg/mlまで上昇したが，呼吸抑制や昇圧剤を要する血圧低下を認めなかった．血中濃度の上昇時に，眠気が強く見られたが，覚醒時には自発運動が活発化するなどの症状の改善を見た．その後PBを内服の維持量としたが，PBの血中濃度の低下に伴い，けいれんの再発傾向があり，そのつどPBを増量している．なお，γ-GTPの高値（57～114U/l）が持続している．

II 考　　察

Crawfordらは難治性てんかん重積に対するPBの超大量療法（VHDPB）の有効性を初めて報告した[6]．けいれん重積の治療で，PBの静注剤を用いてPBの血中濃度を60μg/ml以上を要した48例50回に対し，けいれんが止まるまでPBを30分ごとに10 mg/kgを静注し24時間で30～120 mg/kg（平均60 mg/kg）を投与するbolus VHDPBを40例42回で，40 mg/kg/dayの静注を5日間連続投与するnonbolus VHDPBを8例で行った．この報告では，難治性のてんかん重積48例50回全てに効果があった．最高血中濃度は70～344（平均114）μg/mlと非常に高値であったが，血圧低下は容易にコントロールでき，呼吸抑制も一時的で，人工呼吸器を使用していた例でも早期に離脱できた．

VHDPBは，PTBの点滴静注に比較してburst suppressionにするための脳波の頻回モニタリングが必要でなく，その効果は臨床的に確認しやすいこと，また，昇圧剤を必要とする血圧低下がまれにしかおきないことより，PTBの持続静注より，好ましい治療である[7]との意見が出ている．

以上の報告より，RSEの治療としてVHDPBは有効な治療法の一つであると考えられるが，効果が出現するまでに数時間から数日かかるため，即効性という点ではMDLやPTBの持続静注に劣り，RSEの第一選択にはなりえない．

しかし，RSEに対してPTBの持続静注を行い，ある程度の効果を認めたが，減量によりけいれんが再発する場合に，VHDPB（血中濃度として220～290μg/ml）を行い，PTBの持続静注から離脱できた報告がある[8]．従って，MDLやPTBの持続点滴で，けいれんのコントロールが不十分であったり，効果はあったが，減量または中止により再発する持続静注からの離脱困難例では，PBの大量投与は次の選択肢にあげて良い治療法と考えられる．

日本では，PBの静注剤がないためにVHDPBは，一般に行われていない．しかし，PBの筋注製剤や，坐薬は市販されており，これらの製剤を使用して，PBの血中濃度を早期に高濃度に上げることは可能であると考えられる．

今回提示した，3症例は，当院に入院した，難治性のてんかん重積または群発の患者であり，MDLやPTBの持続静注でもコントロールが不十分で，効果があっても減量によりけいれんが再発する離脱困難な例であったが，いずれもPBの筋注または坐薬による大量投与が著効し，投与後1～5日で重積から離脱でき，2～10日でけいれんが消失した（表1）．昇圧剤が必要な血圧低下はなく，PB投与前に人工呼吸管理をしていた症例1を除いて呼吸抑制もなかった．症例1でも，PBが高濃度のうちから呼吸抑制は改善した．眠気は，全例でPBの血中濃度の上昇時に強く見られたが，PBの血中濃度が安定してからは，徐々に軽減し，意識レベルの改善が見られた．それ以外の副作用として，γ-GTPの上昇が見られたが，肝トランスアミナーゼは正常で，PBを中止する必要はなかった．PTBとは異なり，PBでは高濃度でも，脳波でburst suppressionパターンは示さず，てんかん性の突発波は消退し，背景波の改善も認められた．

このように，欧米で行われている静注剤によるVHDPBのかわりに，筋注剤や坐薬によるPB大量投与も，難治性のてんかん重積に安全で，かつ十分効果があることが示された．

PBの血中濃度が最大となる時間は，坐薬では投与後30～60分，筋注では投与後1～2時間とされている．坐薬は即効性で優位な反面，吸収性が不安定な時もある．それゆえ，本人の状態を見ながら，筋注，坐薬のいずれかを使用し，その1～2時間後に呼吸抑制，血圧低下がなければ，再投与を可能とすると決めると，比較的安全に大量投与が可能と思われる．

