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Correct localization of epileptogenic focus with I-123 iomazenil cerebral benzodiazepine receptor imaging: a case report of temporal lobe epilepsy with discordant ictal cerebral blood flow SPECT

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A 26-year-old female with intractable epileptic seizures was studied with I-123 iomazenil cerebral benzodiazepine receptor, I-123 IMP inter-ictal and Tc-99m ECD ictal cerebral blood flow SPECT. The ictal cerebral blood flow SPECT indicated the location of the seizures to be in the left temporal lobe, where increased regional cerebral blood flow was noted in marked contrast to the inter-ictal SPECT. Ictal electroencephalograms (EEGs) recorded with scalp and sphenoidal electrodes also suggested the left temporal lobe as the location of the seizures. On I-123 iomazenil SPECT, however, decreased benzodiazepine receptor density was demonstrated in the right temporal lobe. MRI showed mild atrophy and abnormal signal intensity in the right temporal lobe. Ictal EEGs recorded with intracranial electrodes revealed that abnormal electrical activity of the brain always emerged from the right temporal lobe and then propagated to the contralateral side. Based on the findings of intracranial EEGs, partial resection of the right anterior temporal lobe including hippocampus was performed. After the surgery, no seizure occurred. Pathological examination of the surgical specimens revealed hippocampal sclerosis. This case suggested that cerebral benzodiazepine receptor imaging with I-123 iomazenil can be helpful for correct localization of epileptogenic foci.

Key words: I-123 iomazenil, benzodiazepine receptor, epilepsy, cerebral blood flow, SPECT

INTRODUCTION

BENZODIAZEPINE, an anxiolytic agent, has a specific binding site in the brain known as benzodiazepine receptor (BZDR). BZDR is structurally linked with a major type of γ-amino butyric acid (GABA) receptor ($GABA_A$ receptor), which forms functional chloride ion channels distributed widely in the brain. $GABA_A$ receptor consists of 5 distinct classes of polypeptide subunit (α, β, γ, δ, ρ). In these subunits, BZDR resides on the α-subunit.[1] Thus, BZDR is a part of the $GABA_A$ receptor complex. Binding of benzodiazepine-related ligands (benzodiazepine agonists or inverse agonists) to BZDR could enhance or decrease the electrophysiological effects of GABA by modulating chloride ion flux.[1]

As a benzodiazepine antagonist, which can be labeled with C-11, flumazenil was developed and has been used for *in-vivo* mapping of BZDR in clinical studies.[2,3] Past studies on flumazenil demonstrated that various pathological conditions of the brain, such as seizures could alter the regional density of BZDR.[4–6] Although evaluation of BZDR with flumazenil was of great clinical interest, its use was limited to institutions where positron emission computed tomography was available. As an analogue of flumazenil, which could be labeled with I-123 and was intended for routine clinical use, iomazenil was developed.[7] Suitable physical properties of I-123 for SPECT imaging and its appropriate affinity to BZDR made this ligand practical for clinical BZDR imaging.[8] To date, many studies have been done on this ligand, suggesting its feasibility for *in-vivo* BZDR mapping and usefulness in the evaluation of various pathological conditions of the

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central nervous system.[9–11]

In clinical application of BZDR imaging with iomazenil, it is useful particularly for the detection of epileptogenic foci of partial seizures, where BZDR density is decreased.[5,6,12] It can be done in the inter-ictal phase with good diagnostic accuracy.[13] On the other hand, cerebral blood flow SPECT has also been performed for the evaluation of epileptogenic foci of partial seizures. In particular, comparison of ictal and inter-ictal cerebral blood flow SPECT images could provide helpful information for determining epileptogenic foci.[14,15] In this context, one question that arises is whether BZDR imaging could have additional diagnostic value in partial seizures, particularly for determining epileptogenic foci. We experienced an interesting case of temporal lobe epilepsy that sheds light on this issue and report it here.

CASE REPORT

A 26-year-old female presented with a history of intractable epileptic seizures. She was the product of a normal birth and delivery and had normal developmental milestones. She had no remarkable medical history such as febrile convulsions or head trauma. At the age of 23 years, she was first noticed to have seizures. Her typical seizures were manifested by becoming spacy, laughing, and nodding the head which continued for 10–20 seconds. Except for these partial seizures, she experienced generalized seizure attacks twice. She had been treated with anticonvulsants including carbamazepine, zonisamide, and clobazam, but the seizures could not be controlled well by medication. By changing the combination of these anticonvulsants and their doses, they were temporarily effective for decreasing the frequency of seizures, but they soon became ineffective. In these circumstances, she was admitted to the hospital to decide her suitability for surgical intervention.

