This observation may render new insight into epileptogenesis and provide additional information concerning the epileptogenic zone as well as prediction of epileptic seizures.

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Electroencephalography (EEG) is essential for assessing patients with epilepsy. Conventionally, EEG is usually analyzed at a narrow frequency band ranging from 0.5Hz to 70Hz. However, brain activities beyond the conventional frequency range, such as high-frequency oscillation (HFO) ranging from 100Hz to 500Hz,[1,2] very high frequency oscillation (VHFO)[3] (over 1,000Hz), infraslow brain activity,[4] and ictal direct current shift (IDS)[5] have also been observed. In recent years, these unconventional EEG findings have remained a topic of intensive investigation for their clinical significance.

We first report here a distinct ictal electrophysiological activity in the infraslow band, which was detected in 3 patients with refractory neocortical epilepsy by means of subdural electrodes. It was characterized by very early occurrence before the clinical seizure onsets, periodical appearance of slow negative baseline shifts, gradual evolution in amplitude, frequency, and distribution, and disappearance soon after the clinical seizures. Since it was distinguishable from any previously known ictal EEG patterns, we named it "ictal very low frequency oscillation" (VLFO) to highlight its unique neurophysiological features.

Patients and Methods

We investigated 26 patients with intractable neocortical epilepsy who underwent presurgical evaluation with subdural electrodes because noninvasive investigations could not delineate their epileptogenic zone (EZ), between July 2004 and June 2009 at the Shizuoka Institute of Epilepsy and Neurological Disorders. A low-frequency filter of 0.016Hz, which was in accordance with a time constant (TC) of 10 seconds was used during recording in these patients.

We used a digital EEG machine (Neurofax, Nihon-Koden Corp., Tokyo, Japan). The invasive electrodes were placed according to the clues indicated by noninvasive studies. Each subdural electrode was 2.3mm in diameter, linearly arrayed, made of platinum-iridium alloy, and with a center-to-center electrode distance of 10mm (Ad-Tech Medical Instrument Corp., Racine, WI). Recording sessions started 1 week after the implantation of electrodes, and lasted for 2 weeks.

The parameters for the conventional analysis of EEG are TC of 0.1 second, high frequency filter (HFF) of 70 Hz, and 10 seconds per epoch of EEG display. To pick up very slow periodic electrical potentials, we evaluated the EEG with TC of 10 seconds and a highly compacted EEG display with 5 minutes per epoch (30 times the routine EEG display). For each patient, a 2-hour EEG window with 1 hour before and 1 hour after the clinical seizures, and 5-hour continuous interictal EEG was evaluated.

Results

Among 26 patients, only 3 patients clearly demonstrated VLFO (Figs 1–3, Supporting Fig S1D, and Supporting Figs S2–S4). Patient 1 was an 18-year-old female, having drug-resistant seizures including simple partial seizures (SPS) manifesting focal motor symptoms and secondarily generalized tonic-clonic seizures (sGTC) since 2 years of age. Her brain magnetic resonance imaging (MRI) showed increased signal intensity on the right parietal cuneus in fluid attenuation inversion recovery (FLAIR) imaging. The scalp EEG demonstrated interictal low-amplitude spikes or sharp waves over the right parietal area. Ictal discharges started with low-amplitude slow waves over the right occipital and posterior temporal areas. Patient 2 was a 30-year-old female whose seizures occurred at the age of 16 years. Her seizures, including auras manifesting as complex auditory symptoms, complex partial seizures (CPS), and sometimes followed by sGTC, were refractory to antiepilepsy drugs (AEDs). Her brain computed tomography (CT) and MRI were normal. Scalp interictal EEG showed epileptiform discharges in the left anterior temporal area, and ictal discharges started with 6Hz, theta activities over the left anterior temporal area, evolving into the surrounding areas. Patient 3 was a 23-year-old male having seizures since 12 years of age. His refractory CPS started with the eyes and head turning to the left side, sometimes followed by sGTC. Surface interictal EEG showed intermittent spikes over the right frontal, temporal, and parietal lobes dependently, while diffuse ictal discharges were found widely over the right hemisphere. His brain MRI showed mild increased signal intensity in the right frontal inferior sulcus in FLAIR imaging (see Fig 3).

During intracranial EEG monitoring, 9 SPS and 7 sGTC in Patient 1; 2 SPS, 4 CPS, and 2 sGTC in Patient 2; and 4 CPS and 11 sGTC in Patient 3 were captured and analyzed in total.

With highly compacted EEG display and long TC of 10 seconds, very slow, irregular, low-amplitude baseline fluctuations were found during the interictal period. However, there was no regular, periodic, or evolving pattern (see Supporting Fig S1B). In contrast, VLFO were clearly identified only prior to CPS (8/8 seizures) and sGTC (20/20 seizures) but not SPS (0/11 seizures) in these 3 patients. The pattern of VLFO was homogenous, but with variation of time duration and amplitude

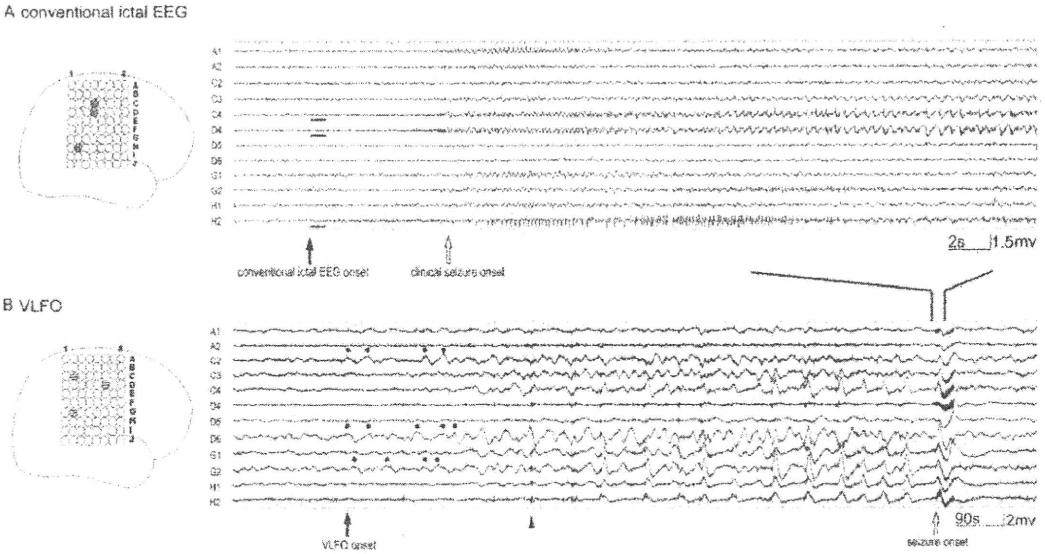

FIGURE 1: Ictal EEG changes during one sGTC with schematic location of electrodes in Patient 1. (A) Conventional ictal discharges (a TC of 0.1 second, HFF 70Hz) started with low amplitude, followed by fast activities originating from C4, D4, and H2 *(black arrow and bold lines)* 6 seconds before clinical onset *(white arrow).* (B) VLFO (a TC of 10 seconds, HFF 70 Hz, highly compacted display) developed over C2, D6, and G2 *(black dots)*, followed by gradual evolution in morphology, amplitude, frequency, and wider distribution. A particularly well-organized periodic pattern developed with an interpeak interval from 40 to 60 seconds over C4, G1, G2, H1, and H2. The maximal amplitude became more than 3mV. The onset of VLFO *(black arrow)* preceded clinical seizure onset *(white arrow)* by 18 minutes 10 seconds. Notably, positive IDS could be detected in the initial stage of seizure onset on A1, A2, D4, and D5, channels in which VLFO was insignificant. The *black triangle* marks enhanced interictal discharges, which were superimposed over VLFO. The *open frame of black lines* indicates the time window in A.

among seizures in individual patients. No subjective complaints or objective symptoms were reported during VLFO. The observation of the interictal discharges, conventional ictal EEG, VLFO, and cortical mapping are summarized in Supporting Table S1.

VLFO in 3 patients shared common essential features: (1) The occurrence always preceded clinical seizure onset and conventional ictal EEG onset by a period of time ranging from 8 minutes 10 seconds to 22 minutes 40 seconds. Gradually, repetitive negative slow baseline shifts developed from very limited areas involving a few electrodes. (2) The morphology, amplitude, frequency, and distribution of VLFO evolved progressively. Generally, VLFO became more regular and periodical. Interpeak intervals of 40–120 seconds and more than 3mV of maximal amplitudes were detected. (3) The intensive interictal discharges in Patient 1 and subclinical discharge in Patient 2 were superimposed on the VLFO waveform several minutes after VLFO occurrence. (4) The spatial distributions of VLFO were in the vicinity of, or even overlapped with the conventional ictal EEG onset and IDS. (5) Finally, VLFO disappeared or significantly attenuated after cessation of the clinical seizure.