当科では，その後もPTBやMDLに加えてthiopentalの持続静注から離脱困難な難治性のてんかん発作重積に対しても，非経静脈的PB大量療法を行い，効果を得ている．追加例の，重積離脱時のPB血中濃度は，50～70μg/mlであった．その際，著しい呼吸抑制や血圧低下はなかった[9]．

PBのてんかん重積に対する効果は，PTBのような麻酔作用によるものではなく，抗けいれん作用にあると考えられる[9]．それゆえ，PTBなどの麻酔剤に比較して，意識や脳波所見の改善が早く，臨床的にその効果を評価しやすいと考えられる．

PBの大量療法に関しては，超低出生体重児や満期新生児仮死児の後遺症の予防としての効果も研究報告されている[10][11]．PBの投与量は初日30～40 mg/kgで行われているが，問題となる副作用はなかった．従って，新生児期からPBの大量療法は，使用可能と思われる．新生児期の脳内出血予防効果の説明として，動物実験（ブタ）の結果より，PBは体血圧が変動しても，脳血流を一定に保つ作用があるためであるとの説明がある[12]．

PB大量投与の問題点としては，本症例3例とも，内服の維持療法に変更後，PBの濃度が低下すると，けいれんが再発する傾向を認めた点である．いずれもPBを再び増量することで，てんかん発作の重積は避けることができたが，PBの高濃度治療からの離脱に時間がかかっている．今後，PB大量療法からも離脱困難となった場合，どう対処すべきかが検討課題である．臭化カリウムによりPB大量投与から離脱できた報告[13]もあるが，本症例2では奏効は見られず，症例3ではすでに臭化カリウムを使用していたが，離脱困難であった．本報告では懸念された副作用がγ-GTPの上昇のみで，PBの継続には問題がなかったが，症例数を増やした場合，中止を余儀なくされる副作用も出現するかもしれない．過去の報告では再生不良性貧血の報告[13]もあることから，注意が必要である．また，今回の3症例はいずれも重症心身障害児（者）であり，この治療法が日常生活可能なてんかん児に対して情動・学習面での影響はどうかなど不明確であり，現段階では，対象を選んで試みられる治療と思われる．

結論として，本報告により，難治性のてんかん重積やその後のけいれん群発に対して，筋注や坐薬によるPB大量投与は，効果が期待でき，管理も容易なことが示された．今後，症例数を増やして，より適切なプロトコールが作成されれば，日本でも選択可能な治療法になると考えられた．今後，PB大量投与による合併症や神経学的長期予後についても，詳細に検討していく必要がある．

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Non-Intravenous High-Dose Phenobarbital Therapy for Status Epilepticus Refractory to Continuous Infusion of Midazolam or Pentobarbital: Report of Three Cases

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The management of refractory status epilepticus (RSE) is crucial in preventing neurologic impairment. Although a variety of treatments for RSE including continuous infusion of midazolam (MDL) or pentobarbital (PTB) have been carried out, they are not always effective. Intravenous very-high-dose phenobarbital (PB) has been recommended as having many advantages in the United States, but is not available in Japan.

We treated 3 patients suffering from long term RSE with non-intravenous high-dose PB (NIHDPB). Their seizures were not controlled by continuous infusion of MDL and/or PTB. PB was initially given intramuscularly or rectally and then orally. Within a few or ten days, seizures were completely controlled, and consiousness level gradually improved in all cases. The serum levels of PB at seizure control ranged from 50 to 58 μg/ml. The epileptiform activities on EEG nearly disappeared in the absence of the burst suppression pattern. Hypotention and respiratory depression did not develop during NIHDPB. Elevated gamma-GTP levels with normal hepatic transaminases were seen in all cases, but it was not necessary to discontinue NIHDPB. NIHDPB may be one of the most effective and safe treatments in Japan for status epilepticus refractory to continuous infusion of MDL or PTB.

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