On admission, neuropsychological and physical examinations revealed no marked abnormality, also with regard to intelligence. Inter-ictal EEG showed scattered spike waves over the left temporal lobe. She underwent video-EEG monitoring of her seizures with scalp and sphenoidal electrodes. Totally 6 seizures were recorded. On ictal EEGs, initial changes (rhythmic δ wave) occurred always over the left temporal lobe, accompanied with her typical behavioral manifestations such as becoming spacy and laughing. MRI was performed to check for any structural brain abnormalities. The T2-weighted image (TR = 5000 msec/TE = 242 msec) and FLAIR image (TR = 10002 msec/TE = 133 msec) of MRI performed on a unit with 1.5 T superconducting magnet (Signa, GE Yokogawa Medical System, Tokyo, Japan), depicted mild atrophy of the right hippocampus with slight high intensity and no obvious abnormality in the left temporal lobe (Fig. 1). Then ictal and inter-ictal cerebral blood flow SPECT studies were performed with Tc-99m

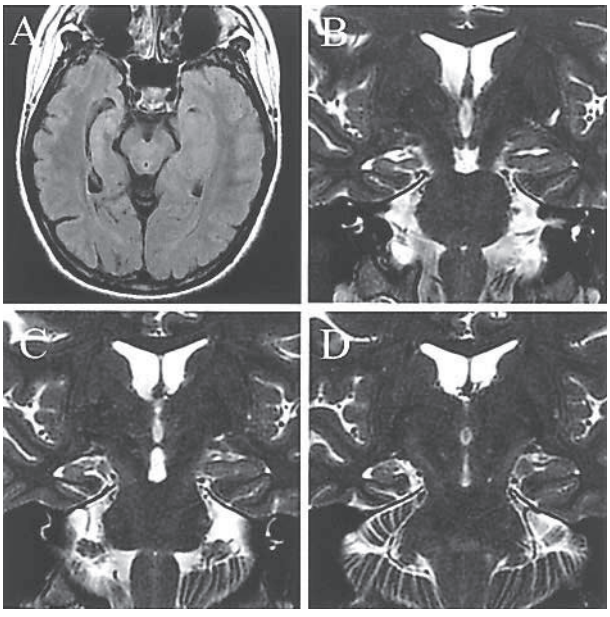

Fig. 1 FLAIR axial image (A; TR = 10002 msec/TE = 133 msec) and T2-weighted coronal images (B–D; TR = 5000 msec/TE = 242 msec). Mild atrophy of the right hippocampus is demonstrated. Slight high intensity is seen in the right medial temporal lobe on the FLAIR and T2-weighted images. In the left temporal lobe, no obvious abnormality is demonstrated.

ECD and I-123-IMP. In the ictal study, after confirming the occurrence of her seizure manifested by laughing, seven hundred and forty MBq of Tc-99m ECD (Daiichi Radioisotope Laboratories, Tokyo, Japan) was injected within 20 seconds through a venous line kept in a cubital vein. Twenty minutes after the injection, sixty projection data were acquired in a 128 × 128 matrix (pixel size: 1.7 × 1.7 mm) using a energy window of 10% centered at 140 keV, in a 360-degree step rotation mode with an acquisition time of 30 seconds each, by means of a triple head digital gamma camera equipped with low energy super high resolution fan-beam collimators (GCA 9300A, Toshiba Medical, Tokyo, Japan). The in-plane spatial resolution of this gamma camera was 7 mm FWHM. Two weeks after the ictal study, inter-ictal study was performed with I-123 IMP. Twenty minutes after an intravenous injection of 167 MBq of I-123 IMP (Nihon Medi-Physics, Hyogo, Japan), SPECT data acquisition was done on the same gamma camera system equipped with low energy high-resolution fan-beam collimators. Acquisition parameters were the same as used for Tc-99m ECD, except acquisition time (60 seconds/projection) and energy peak (160 keV). The image reconstruction was done by a filtered back-projection method with a ramp filter after preprocessing with Butterworth filter (cutoff frequency, 0.647 cycle/cm; order 8) for both ictal and inter-ictal SPECT. On the ictal SPECT, regional hyperperfusion was demonstrated in the left temporal lobe (Fig. 2). On the inter-ictal SPECT, regional blood flow