Patients 1 and 2 were not operated on because the EZ could not be localized clearly and/or the eloquent areas overlapped with the possible EZ. Patient 3 underwent lesionectomy (see Supporting Fig 1C). The lesion was confirmed as focal cortical dysplasia histologically. His seizures reduced by about 50%, although the follow-up period is still less than 1 year.

Discussion

The current study revealed a distinct ictal brain activity in the range of the infraslow band. Theoretically, if EEG recording is carried out with direct current (DC) amplification or alternate current (AC) amplification, but with very long TC, slow potentials can be evaluated.[6] Nevertheless, significant artifacts in surface EEG, the routinely-used short TC, or unavailability of a DC amplifier made it difficult or even impossible to observe DC shift. Intracranial recording, very long TC, and highly compacted EEG display were necessary to identify VLFO. The platinum-iridium alloy electrodes are optimal to minimize electrode potentials, which could distort slow potential signals.[7] It is essential to differentiate real activities from artifacts resulting from electrode placement, patient movements, or other noise in the evaluation of VLFO. Artifacts are readily detected based on irregularity or bizarre morphology, long-lasting instability of the

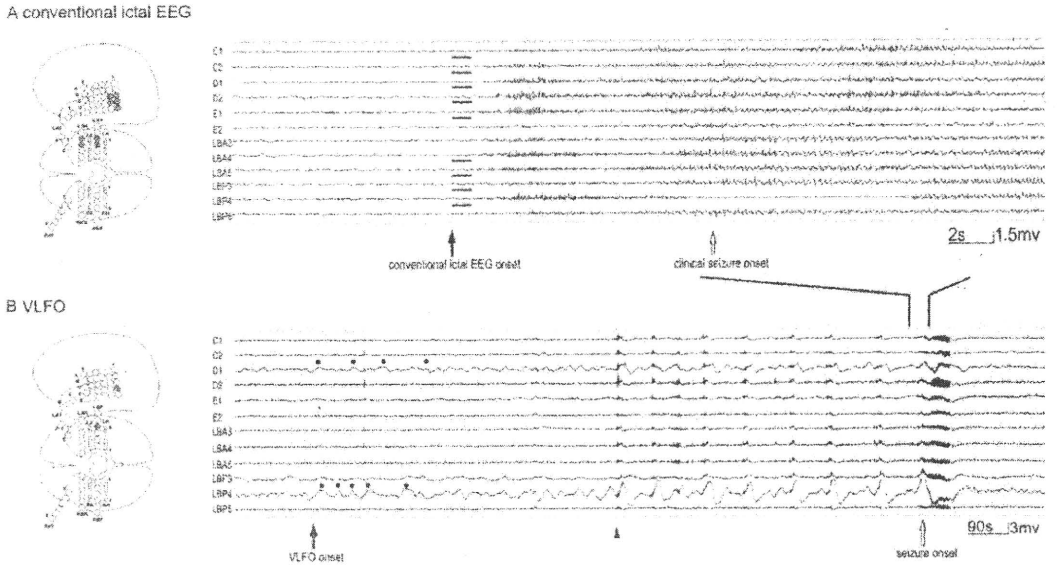

FIGURE 2: Ictal EEG changes during 1 CPS with schematic location of electrodes in Patient 2. (A) Conventional ictal discharges (a TC of 0.1 seconds, HFF 70Hz) started with low-amplitude fast activity *(black arrow and bold lines)* 12 seconds before clinical onset *(white arrow)* over the basal temporal and posterior lateral temporal lobes simultaneously. (B) VLFO (a TC of 10 seconds, HFF 70 Hz, highly compacted display) developed at LBP4 and D1 *(black dots)*, evolving into a higher-amplitude and well- organized periodic pattern with interpeak interval from 90 to 120 seconds. The maximal amplitude became more than 3mV. The onset of VLFO *(black arrow)* preceded clinical seizure onset *(white arrow)* by 22 minutes 40 seconds. The *black triangle* indicates onset of subclinical discharges, which were superimposed over VLFO. The *open frame of black lines* indicates the time window in A.

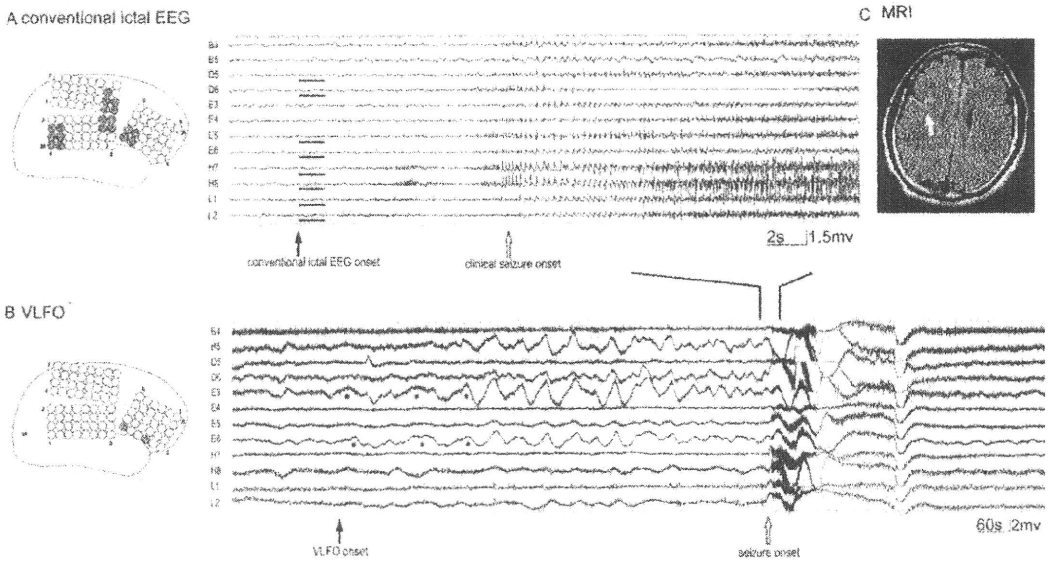

FIGURE 3: Ictal EEG changes during one sGTC with schematic location of electrodes in Patient 3. (A) Conventional ictal EEG (a TC of 0.1 seconds, HFF 70Hz) started with low-voltage fast activities regionally 10 seconds prior to clinical onset *(white arrow)* in a start-attenuation-restart pattern *(black arrow and bold lines)*. (B) VLFO (a TC of 10 seconds, HFF 70 Hz, highly compacted display) developed at E3 and E6 *(black dots)*, becoming higher, wider, and periodic, and disappeared with seizure cessation. A particularly well-organized periodic pattern developed with an interpeak interval from 40 to 60 seconds over B5, E3, and E6. Clearly, negative IDS could be identified in the initial stage of seizure onset over E5, H7, H8, L1, and L2, channels in which VLFO was insignificant. VLFO onset *(black arrow)* preceded clinical seizure onset *(white arrow)* by 13 minutes 20 seconds. The *open frame of black lines* indicates the time window in A. (C) MRI findings demonstrated the thickness of gyrus with mildly increased signal in the right inferior frontal lobe *(white arrow)*.

baseline, lack of evolution pattern, or continuation after the seizures.

Identification of VLFO would expand the brain activity spectrum, and it is different from any other previously known slow activities. The exclusive correlation between VLFO and clinical seizure distinguish it from interictal infraslow activity,[4] which might represent the slow, cyclic modulation of cortical gross excitability. Also, it is easily distinguished from IDS, which occurred with conventional EEG onset almost simultaneously and is supposed to result from astrocytic depolarization due to the increased extracellular potassium released from the vicinity of firing neurons,[8] because of its very early appearance, periodic evolving pattern, and the discrepancy in the distribution.

The observation of VLFO would also broaden our understanding of epileptogenesis. Traditionally, epileptic physiology was neuron-centric. A 50-msec to 200-msec paroxysmal depolarization shift (PDS) was considered a hallmark of epilepsy.[9] However, epileptogenesis might be heterogeneous. The role of astrocytes is especially interesting, for they not only can exhibit excitability in the form of spontaneous calcium oscillation with an interval of up to several minutes,[10,11] but also have a complex interaction with neurons.[12,13] Astrocytes are found to express similar ion channels and receptors to neurons and release gliotransmitters, including glutamate, to act on neurons, resulting in synchronizing neuronal activity[14,15] or triggering PDS-like events.[16] Therefore, it is assumed that astrocytes might initiate the VLFO, followed by activating neurons and driving epileptiform discharges, finally resulting in clinical seizure.

VLFO may be of clinical significance for identification of reliable biological markers for EZ, since currently no single technique can point out the EZ perfectly.[17] Since VLFO was only identified with seizure, and the spatial distributions of interictal discharges, conventional ictal EEG onset, IDS and VLFO were adjacent, or even overlapped, VLFO has the potential to provide valuable additional information to determine EZ despite the limited number of patients in this study. Furthermore, VLFO provides evidence for the dynamic preictal state that has long been debated. One of the most disabling aspects of epilepsy is the unpredictability of seizures. If reliable prediction is possible, epilepsy treatment will improve dramatically.[18] Although many efforts have been made to extract preictal EEG changes from continuous EEG since the 1970s,[19] more recent studies could not reproduce previously optimistic findings.[20] Hence, the relatively long time lag between occurrence of VLFO and clinical seizure makes VLFO potentially a potent parameter for predicting seizures.

