Original Article

Usefulness of ^{123}I -iomazenil SPECT for childhood focal epilepsies

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Abstract

Purpose: We investigated the usefulness of ^{123}I -iomazenil (IMZ-) SPECT to detect epileptic foci in children with symptomatic focal epilepsy (SFE).

Subjects: 21 children with SFE who underwent IMZ-SPECT to identify the epileptic focus were studied.

Methods: We retrospectively compared the localization and lateralization of epileptic foci

obtained from visualization of IMZ-SPECT images and those speculated based on a combination of clinical manifestations, EEG findings, and brain MRI. We then verified the concordance of the results between the two methods.

Results: There was concordance in both lateralization and localization in 9/12 patients with temporal lobe epilepsy (75%), in 2/5 patients

with frontal lobe epilepsy (40%), and in 2/4 patients with parieto-occipital lobe epilepsy (50%). Overall, the epileptic foci detected by IMZ-SPECT was consistent with those speculated based on other findings at least in 13 of 21 patients (62%) with SFE.

Discussion: As IMZ-SPECT is a potentially useful method for detecting epileptic foci, we should accumulate cases to verify the limitations and appropriate application of this method in the diagnosis of childhood SFE.

Introduction

In children with focal epilepsy refractory to antiepileptic drugs for longer than 2 years, surgery for epilepsy is considered at any age if the epileptic focus is clearly localized in a resectable brain region. As it is difficult to identify the precise location of an epileptogenic lesion, a combination of methods including long-term EEG/video monitoring, neuropsychological analysis, and neuroimaging is usually employed to achieve this task. In particular, when brain magnetic resonance imaging (MRI) reveals a localized structural abnormality in the assumed epileptogenic zone, the postoperative prognosis is the most favorable [1]. However, some children with intractable focal epilepsy do not show any abnormal findings on brain MRI, and it is not always straightforward to identify the epileptic focus precisely based on clinical and EEG findings alone. In such cases, brain functional neuroimaging studies may be useful [2-7]. Many studies have reported the usefulness of

interictal/ictal cerebral blood flow single photon emission computed tomography (SPECT) [8-12] and interictal ^{18}F -fluorodeoxyglucose positron emission tomography (FDG-PET) [2, 3, 7, 10, 13]. ^{123}I -iomazenil SPECT (IMZ-SPECT) was developed based on biochemical abnormalities existing in the epileptogenic brain lesion, and is able to detect the original epileptic focus effectively in the interictal state [14, 15]. In the field of epilepsy surgery in adults, several studies have employed this procedure as a presurgical evaluation, suggesting its usefulness for accurate identification of the epileptogenic lesions [16-18]. However, few studies have examined its usefulness in children with intractable focal epilepsy. In this study, we investigated the usefulness of IMZ-SPECT in children with symptomatic focal epilepsy who were refractory to antiepileptic drug treatment.

Subjects and Methods

We reviewed the records of patients with intractable focal epilepsy who were treated in our hospital and underwent IMZ-SPECT between 2006 and 2008. From these patients, we enrolled those whose epileptic focus was determined based on the concordance of at least two of the following findings: seizure semiology with localizing and lateralizing values [19, 20], interictal EEG, ictal EEG, and brain MRI findings.

We examined the concordance in lateralization and localization between the estimated epileptic focus with the decreased IMZ-uptake

region visualized on IMZ-SPECT. Localization was evaluated as completely concordant, partially concordant, or discordant between the two methods. When an abnormal site visualized on IMZ-SPECT was discordant with the estimated epileptic area (for example, cases in which the former was present in the fronto-temporal regions, but the latter was present in the frontal region), or when the former involved 2 independent sites and 1 of these was concordant with the latter, the localization was regarded as partially concordant between the two methods.

Furthermore, as it has been shown that the administration of benzodiazepines may influence the results of IMZ-SPECT [21], we investigated the consistency of lateralization and localization with respect to the presence or absence of these agents.

EEGs with a zygomatic/supraorbital lead were repeatedly performed. In most patients, long-term EEG/video monitoring was conducted to record seizures. Horizontal and coronal sections of high-resolution (1.5 T) T1/T2-weighted and FLAIR MRI of the head were evaluated.

For IMZ-SPECT, a 3-detector-type gamma camera (GCA9300 PI, Toshiba Co., Ltd.) and FAN BEAM LEHR high-resolution collimator were used. For rearrangement, Butterworth (cutoff: 0.10 cycles/pixel, order 8) and Shepp & Logan filters were employed as pretreatment and rearrangement filters, respectively. The attenuation-correction method was not used. IMZ at 167 MBq was injected intravenously, and imaging was performed for

35 minutes starting from 180 minutes after intravenous injection. IMZ-SPECT images were visually interpreted by one or two experienced radiologists who were blinded to all clinical information. For statistical analysis, the chi square test was employed. $P < 0.05$ was regarded as significant. The protocol of this study was approved by the Ethics Review Board of Tokyo Women's Medical University.