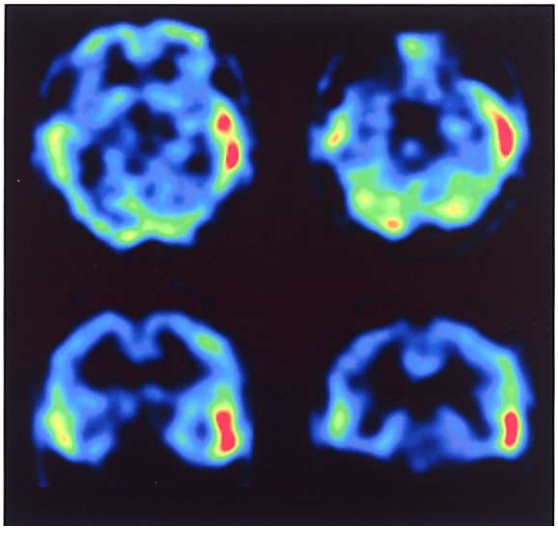

Fig. 2 Tc-99m ECD ictal cerebral blood flow SPECT, axial (*upper rows*) and coronal (*lower rows*) images. Regional hyperperfusion in the left temporal lobe is depicted.

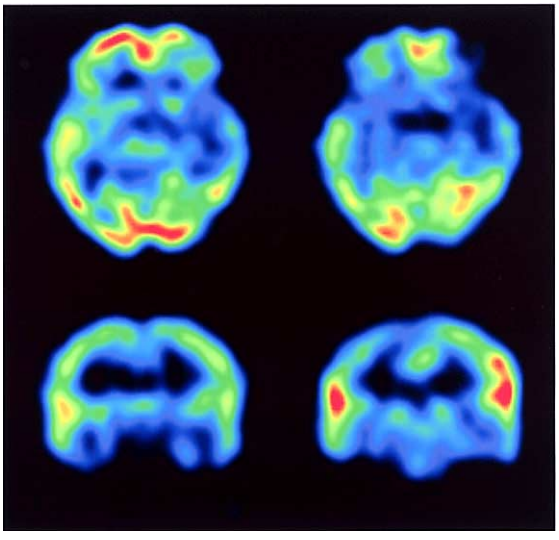

Fig. 3 I-123 IMP inter-ictal SPECT, axial (*upper rows*) and coronal (*lower rows*) images. In good contrast to the ictal cerebral blood flow SPECT (Fig. 2), regional blood flow of the left temporal lobe is rather decreased.

of the left temporal lobe was rather decreased (Fig. 3). Thus, comparison of ictal and inter-ictal cerebral blood flow SPECT indicated the left temporal lobe as the location of the seizures, which agreed with the findings of ictal EEGs. As a part of an additional phase 3 clinical trial of I-123 iomazenil, I-123 iomazenil SPECT study was performed after obtaining informed consent from the patient. Two hours and fifty minutes after the intravenous injection of 167 MBq of I-123 iomazenil (Nihon Medi-Physics, Hyogo, Japan), SPECT data acquisition was performed using the same gamma camera system and

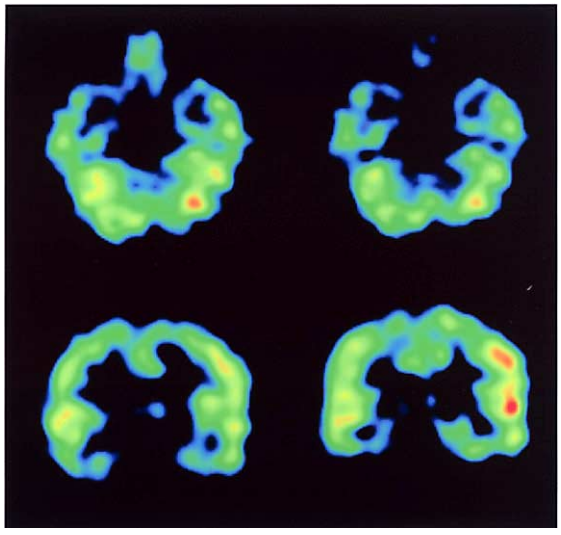

Fig. 4 I-123 iomazenil SPECT, axial (*upper rows*) and coronal (*lower rows*) images. Decreased BZDR density is demonstrated in the right medial temporal lobe, contrary to the findings of ictal and inter-ictal SPECT (Figs. 2, 3).

acquisition parameters as in the I-123 IMP SPECT. Image reconstruction was done also using the same method and reconstruction parameters as in the I-123 IMP SPECT. On the I-123 iomazenil SPECT, decreased BZDR density was demonstrated in the right medial temporal lobe, contrary to the findings of ictal EEGs and cerebral blood flow SPECT (Fig. 4).

After these non-invasive evaluations, intracranial EEG study was performed to confirm the epileptogenic focus. Video-intracranial EEG monitoring recorded 8 seizures. On ictal intracranial EEGs, initial rhythmic waves were detected always over the right temporal lobe, and then propagated to the left temporal lobe. Behavioral manifestation of laughing was observed after the abnormal electrical activity reached the left temporal lobe. Based on the findings of intracranial EEGs, right temporal lobe epilepsy was diagnosed, and partial resection of the right anterior temporal lobe including hippocampus was carried-out. Pathological examination of the resected surgical specimens revealed hippocampal sclerosis. After the surgery, the patient achieved seizure-free status without any neuropsychological deficit.