Acknowledgments

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Potential Conflicts of Interest

Nothing to report.

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Large Genomic Deletions: A Novel Cause of Ullrich Congenital Muscular Dystrophy

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Two mutational mechanisms are known to underlie Ullrich congenital muscular dystrophy (UCMD): heterozygous dominant negatively-acting mutations and recessively-acting loss-of-function mutations. We describe large genomic deletions on chromosome 21q22.3 as a novel type of mutation underlying recessively inherited UCMD in 2 families. Clinically unaffected parents carrying large genomic deletions of *COL6A1* and *COL6A2* also provide conclusive evidence that haploinsufficiency for *COL6A1* and *COL6A2* is not a disease mechanism for Bethlem myopathy. Our findings have important implications for the genetic evaluation of patients with collagen VI–related myopathies as well as for potential therapeutic interventions for this patient population.

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Ullrich congenital muscular dystrophy (UCMD; MIM 254090), Bethlem myopathy (BM; MIM 158810) and phenotypes intermediate to UCMD and BM form a group of congenital muscular dystrophies known as the collagen VI–related myopathies.[1] Underlying these conditions is a decrease, absence, or dysfunction of the extracellular matrix protein collagen VI. The collagen VI heterotrimeric monomer is composed of 3 alpha chains: α1(VI), α2(VI), and α3(VI),[2,3] each containing a short triple helical domain flanked by globular domains. Assembly of collagen VI proceeds intracellularly with monomers aligning in an antiparallel fashion to form dimers, which then align laterally to form tetramers. The tetramers are secreted and align extracellularly in an end-to-end fashion, forming beaded microfilaments as the final product of collagen VI assembly.[4–6]

Mutations in any of the 3 genes coding for the 3 collagen VI alpha chains, *COL6A1*, *COL6A2*, or *COL6A3*, can affect the complex assembly and secretion of collagen VI, resulting in the phenotype of a collagen VI–related myopathy. *COL6A1* and *COL6A2* are located on chromosome 21q22.3 (Heiskanen and colleagues[7]) and *COL6A3* is located on chromosome 2q37 (Weil and colleagues[8]). UCMD results from either recessive or dominantly-acting mutations[9,10] and is characterized by a combination of early-onset muscle weakness, congenital contractures of the proximal joints, and hyperlaxity of the distal joints.[11] BM typically follows autosomal dominant inheritance; however, autosomal recessive inheritance has recently been described as well.[12,13] BM is characterized by slowly progressive muscle weakness and joint contractures.[14]

Here we describe a novel type of mutation underlying recessively inherited UCMD by delineating large genomic deletions on chromosome 21q22.3, resulting in loss of *COL6A2* or both *COL6A1* and *COL6A2*, and occurring in combination with a mutation in *COL6A2* or a deletion of *COL6A2* on the other allele to cause disease. We also conclusively demonstrate that haploinsufficiency for *COL6A1* and *COL6A2* is associated with decreased collagen VI deposition but is not associated with clinical neuromuscular disease.

Patients and Methods

Clinical details were collected according to a protocol approved by the institutional review board and are summarized in the Table 1.

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Case Report

Ear movement induced by electrical cortical stimulation

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ABSTRACT

Cortical areas that control ear movement have not been reported in humans. We describe a rare case in which ear auricle movement was induced by extraoperative electrical cortical stimulation. A 21-year-old man with intractable localization-related epilepsy was admitted for presurgical evaluation. Subdural electrodes were implanted over the right temporal and frontal regions. Tonic upward contraction of the left ear auricle was elicited by stimulating the subdural electrode on the posterior portion of the right superior temporal gyrus close to the end of the Sylvian fissure. No other body movements or auditory symptoms were elicited. A possible mechanism underlying this rare phenomenon is discussed.

1. Introduction

The somatotopical representation of the cortical areas was clarified by the pioneering work of Penfield and Jasper [1]. However, ear movement has never been evoked by electrical cortical stimulation in previous human studies. We experienced a rare case of localization-related epilepsy in which ear movement was induced by electrical stimulation of the brain through subdural electrodes. Although ear movement by cortical stimulation has been reported in monkeys [2–4], this is the first report of ear movement elicited by electrical cortical stimulation in humans.

2. Case report

2.1. Medical history and noninvasive presurgical evaluation

A 21-year-old right-handed man was admitted for presurgical evaluation for epilepsy surgery. The patient had no specific past medical or familial histories, and had experienced intractable seizures since 9 years of age. His seizures were characterized by motionless staring, followed by vocalization, stiffening of all limbs, and generalized violent movements, lasting less than 1 minute. Seizures tended to occur during sleep with a frequency of several times per day to once per month. An interictal scalp electroencephalogram (EEG) showed epileptiform discharges in the right anterior temporal (maximum in Sp2) and right frontal (F4) regions. The ictal EEG showed rhythmic slow waves in the right midposterior temporal region (T4 and T6). Brain MRI revealed no abnormality. Interictal single-photon-emission computed tomography (SPECT) with N-isopropyl-4-[^{123}I]iodoamphetamine ([^{123}I]IMP) showed hypoperfusion in the right posterior temporal region. Interictal SPECT with Technetium-99 *m* ethyl cysteinate dimer (^{99m}Tc-ECD) showed hypoperfusion in the right frontal pole and posterior temporal regions. Ictal SPECT with ^{99m}Tc-ECD revealed hyperperfusion in the right midtemporal and frontal regions. Neurological examination revealed no significant abnormality. The patient could not move his ears voluntarily.

2.2. Intracranial EEG and functional mapping

The patient underwent a right frontotemporal craniotomy, and subdural electrodes were implanted over the right temporal and frontal regions. In addition to the electrodes covering the basal frontal (OF), anterior temporal (AT), and basal temporal (TBA and TBP) regions, the right lateral temporal–frontal–parietal areas were also covered by a 4×6 subdural grid (Fig. 1). Each electrode was 2.3 mm in diameter, and the center-to-center interelectrode distance was 1 cm. The location of the grid was confirmed before and after functional mapping by X-ray. Electrical stimulation was performed via the implanted subdural electrodes for functional mapping. Repetitive square wave electric currents of alternating polarity with a pulse

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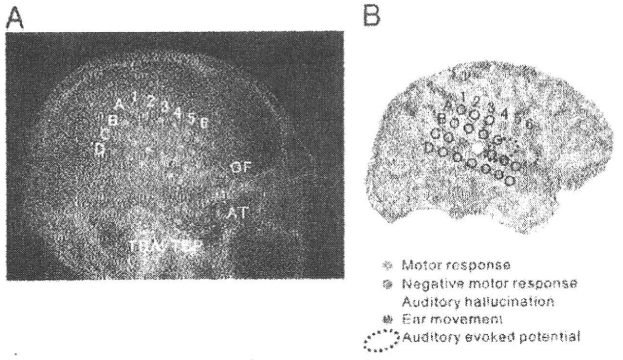

Fig. 1. Skull X-ray showing the location of the electrodes (A) and reconstructed MRI scan with the electrode placement and the results of functional mapping (B). (A) Electrodes A1 through D6 are displayed. (B) The locations of the motor, negative motor, and auditory areas are indicated. The blue circles at A4, B5, and B6 correspond to positive motor responses; the green circles at A5 and A6 to negative motor responses; the yellow circle at C3 to an auditory hallucination; and the red circle at C2 to the ear motor response. The C2 electrode is at the end of the Sylvian fissure. Auditory evoked potentials are identified at B5 and C4 (dotted ellipse). OF indicates the electrodes covering the basal frontal region; AT, anterior temporal region; TBA, anterior of basal temporal region; TBP, posterior basal temporal region.

width of 0.3 ms and a frequency of 50 Hz were delivered to each subdural electrode. Throughout the stimulation, an electrocorticograph (ECoG) was monitored continuously to detect induced afterdischarges or EEG seizure patterns. Stimulus current was increased gradually until (1) a maximum of 15 mA was reached, (2) afterdischarges were elicited, or (3) clinical symptoms were evoked.

The results of functional mapping are shown in the Fig. 1. Tongue motor (A4 and B5 both at 5 mA of intensity), left hand motor (B6 at 5 mA), and negative motor (A5 and A6 both at 5 mA) responses were elicited by electrical stimulation. Brief tonic upward contraction of the left (contralateral) ear auricle was induced by stimulating the C2 electrode with an intensity of 9 mA (see Appendix A). This response was reproducible. No other clinical symptoms (such as movements of other parts of the body including the right ear or auditory symptoms) or afterdischarges were elicited. The C2 electrode was located in the posterior portion of the superior temporal gyrus close to the end of the Sylvian fissure. When an adjacent electrode (C3 electrode) was stimulated with an intensity of 9 mA, the patient had an auditory hallucination (voices of his classmates). No other sensory response was observed in any other areas, even though it was likely some electrodes covered the postcentral gyrus. This was probably because the patient was less sensitive to these stimulations. Auditory evoked potentials (AEPs) demonstrated middle latency responses at B5 and C4, indicating that the generator of AEPs, supposed to be on the superior temporal gyrus [5], was around these electrodes. Because motor response of the tongue was evoked by stimulating A4 and B5, and because the location of the electrodes was suspected to be too lateral for the generation of somatosensory evoked potentials (SSEPs), SSEPs were not applied to verify the localization of the central sulcus in the current patient. Because the intracranial EEG could not delineate the epileptogenic zone, the surgical resection was not performed.