Results

Overall concordance

A total of 45 patients with intractable epilepsies underwent IMZ-SPECT, and 21 who satisfied the selection criteria were enrolled in this study. Before IMZ-SPECT, the 21 patients were classified into those with temporal lobe ($n=12$), frontal lobe ($n=5$), and parieto-occipital lobe ($n=4$) epilepsy based on seizure manifestations, interictal /ictal EEG, and brain MRI findings. Their ages at onset of epilepsy ranged from 2 months to 13 years and 9 months (mean: 6 years and 2 months, standard deviation [SD]: 4 years and 6 months). Ages at IMZ-SPECT study ranged from 1 year and 2 months to 18 years and 1 month (mean: 11 years and 4 months, SD: 4 years and 4 months).

In the temporal lobe epilepsy group, the mean ages at epilepsy onset and IMZ-SPECT study were 6 years and 11 months, and 11 years and 11 months, respectively (Table 1). Auras such as palpitation and an uprising gastric sensation characteristic of temporal lobe

Table 1. Demographic and clinical data of the 21 patients

Case No.	Epilepsy types	Age at IMZ-SPECT	Gender	Age at epilepsy onset	Aura	Seizure symptoms	Seizure frequency	Ictal EEG	Interictal EEG discharge	Brain MRI	Estimated epileptic focus	Decreased iomazenil-uptake	Use of BZD	Concordance of lateralization	Concordance of localization
T1	TLE	7y1m	F	5y10m	-	Clouding of consciousness with twitching of corner of mouth and eye deviation	Weekly	Lt. temporal region	Lt. temporal region	Thickening of gyrus in Lt. temporal lobe	Lt. temporal lobe	Lt. medial temporal lobe	CLB	Y	Y
T2	TLE	7y7m	M	6y7m	-	Arrest of motion with oral automatism Rt. clonic convulsion	Weekly	-	Lt. rolandic spike	Hypoplasia of Lt. temporal lobe	Lt. temporal lobe	Lt. temporal lobe	-	Y	Y
T3	TLE	9y6m	F	8y9m	Nausea	Loss of consciousness with atonic posture	Monthly	-	None	Lt. hippocampal atrophy	Lt. temporal lobe	Lt. temporal lobe	-	Y	Y
T4	TLE	10y7m	M	1y6m	-	Oral automatism Dream-like state	Monthly	-	Lt. temporal region	Lt. hippocampal atrophy	Lt. temporal lobe	Lt. temporal lobe	-	Y	Y
T5	TLE	11y4m	F	2y10m	-	Oral automatism	Monthly	-	Lt. temporal region	Normal	Lt. temporal lobe	Lt. temporal lobe	CLB	Y	Y
T6	TLE	11y9m	F	10y5m	-	Oral automatism	Monthly	-	None	Rt. hippocampal atrophy	Rt. temporal lobe	Rt. superior frontal lobe, Rt. inferior temporal lobe	-	Y	Partially concordant
T7	TLE	13y2m	M	12y11m	Palpitation Impatience	Verbal automatism	Monthly	-	Rt. temporal region	Thickening of Rt. temporal neocortex	Rt. temporal lobe	Rt. temporal lobe	-	Y	Y
T8	TLE	13y6m	M	4y10m	Floating feeling	Oral automatism	Monthly	-	None	Bilateral R>L hippocampal sclerosis	Bilateral temporal lobes	Rt. temporal lobe	CLB	N	Y
T9	TLE	13y10m	M	3y5m	-	Loss of consciousness	Monthly	Lt. temporal region	Lt. temporal region	Lt. hippocampal atrophy	Lt. temporal lobe	Lt. temporal lobe	CLB	Y	Y
T10	TLE	13y10m	F	11y6m	Ascending nausea	Loss of consciousness Oral automatism	Weekly	Lt. hemisphere	Lt. temporal region	Lt. hippocampal atrophy	Lt. temporal lobe	Lt. anterior-inferior temporal lobe > Lt. superior-frontal lobe	CLB	Y	Y
T11	TLE	15y0m	F	13y9m	Palpitation	Loss of consciousness Dream-like state	Monthly	-	Rt. temporal region	Dysplasia of Rt. temporal neocortex	Rt. temporal lobe	Rt. temporal lobe	-	Y	Y
T12	TLE	15y9m	M	1y11m	-	Loss of consciousness Oral automatism Visual hallucination	Monthly	-	Lt. central, temporal regions	Lt. hippocampal atrophy	Lt. temporal lobe	Rt. frontal lobe, Rt. parietal lobe	CLB	N	N
F1	FLE	1y9m	F	10m	-	Groaning with eye-rolling-up and elevation of both arms	Weekly	-	Bilateral frontal	Thickening of gyrus in R>L frontal lobe	Rt.>Lt. frontal lobe	Lt. temporal lobe, Rt. frontal lobe	CZP	N	Partially concordant
F2	FLE	6y11m	F	1y6m	Cephalic aura	Twitching of the Lt. palpebra, bilateral facial contraction, and groaning	Monthly	Bilateral frontal regions	None	Normal	Lt. frontal lobe	Lt. frontal lobe	-	Y	Y
F3	FLE	10y1m	F	2m	-	Postural tonic seizures with elevation of the Rt. arm	Monthly	Rt. frontal region	Rt. frontal	Mild atrophy of Rt. frontal lobe	Rt. frontal lobe	Rt. frontal lobe	CLB	Y	Y
F4	FLE	15y6m	F	4y4m	Cephalic aura	Lt. buccal clonic movement with deviation of the tongue to the Lt.	Daily	Rt. frontal	Rt. frontal	Normal	Rt. frontal lobe	Lt. frontal lobe	-	N	Y
F5	FLE	18y1m	F	13y7m	Sick feeling	Generalized tonic seizure	Monthly	-	Rt. temporal	Polymicrogyria of sylvian fissure in bilateral frontal lobe	Bilateral frontal lobe, Rt. temporal lobe	Bilateral superior-medial frontal lobe (Rt.>Lt.)	CLB	Y	Partially concordant
O1	OLE	1y2m	M	10m	-	Arrest of motion with oral automatism	Monthly	-	Bilateral occipito-temporal regions	Cortical dysplasia of Lt. occipito-temporal lobe	Lt. occipito-temporal lobe	Lt. occipito-temporal lobe	-	Y	Y
O2	OLE	12y	M	5y6m	Flashing object in the Lt. eye-field	Deviation of eye and face to the Lt.	Weekly	-	Rt. occipito-temporal regions	Bilateral parieto-occipital lobe	Rt. parieto-occipital lobe	Rt. parieto-occipital lobe, Lt. postcentral gyrus	-	N	Partially concordant
O3	OLE	13y3m	F	9y7m	Cephalic aura	Rt. aversive seizures, GTCS	Weekly	Lt. posterior hemisphere	Lt. central and Lt. occipital	Atrophy of Lt. parieto-occipital lobe	Lt. parieto-occipital lobe	Lt. occipital lobe	CLZ	Y	Y
O4	OLE	15y7m	F	10y3m	Blindness	Numbness of Lt. hand with tonic extension of both arms (L>R)	Monthly	Rt. dominant fronto-centro-parietal regions	Rt. centro-parietal regions	Normal	Rt. parietal lobe	Rt. dominant bil. parietal lobe, Lt. Superior frontal lobe	-	N	Partially concordant