DISCUSSION

Epilepsy surgery is a good treatment option for intractable epileptic seizures. More than half of the patients undergoing epilepsy surgery achieve seizure-free status.[16,17] To obtain a good outcome by surgery, it is essential to determine the location of the seizures correctly. As noninvasive pre-surgical examinations of epileptogenic foci, MRI as anatomical and cerebral blood flow SPECT as functional brain imagings are usually performed in

addition to EEG. If all of MRI, cerebral blood flow SPECT, and EEG showed concordant results for localization of epileptogenic foci, it would increase their reliability. However, if they were discordant, it would be problematic as seen in our case.

MRI can depict structural abnormalities, which often correlate with the location of seizures. However, a certain fraction of patients with epilepsy have normal MRI findings,[18] and structural abnormalities seen on MRI do not necessarily indicate the epileptogenic focus.[19]

Cerebral blood flow SPECT is useful for determining epileptogenic foci, especially if ictal SPECT is performed. Even in the cases in which EEG or MRI could not localize the focus, ictal SPECT might be able to determine it.[20,21] A pitfall of ictal cerebral blood flow SPECT, however, is that the diagnostic finding of hyperperfusion is the secondary change caused by abnormal regional neuronal excitation. Correct localization of epileptogenic foci could not be obtained if the blood flow tracer was injected after the abnormal neuronal activity had been propagated from the origin to the other sites. It is difficult for the cerebral blood flow tracer to reach brain tissue at the moment of initial EEG change or emergence of behavioral manifestation because it is injected intravenously, even if the timing of the injection is appropriate. This inevitable delay and duration of seizures could influence the results of ictal cerebral blood flow SPECT. Surface EEG, which records temporal change in spatial summation of electrical neuronal activity, also has disadvantage in limited spatial resolution inversely correlated to the number of sampling electrodes. This disadvantage is more obvious especially in probing deep sites such as medial temporal lobe, aggravating difficulty in discriminating original and propagated seizures. Even relatively excellent temporal resolution of EEG might not be sufficient to overcome this difficulty. The false positive results of EEG and cerebral blood flow SPECT seen in our case could be attributed to these methodological limitations and nature of the patient's epilepsy, namely, rapid propagation from the origin to contralateral side. To supplement these methodological limitations in cerebral blood flow SPECT and EEG, BZDR imaging with iomazenil is thought to be helpful. BZDR imaging has an advantage over cerebral blood flow SPECT or EEG since it could determine the location of seizures from an aspect of BZDR density that could reflect neuronal tissue integrity, which could not be influenced by temporal change in electrical neuronal activity or cerebral blood flow.

According to the results of the European multicenter study of iomazenil, 23 of 89 epilepsy cases showed discordant results between iomazenil and inter-ictal cerebral blood flow SPECT. For identification of epileptogenic foci, sensitivity and specificity were 93 and 100% for iomazenil, 80 and 75% for cerebral blood flow SPECT, respectively.[13] Description of ictal cerebral blood flow SPECT was not provided in this report. In the report of the Japanese phase II clinical trial of iomazenil, iomazenil SPECT showed discordant results with ictal and inter-ictal cerebral blood flow SPECT in 4 of 21 and 21 of 69 epilepsy cases, respectively.[22] Statistical parameters such as sensitivity and specificity were not available in this report. Tanaka reported 10 cases of epilepsy, in which iomazenil SPECT showed discordant results with ictal and inter-ictal SPECT in 2 of 6 and 6 of 10 cases. Sensitivity, specificity, positive and negative predictive values were 90, 80, 82 and 89% for iomazenil, 80, 60, 67 and 75% for inter-ictal cerebral blood flow, 50, 83, 75 and 63% for ictal cerebral blood flow SPECT, respectively.[23] According to these past studies, discrepant results between iomazenil and inter-ictal or ictal cerebral blood flow SPECT were seen in about 20–60% of epilepsy cases, showing more correct localization of epileptogenic foci with iomazenil. Also in our case, although discordant with both cerebral blood flow SPECT and EEG, the findings of iomazenil supported the findings of MRI and provide correct information about the epileptogenic focus, which was of great help in placing intracranial electrodes and for determining the best surgical procedure. This case suggested that BZDR imaging with I-123 iomazenil could provide additional diagnostic value for pre-surgical evaluation of partial seizures, even after cerebral blood flow SPECT and EEG gave concordant results.

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