3. Discussion

The movement seen in the current patient was probably caused by contraction of the superior and/or posterior auricle muscles innervated by the ipsilateral facial nerve. Because the contralateral hemisphere was stimulated, it is very unlikely that direct activation of the auricle muscles or the facial nerve evoked this movement. It is most likely that this auricle movement was caused by brain activation.

The ear movement seen in the current patient was not accompanied by any other symptoms, such as somatosensory, auditory, autonomic, or other higher cortical functions. Therefore, it is assumed that this movement was caused by activation of the pure motor function of the ear, rather than by the activation of the auditory association cortex.

Most of the somatotopical representations have been identified in human brain [1]. However, a cortical area that controls ear movement has not been reported in humans, although the primary sensory area of the ear was identified around the primary sensory area of the neck and face [6,7]. In studies of macaque monkeys, Bon et al. [4] reported that electrical stimulation of area 8b, which is in the rostral area of the frontal cortex, evoked contralateral ear movements with or without conjugate movements of the eyes. Other investigators also evoked ear movements by stimulating the frontal eye field and the supplementary eye field associated with the eye movements [2,3]. Considering the location of the ear sensory area and these animal studies, it is likely that the "ear motor center" is in the frontal lobe, probably within or close to the eye fields, even in humans.

There are, however, no previous reports demonstrating ear movements on stimulation of such frontal areas in humans. This discrepancy may be explained by the evolution of the species. Ear movements are important in localizing the origin of sound in monkeys and other animals, but are not as useful in humans. Therefore, it is presumed that the human "ear motor center" has degenerated or even disappeared in the course of evolution.

In the current study, auricle movement was evoked by stimulating the posterior portion of the superior temporal gyrus. The location was within or close to the auditory association cortex, but far from motor areas. Therefore, it is very unlikely that this stimulated point itself has a motor function, and it is possible that the electrode position that induces ear movement may have some neural connections with an "ear motor center." This kind of response was previously reported by Penfield and Jasper as a "distant response" [1].

Reasons why direct stimulation of the frontal areas, which may include an "ear motor center," failed to show ear movements, not only in this study but also in previously reported patients, may be: (1) The cortical representation of the area responsible for ear movement may be very small in humans; (2) the electrical threshold to stimulate ear movement may be higher than that of other body parts; (3) not all humans may have an "ear motor center" as expected from clinical observations; and/or (4) physicians have not paid much attention to ear movements previously.

In addition to these reasons, distortion of normal cortical function by epileptogenicity may play some role in the ear movement elicited in the current patient. Repeated epileptic seizures could alter normal brain function, and nonphysiological ear motor function may appear within the temporal cortex. This phenomenon may also explain why a hand motor response could be recorded by stimulating B6, an area located lateral to the tongue motor area (A4 and B5). This phenomenon was called "epileptic sensitization" by Penfield and Jasper [1].

Although it is still uncertain if an "ear motor center" is present in all humans, if the center is in the frontal area or in the temporal area, and if a "distant response" or "epileptic sensitization" distorted the normal function in this patient, it is still interesting that the ear movement could be seen by stimulating the superior temporal gyrus. It might be clinically useful in functional mapping if ear movements could be elicited only when the superior temporal lobe is stimulated. In addition, because repeated epileptic seizures may alter normal brain function, if ear movement associated with the remote auditory center is found, a stricter and more careful presurgical evaluation for locating the epileptogenic zone and brain function areas could be performed by clinicians before epilepsy surgery. However, because this is only a single case report, additional research is required to clarify the clinical usefulness of this ear movement, as well as the underlying mechanism.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.yebeh.2010.05.016.

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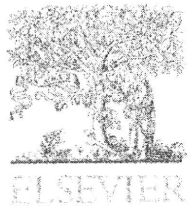

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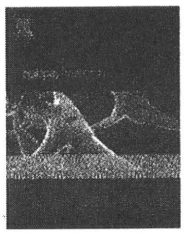

Epileptic negative myoclonus: A combined study of EEG and [^{123}I]iomazenil (^{123}I-IMZ) single photon emission computed tomography indicating involvement of medial frontal area

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EEG

Summary Negative myoclonus (NM) is a sudden brief atonia in muscle that causes jerky lapses of posture. This study employed an electrophysiological technique (silent-period-locked-averaging (SPLA) electroencephalography (EEG)) and a pharmacodynamic imaging technique (^{123}I-IMZ-SPECT) to examine epileptic NM (ENM).

Delayed-phase ^{123}I-IMZ-SPECT images, which reflect the specific binding of the tracers to GABA-A receptors, exhibited significant decrease in the left medial frontal area. The deficit in GABA-A receptors indicated that abnormal synchronization was mediated by the lack of inhibitory postsynaptic mechanism.

The SPLA-EEG recorded spike-like notches superimposed on the slope of negative slow activity in the contralateral fronto-central region. The slow activity started around 100 ms before and the peak of the spike-like component was 30 ms before the onset of ENM.

Since the ^{123}I-IMZ-SPECT shows the actual distribution of the tracers, the abnormal area associated with ENM in this particular patient was supposed to be on the left medial frontal lobe. Scalp EEG, though it cannot always accurately locate the abnormal area, was highly sensitive to be able to detect electrical activities transmitted through neuronal network or volume conductor.

Combined use of the two methods provided high resolution both in spatial and temporal domain.

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Introduction

Negative myoclonus (NM), termed as such by Shahani and Young (1976), is a sudden brief atonia in muscle that causes jerky lapses of posture (Shibasaki and Hallett, 2005). In electromyogram (EMG), NM is recorded as a brief (<500 ms) silent period, without any preceding abrupt muscle contraction (Tassinari et al., 2005). While the phenomenon occurs in a variety of pathological conditions such as asterixis in patients with hepatitis (Adams and Foley, 1949) and with hypoxic encephalopathy (Lance and Adams, 1963), NM as an epileptic symptom (epileptic negative myoclonus, ENM) is characterized by an epileptiform discharge on the contralateral hemisphere, time-locked to NM (Tassinari et al., 1968; Tassinari, 1981). Although some cortical areas have been identified to be associated with the phenomenon by invasive studies using subdural or depth electrodes placed on the brain of patients who underwent surgical treatment of refractory epilepsy, the mechanism of ENM is still not fully understood.

Invasive procedures are considered to be able to specify the details of a wide variety of functions and/or phenomenon in the brain. However, number of cases where invasive methods can be applied, and the types of method(s) that can actually be used are limited. Even if invasive procedure is possible, combined use of invasive and non-invasive techniques is essential in actual clinical evaluations and research.

We have chosen [^{123}I]iomazenil (^{123}I-IMZ) single photon emission computed tomography (^{123}I-IMZ-SPECT) as a non-invasive method in our study of a patient with ENM. Although ^{123}I-IMZ is a relatively new radioactive tracer which has been applied to the SPECT study of brain activities only recently (Beer et al., 1990; Johnson et al., 1990), it has been proved to be useful to identify the pathological areas in patients with temporal lobe epilepsy (Shuke et al., 2004; Morimoto et al., 2005; Umeoka et al., 2007). Compared with other conventional techniques using perfusion agents, which usually detect regional cerebral blood flow, one of the advantages of ^{123}I-IMZ-SPECT is its selectivity to the central-type gamma-aminobutyric acid-A ($GABA_A$)/benzodiazepine receptors (Van Huffelen et al., 1990; Bartenstein et al., 1991; Cordes et al., 1992). Since GABA is known to be the major inhibitory neurotransmitter in the brain, the ^{123}I-IMZ-SPECT enables the detection of the activity of GABA, which leads to pharmacodynamic imaging of the central nervous system.

In this paper, we report the results of a combined use of ^{123}I-IMZ-SPECT and silent-period-locked-averaging (SPLA) electroencephalography (EEG) (Ugawa et al., 1989), which delineate the feature of ENM with high temporal and spatial resolution. We also demonstrate the potential of ^{123}I-IMZ-SPECT as a useful technique in the evaluation of functions in extra-temporal epilepsy.

Methods

Patient

The subject was a 19-year-old right-handed college student. The etiology of his epilepsy was unknown. He had two types of epileptic seizures; one was a tonic seizure and the other NM. Tonic seizures occurred since the age of 4 months. EEG was taken at the age of 1 year, revealing focal spikes on the left frontal area. With the administration of anti-epileptic drugs (AEDs), the patient had seizures only occasionally. At the age of 18 years, he started to have a tonic seizure 2–3 times per month. The tonic seizures occurred only when the patient was asleep.

NM started at the age of 13 years. The movement was characterized by brief and repetitive loss of postural tone of the right upper extremity when the arms were held upright. Consciousness was fully preserved. On admission, the NM on the right upper extremity was observed in the daytime when the patient was fully awake, almost everyday.

Neurological examination was unremarkable and 1.5-Tesla MR FLAIR, T1-, and T2-weighted images of the brain were normal (Fig. 1A). Somatosensory evoked potentials (SEPs) obtained by stimulating the median nerve at the wrist were normal both in amplitude and latency in ipsi- and contralateral hemispheres to the NM. No giant SEPs were observed.

The conventional EEG recorded with the electrodes positioned in accordance with the international 10–20 system showed interictal focal spikes in the left parasagittal fronto-central region, every 2–3 min, in sleep. In awake EEG, when the patient had NM, intermittent irregular slow activity was recorded in the left parasagittal and midline fronto-central region. The voltage of the slow activity was largest at Fz and second largest at C3 and Cz. By visual inspection, the temporal relationship between the slow activity and NM was not apparent. In tonic seizures, which occurred exclusively in sleep at night, movement artifact and electromyographic (EMG) artifact obscured the EEG in most of the seizures, except one. The seizure, in which EEG abnormality was successfully recorded, began with repetitive spikes at F3 and C3 followed by paroxysmal beta activity at C3. After the clinical onset, EMG artifacts obscured the EEG.

^{123}I-IMZ-SPECT

The SPECT was conducted in the daytime, when the patient was fully awake. 167 MBq of ^{123}I-IMZ was intravenously injected, with the patient's arms placed in rest. Brain scintigram was obtained using a dual-head gamma camera (Millennium VG, GE Medical Systems, Japan) equipped with a pair of low-energy, high resolution collimators. The patient was scanned twice after injection; 5–35 min (early image) to examine the tracer uptake in brain in proportion to blood flow at an early phase, and 165–195 min (delayed image) to examine the retention of tracer at specific binding sites at a late phase (Umeoka et al., 2007).

SPECT images were acquired in a 128 × 128 matrix at 5° angular steps, with 45 s in each step. Raw SPECT data were reconstructed by using a Ramp filter and then post-filtered using a Butterworth filter (order 10) with a cutoff value of 0.45 cycle/pixel. Transaxial slices were reoriented to "sagittal" (parallel to the midsagittal plane), "oblique transaxial"(parallel to base of the temporal lobe), and "oblique coronal" (perpendicular to the two aforementioned directions) slice orientations. No attenuation correction was applied. The final reconstructed pixel size was 3.16 mm × 3.16 mm × 3.16 mm.

SPECT MRI co-registration and statistical analysis

The SPECT images were anatomically standardized based on the patient's T1-weighted MR images with a slice thickness of 1 mm (FSPGR) obtained by a 1.5-T machine (Signa Twin Speed 1.5 Tesla system, General Electric, Yokogawa, Japan), and analyzed by using a modified version(Nihon Medi-physics, Japan) of the software 3-DSSP (Minoshima et al., 1994).

The patient's data was compared with the database made of the data from control group consisting of 20 healthy normal volunteers of the age between 19 and 21 years. Accurate anatomic

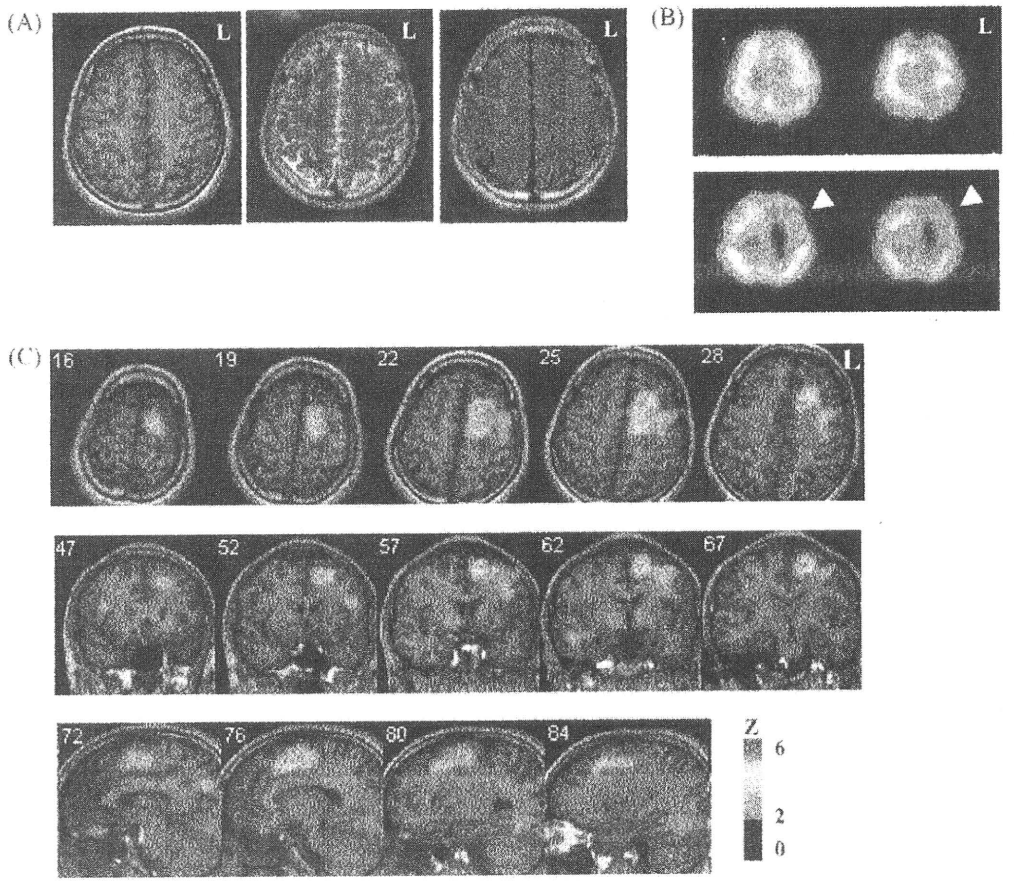

Figure 1 MRI, co-registered IMZ-SPECT and 3D-SSP analysis. (A) T1-, T2-weighted and FLAIR MR axial images were unremarkable. (B) MRI co-registered SPECT showed normal uptake after 30 min from injection (upper panel). 3 h after injection, decreased uptake was identified on the left frontal region (lower panel, white arrowhead). (C) 3D-SSP shows the area with significant decreased uptake on the medial aspect of the left frontal region.

reference of uptake change was statistically analyzed using the Z-score calculated by the following equation

$$Z\text{-score} = \frac{\text{standardized tracer uptake count of DB} - \text{tracer uptake count of the subject}}{\text{standard deviation of DB}}$$

where DB is the database made of the data of 20 healthy normal volunteers.

Significant uptake change ($Z \geq 2$) was superimposed on the patient's 3D-MR images.

Silent-period-locked-averaging EEG

Polygraphic recordings with video monitoring were performed using a computerized EEG system (EEG-1100, Nihon Kohden, Japan). The bioelectrical signals were digitized with a bandpass filter of 0.016–300 Hz at a sampling rate of 1000 Hz. The resolution of A/D converter was 16 bits. Electrodes were positioned over the scalp based on the international 10–20 system. Muscle activities were simultaneously registered with surface EMG electrodes placed on the right wrist extensors and flexors, biceps, and triceps muscles. Recordings were performed during bilateral arm elevation with wrist extension. Two 2-min periods of hand-holding were performed with 3-min intervals between each period. The acquired data were stored digitally on a digital versatile disc and the signal was off-line averaged using Matlab, with respect to the onset of silent period which was determined visually in the EMG. Epochs starting 200 ms before and terminating 300 ms after each onset of silent period were averaged. Epochs with eye blinks or other artifacts were excluded from averaging. More than 30 epochs were averaged in one measurement.

All the procedures were approved by the ethics committee of National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders. Written informed consent was obtained from the patient and normal volunteers.

Results

^{123}I-IMZ-SPECT

The early ^{123}I-IMZ-SPECT imaging did not reveal observable unusual distribution (Fig. 1B upper panel). In the delayed images, abnormal area of decreased uptake was identified (Fig. 1B lower panel). The focus with statistically signifi-

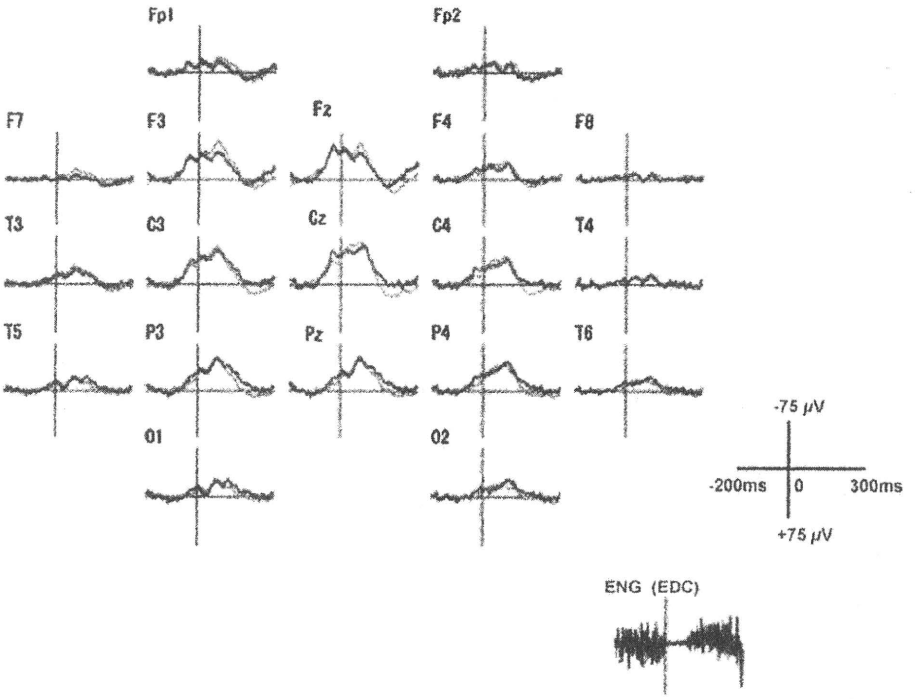

Figure 2 Silent-period-locked-averaging EEG. Averaged signals showed a slow activity on the midline fronto-central area extending more toward the left hemisphere. The slow activity started 100 ms before the onset of muscular silent period (SP). A small notch was superimposed on the slope of slow activity at Fz, Cz, F3, and C3. The peak of the notch was 30 ms before the onset of SP. No spikes preceding the SP was identified on the right. EMG: electromyogram; EDC: extensor digitorum communis.

cant decreased uptake was on the medial aspect of the left frontal area rostral to the precentral gyrus, which largely corresponded to Broadmann area 6 (Fig. 1C). No significant change in uptake in primary motor or somatosensory cortex was observed.

NM-related cortical activities studied by silent-period-locked-averaging EEG

By investigating the raw data, it was confirmed that the recorded NM, in other words, muscular silent period (SP), was not preceded by any enhancement of muscle contraction.

The averaged waveform of silent-period-locked-averaging (SPLA) showed a relatively large surface-negative slow activity starting almost 100 ms before the onset of the SP and lasting about 300 ms. The amplitude of SPLA-EEG signal was largest at the midline fronto-central area extending more toward the left hemisphere (Fig. 2). Signals exhibiting the slow activity in the left fronto-central area (Fz, Cz, F3, C3), which were contralateral to the hand with NM, appeared to be superimposed by a small notch. The peak latency of the notch was 30 ms before the onset of SP.

Discussion

Functional abnormality revealed by ^{123}I-IMZ-SPECT

In the past, SPECT study of epilepsy was mainly conducted by using perfusion agents, which detect regional cerebral blood flow (rCBF). Although the number of reports on NM examined by SPECT so far was limited in the literature, one study showed the increased rCBF on the contralateral middle frontal gyrus during the NM (Baumgartner et al., 1996a). They used HMPAO, one of perfusion agents, in their examination. They suspected that the area with increased rCBF was the main source of causing NM.

Although their finding is significant in rare SPECT studies of NM, it should be interpreted with caution because of the use of HMPAO in ictal period. It has been known that rCBF increases in the epileptogenic area in ictal event. The increase in rCBF might be caused by the normal neuronal activities in the cortex responsible for the movement of the extremity. HMPAO cannot distinguish the cause of change in rCBF.

The present study, by using ^{123}I-IMZ as a radioactive tracer, has some advantages for accurate examination of NM. The radioactive tracer IMZ is carried by CBF instantly to the brain tissue, spread into various portion of the brain and selectively bind to the GABA-A/benzodiazepine receptor. Free tracers, by contrast, are taken by the blood flow without being bound to the receptor. Distribution of the radioactive tracer during the early post-injection phase reflects regional CBF, while the distribution during the delayed post-injection phase reflects the existence of stored radioactive tracers bound to the receptors. The distribution of the radioactivity is consistent with the known distribution of the receptor in the human brain (Morimoto et al., 2005). The pattern of storage of radioactive tracers in normal region is different from that in epileptogenic region.

Observed difference in the distribution of the bound radioactive tracer, therefore, can be a useful indicator of normality of the receptor.

In addition, noticeable feature of our patient was that he exhibited epileptic negative myoclonus only when he was awake. We conducted the ^{123}I-IMZ-SPECT receptor imaging study only in the daytime when NM occurred almost everyday. The patient's arms were at rest so that rCBF would not change by the movement of arm. In the delayed-phase ^{123}I-IMZ-SPECT images, which reflect the specific binding of the tracers to GABA-A receptors, we found statistically significant decrease in the left medial frontal area.

The early-phase ^{123}I-IMZ-SPECT imaging and magnetic resonance imaging showed no abnormal findings, indicating that the brain had no macroscopic structural abnormality and that rCBF was preserved. The observation suggested that the neuronal viability was preserved in the cortex even though decreased binding of the tracers was observed. We, therefore, ruled out the possibility that the decrease in binding of the tracers is caused by the loss of neurons.

Since the neuronal viability was preserved, there are two possible mechanisms of reduced receptor-binding distribution: weakened function of GABA-A receptor, or low density of GABA-A receptor. Invasive microscopic techniques are ideal to identify the mechanism. Techniques we were allowed to employ, though not invasive, still enable us to ensure the reliable understanding if we carefully compare possible interpretations.

The finding in the present study was a deficit in GABA-A receptors, which was caused by either weakened function or low density, or by both, in this particular area. Since GABA-A receptor mediates fast-acting inhibitory mechanism on postsynaptic neurons, which prevent the propagation of abnormal synchronization of neuronal populations, the deficit in GABA-A receptors indicates that abnormal synchronization was mediated by the lack of inhibitory postsynaptic mechanism.

NM-related EEG abnormality

Some of the electrophysiological studies in the literature have been demonstrated possible association of EEG waveforms with NM. Findings in most of these studies were regarding spikes and/or sharp waves that were recorded in EEG. Such reports include both non-invasive studies (Ugawa et al., 1989; Oguni et al., 1992; Rubboli et al., 1995; Baumgartner et al., 1996a; Meletti et al., 2000) and an invasive study (Noachtar et al., 1997).

Our results exhibited small spike-like negative notch recorded by SPLA. The notch was recorded on the midline and parasagittal left fronto-central area. The peak latency of the notch was 30 ms before the onset of SP. The characteristics of the small notch and its peak latency were in line with the NM-related spikes reported in the literature mentioned above.

A striking feature in the present study was, however, that the spike-like notch looks as if it is superimposed on the slope of negative slow activity. SPLA revealed the temporal relationship of the slow activity and NM; the slow activity started about 100 ms before the onset of the SP and lasted for around 300 ms.

Since little attention has been paid to this kind of slow activities in the literature so far, only a few researchers mentioned slow activity that was supposed to be related to NM (Cirignotta et al., 1981) or to myoclonic jerks (Wilkins et al., 1985). Cirignotta et al. (1981) reported the slow component of a spike-and-wave-discharge associated with loss of tonus of outstretched arm, which is synonymous to NM. They pointed out that the slow component exerted the inhibitory effect to the arm maintaining the posture.

The mechanism of the slow activity was still to be examined. One possibility is that the jitter in averaging might obscure the electrical activity with shorter duration. The SPLA indicated that the NM-related electrophysiological abnormality existed on the midline and parasagittal fronto-central area on the left hemisphere. Although the functional significance of the slow activity has not been fully understood yet, we can safely say that the slow activity on the midline and parasagittal fronto-central area was associated with NM together with the spike.

Cortex associated with NM revealed by the combined study of IMZ-SPECT and SPLA

Non-invasive studies using scalp EEG reported two different but adjacent locations of NM-associated spikes; contralateral perirolandic area (Ugawa et al., 1989; Oguni et al., 1992) and contralateral frontal area (Rubboli et al., 1995; Baumgartner et al., 1996a). Invasive methods using electrical cortical stimulation by means of subdural and/or depth electrodes provided more detailed information on the cortical areas as generators of ENM. Primary sensorimotor area (Ikeda et al., 2000), post-central somatosensory cortex (Tassinari et al., 1995; Noachtar et al., 1997), and premotor cortex including supplementary motor area (Rubboli et al., 2006) were reported to cause disturbance in sustained muscle contraction. These studies indicate that there are several cortical areas which can generate ENM.

Since the present study lacked the opportunity to apply F1 and F2 or C1 and C2 electrodes due to the limitations of clinical setting, detailed contour map of electrophysiological activities was not obtained. Both ^{123}I-IMZ-SPECT and SPLA we employed, however, captured distinctive abnormal neuronal activities. In pharmacodynamic imaging, ^{123}I-IMZ-SPECT revealed that the uptake of ^{123}I-IMZ was decreased in the contralateral medial frontal area. In our examination using EEG, the NM-related signal was recorded on the contralateral fronto-central region.

Although the abnormal cortical sites in these two methods did not match precisely, we speculate that the abnormal area associated with ENM in this particular patient was on the left medial frontal lobe, as demonstrated by ^{123}I-IMZ-SPECT. The chemical imaging of SPECT shows the actual distribution of the tracers, which reflects the function of different areas in the brain. Focal decrease in IMZ binding indicates either the lowered function of benzodiazepine/GABA-A receptor or decreased neuronal viability in the corresponding cortical area. Since we ruled out the decreased neuronal viability, the result suggested functional abnormality in this particular area.

As a fundamental characteristics of scalp EEG, this technique cannot always accurately locate the cortical source

of abnormal electric activity. When the pathological area is in the interhemispheric fissure, scalp EEG cannot locate the abnormal signal immediately above the source because the dipole is tangentially oriented to the scalp. The zero isopotential line is located on the scalp immediately above the source.

The fact that EEG detects electrical activity the source of which might exists somewhere other than the immediate vicinity suggests that some form of signals may be transmitted from one cortical site to another. Plausible explanations of the spread of electrical activity in the brain are, for example, transmission through neuronal network (Baumgartner et al., 1996b) or volume conductor (Sasaki et al., 1996).

Since the neuronal network is well developed both within and outside of the frontal lobe, one possibility of detecting EEG signal on the scalp electrode is that the electrical activity recorded in the present study was the signals conveyed by this network. It is well known that medial frontal area had strong fiber connection to the primary motor area (Baumgartner et al., 1996b). Since the motor area is located immediately beneath the contralateral convexity, the lateralization is contralateral to the motor phenomenon. The epileptic discharge originated in the medial frontal region was conveyed through cortical network, reached the left precentral motor area, and was recorded on the scalp electrodes placed on this area.

The other possibility is that the signal may reach the detector of EEG through volume conductors, such as the cerebrospinal fluid, which has low impedance and contributes to a so-called 'shunting effect' (Sasaki et al., 1996). Since the signals of abnormal electric activity in the medial aspect of the frontal lobe may go through these transmission routes, the maximal amplitude on the scalp appears not immediately above the source but somewhere apart from the actual location.

In some cases, so-called 'paradoxical lateralization' (Adelman et al., 1982) might be a cause for concern. Paradoxical lateralization is a phenomenon that the voltage of abnormal discharge, such as an epileptic spike, is higher on the ipsilateral side to the affected limb. In the literature, the phenomenon is reported to occur when the generator is in the medial cortical area within interhemispheric fissure and has its spatial dipole oriented obliquely to the recording electrodes on the scalp. We speculate that the spatial orientation of the abnormal discharge in the present study was not oblique to the scalp. The abnormal discharge was recorded on the scalp in the parasagittal areas and with higher amplitude in the pathological (left) side through the cortical network, or by a so-called 'shunting effect'.

Concluding remarks

Abnormal functional area related to ENM was delineated by two different techniques: pharmacological imaging and electrophysiology. The result of ^{123}I-IMZ-SPECT was supposed to identify the location of the area that caused the abnormality.

Silent-period-locked-averaging (SPLA) EEG revealed spike and slow activities both of which are supposed to be associated with NM. Combined use of the two methods provided high resolution both in spatial and temporal domain.

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162 Seizures Induced by Thinking and Praxis

Yushi Inoue

Short Description

Praxis and spatial thinking may precipitate seizures, typically in juvenile idiopathic generalized epilepsies.

Definition of the Terms

Praxis refers to the process of transcoding thinking into voluntary or intentional acts (Inoue et al. 1994). Spatial thinking and the eventual action represent the two ends of the spectrum (◉ *Fig. 162-1*). A seizure may be induced by praxis typically when a patient is required to think of a complicated spatial task in a sequential fashion, to make decision, and to give response by using a part of the body under stressful circumstances. Processing of spatial information (spatial thinking) or ideation of motor activity alone can induce seizures (Inoue and Zifkin 2004). Praxis induction is more than simple seizure triggered by proprioceptive input or simple repetitive movement.

Demographic Data

Onset Juvenile

Prevalence 7.9% (Matsuoka et al. 2000). The vast majority of patients have idiopathic generalized epilepsy, especially juvenile myoclonic epilepsy (JME). Approximately one-third to one-half of the patients with JME demonstrates praxis-sensitivity (Guaranha et al. 2009).

Clinical Manifestation

The precipitating factors include ideation or execution of complicated actions involving sequential spatial processing such as written or mental calculation, playing games, drawing, writing, construction, playing musical instruments and complicated finger manipulations. Calculation, construction and writing are the most effective trigger. Simple handling never constitutes a trigger. Stress and concentration of attention are important additional contributors to precipitate seizures.

The types of seizure induced are typical of juvenile idiopathic generalized epilepsy, including myoclonus, absence and tonic-clonic. Motor symptoms such as myoclonus may predominate in the body part involved in executing the intentional activity, often in the preferred hand. Unprovoked seizures are also common.

Pathophysiological Mechanism

The hyperexcitable regions and systems activated by praxis, which can be diffuse but not necessarily uniform and differ in degree and extent, may produce epileptic activity that involves the cortico-reticular or cortico-cortical pathways (Ferlazzo et al. 2005). The induced clinical manifestations may be symmetrical, asymmetrical, or even localized.

Diagnostic Procedures

Interictal EEG (◉ *Figs. 162-2* and ◉ *162-3*): Runs of spike-wave that may be bilateral and diffuse, predominantly unilateral, or even localized, as often seen in idiopathic generalized epilepsy.

Ictal EEG (◉ *Figs. 162-2* and ◉ *162-3*): Burst of spike-waves or polyspike-waves during neuropsychological activation including spatial and praxis tasks.

Brain MRI Not informative, often normal.

Nosology

Epilepsy with praxis-induced seizures constitutes a subgroup across the whole spectrum of juvenile generalized epilepsy syndromes; in this respect praxis-sensitivity resembles photosensitivity, but the two differ in the location of cortex excitability. There are also many similarities between primary reading epilepsy and epilepsy with praxis induction (Wolf and Inoue 2002): both have juvenile onset, are idiopathic, have a benign course and respond to similar antiepileptic drugs, involve both higher cortical and motor performances, and manifest ictal motor symptoms starting in the same motor segment where the precipitating activity takes place (◉ *Figs. 162-4* and ◉ *162-5*).

Prognosis

Most patients respond well to antiepileptic drugs used for idiopathic generalized epilepsy, but some have intractable course.

C.P. Panayiotopoulos (ed.), *Atlas of Epilepsies*, DOI 10.1007/978-1-84882-128-6_162,

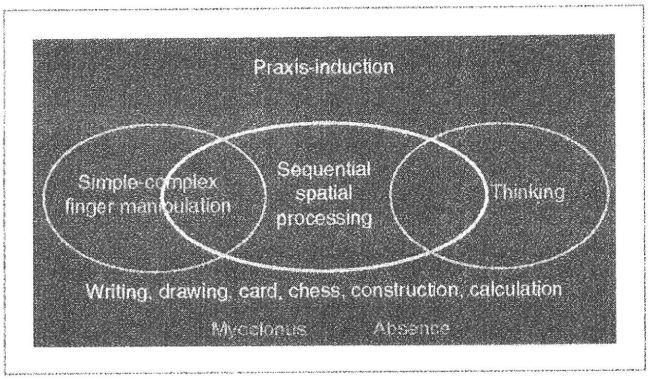

Figure 162-1. Schematic representation of the relation between action, spatial thinking and praxis. Myoclonus occurs more often when the motor component is involved, while spatial thinking alone precipitates absence more frequently

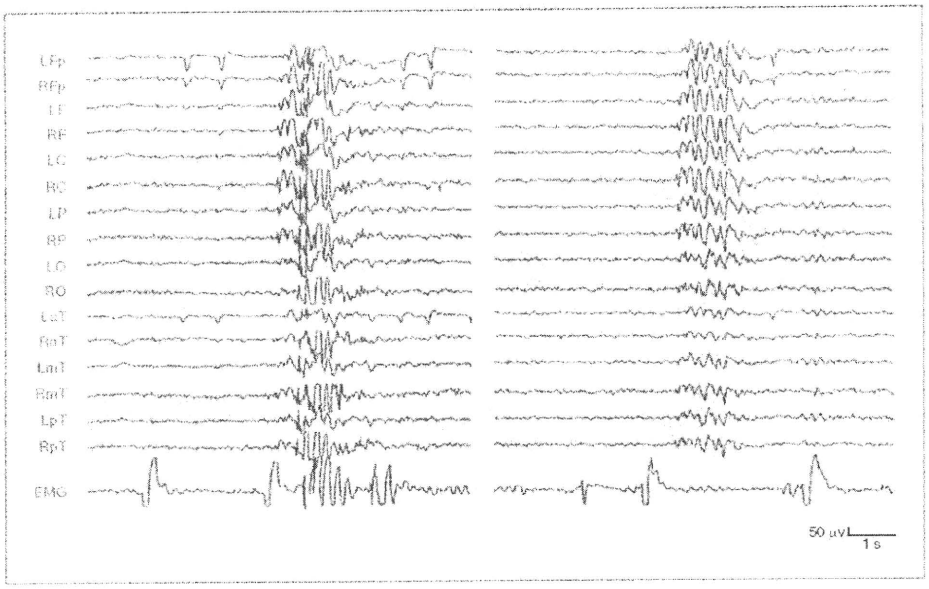

Figure 162-2. EEG paroxysms induced by written calculation in a 49 year-old women with concomitant myoclonus of the upper extremities (*left* part)

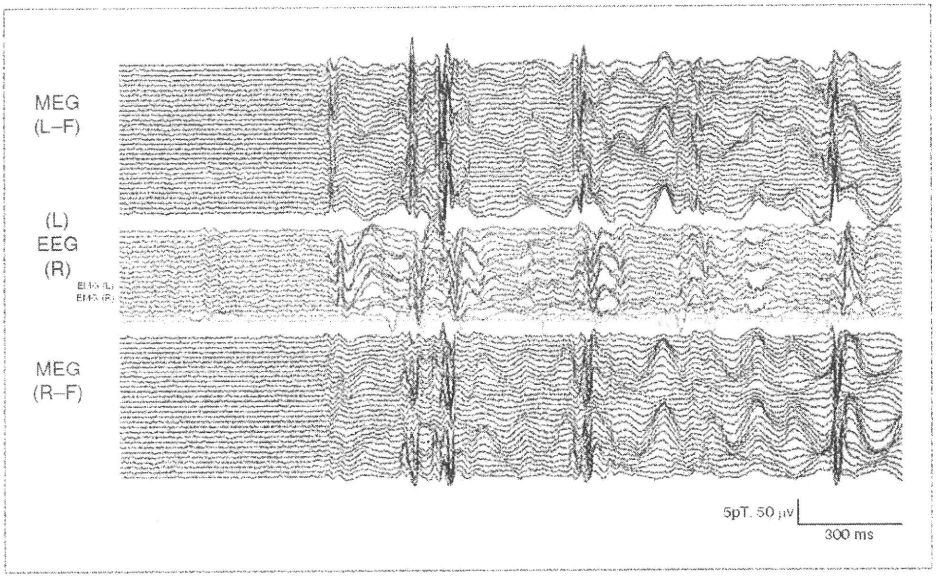

Figure 162-3. EEG and MEG paroxysms induced during game playing in a 19 year-old boy

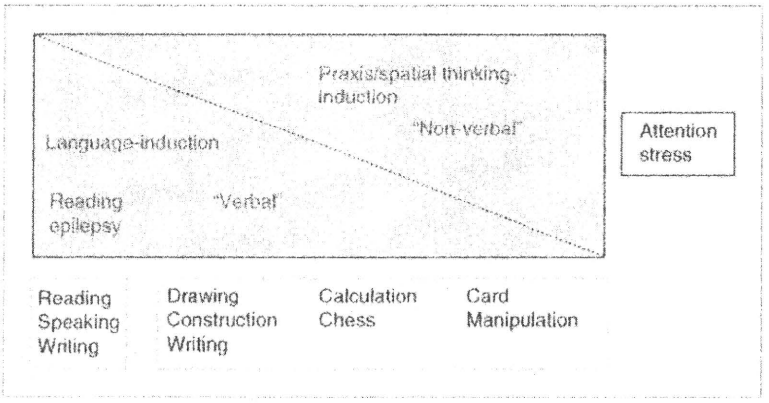

Figure 162-4. Relation of praxis/spatial thinking-induction to language-related induction, and the precipitating activities

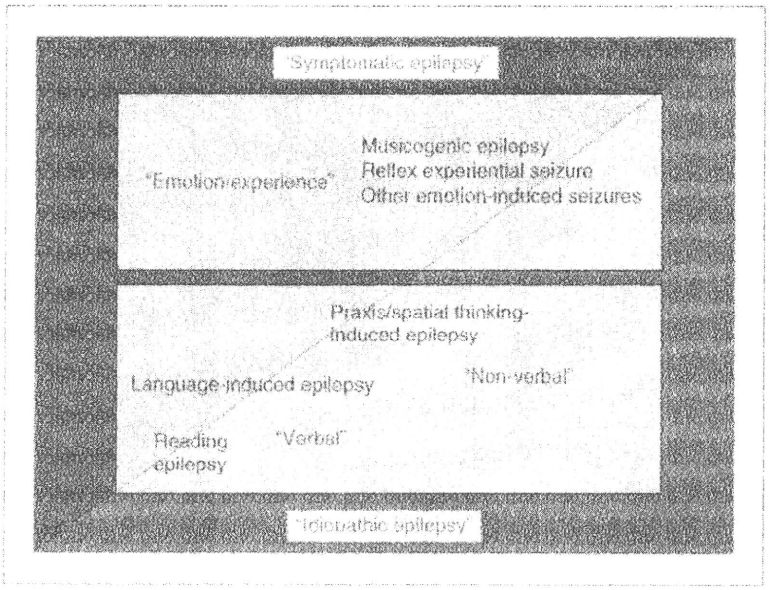

Figure 162-5. Nosology of various epilepsies with seizures induced by higher brain function

Management

Avoidance of precipitating stimuli is usually not possible in daily life. Medical treatment is often necessary and non-specific facilitating factors such as sleep deprivation should be avoided.

Related Topics

- ▶ Focal Myoclonic Seizures
- ▶ Generalized Myoclonic Seizures
- ▶ Juvenile Myoclonic Epilepsy
- ▶ Primary Reading Epilepsy

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抗てんかん薬

須貝研司

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抗てんかん薬

Antiepileptic drugs

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Ⅰ．経口抗てんかん薬

1．てんかんの薬物治療の基本

てんかんの薬物治療は，

・発作型とてんかん症候群に基づく薬剤選択

・抗てんかん薬の臨床薬理動態に基づく薬剤使用

の2点であり，これに基づいて，そのてんかん発作にもっとも適合する薬を，発作が起こりやすい時間に，もっとも高濃度になるように使用することである。

したがって，発作型とてんかん症候群を正確に診断することと，抗てんかん薬の薬物動態と臨床薬理を知っておくことが重要である。本稿では，てんかん治療に必要な臨床薬理と，薬剤選択の基本について述べる。

2．臨床薬理

1．抗てんかん薬の薬物動態（表1）

抗てんかん薬を使用する際に重要な薬物動態のパラメーターは，薬の初期量，維持量，増量幅，治療域の血中濃度，経口からピークに達する時間（Tmax），半減期（T1/2），相互作用，作用機序，および小児ではこれらの多くが年齢により変化することである。

年少児ほど代謝は早いので，半減期は短く，血中濃度のピーク時間は早く，同じ血中濃度を得るのに要する用量（mg/kg）は多く，頻回分服投与を要する。思春期以降は成人と同様になる。年齢によるこの変化を考慮せずに単純に体重1kg当たりの量で使用すると，乳幼児では血中濃度が上がらず発作を抑制できず，思春期では血中濃度が上がりすぎて副作用をきたす。

てんかん診療ではキャリーオーバーしている患者も多いので，成人量も記載し，また，今年の秋に市販される予定のレベチラセタムについても記載した。

2．抗てんかん薬使用時に注意すべき薬理特性

治療を行ううえでは，薬物動態のパラメーター（表1）のほかに，臨床薬理の実際に注意すべきであり（**表2**），また，多剤併用の場合は相互作用に注意する（**表3**）。

血中濃度に対する主な相互作用は，VPAはPB，LTGを，CLBはVPA，PHTを大幅に上げ，PHTはVPA，CBZ，TPM，LTGを大幅に下げ，PB，ZNS以外のほかの薬も下げる。CBZはTPM，LTGを，PBおよびPRMはLTGを大幅に下げる。

3．発作の好発時間と，血中濃度のピーク時間，半減期を考慮した薬物治療

抗てんかん薬の選択はてんかん症候群および発作型に基づくのが第一であるが，そのうえで発作の好発時間に血中濃度がなるべく高くなるように，半減期とピークに達する時間を考慮して（表1）薬の種類と飲み方を考える。

4．作用機序とその応用（表5）

けいれんを抑制する作用機序は，脳の抑制性神経の作用を強めて神経の異常興奮を抑制するか，または興奮性神経の興奮が起こらないようにすることによるが，抗てんかん薬の作用機序は以下のように応用できる。

1）合理的な多剤併用療法

通常よく使われる薬はほとんどがNaチャネル阻害による興奮抑制か，GABA機能増強による抑制増強，またはその両者の作用機序をもつので，併用時には作用機序の異なる薬を組み合わせる。

2）作用機序を考慮した治療薬の変更

ある薬が無効の場合，その作用機序とは異なる作用機序をもつ薬に置換するか，追加する。

Key words: 経口抗てんかん薬，臨床薬理，薬物動態，抗てんかん薬の選択，静注抗けいれん薬

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