Abbreviations: TLE=temporal lobe epilepsy, FLE=frontal lobe epilepsy, OLE=occipito-parietal lobe epilepsy, Lt.=Left, Rt.=Right, BZD=Benzodiazepine drugs, CLB=clobazam, CZP=clonazepam, CLZ=clorazepate

epilepsy were observed in 5 patients (42%). The interictal EEG showed epileptic EEG foci in 9 of the 12 patients: temporal region, 7; and temporal/central region, 2. Brain MRI revealed abnormal findings in either the hippocampus or temporal neocortex in 11 of the 12 patients (Fig. 1). Lateralization was concor-

dant in 10 patients (83%): the side at which IMZ-uptake was reduced on IMZ-SPECT and the side of the estimated epileptic focus were concordant (Fig. 2). Furthermore, localization was concordant in 10 patients (83%), partially concordant in 1, and discordant in 1. Patient T8 was judged to show concordant localiza-

Figure 1

Fluid Attenuated Inversion Recovery-MRI in Patient T9 (coronal view: 13 years and 10 months old). A slightly high-intensity lesion is noted in the left hippocampus, as indicated by the arrow.

Figure 2

IMZ-SPECT in Patient T9 (coronal view: 13 years and 10 months old). ^{123}I -iomazenil-uptake is decreased in the left medial temporal lobe region, as indicated by the arrow.

tion and discordant lateralization, because he had bilateral hippocampal atrophy (right > left) as a sequela of limbic encephalitis but decreased IMZ-uptake in the right temporal lobe. In this patient, IMZ-SPECT findings may have been correct because hippocampal atrophy was clearly right-sided. Overall, both the lateralization and localization were fully concordant in 9 (75%) of the 12 patients with temporal lobe epilepsy. Complete/partial concordance was noted in 10 (83%) of the 12 patients.

Five patients had frontal lobe epilepsy (Table 1). The mean ages at epilepsy onset and IMZ-SPECT study were 4 years and 1 month, and 10 years and 6 months, respectively. In Patient F1, clinical seizure symptoms and brain MRI findings suggested the presence of an epileptic focus in the right frontal lobe. However, IMZ-SPECT revealed reduced IMZ uptake in the right frontal and left temporal lobes; therefore localization was partially concordant. In Patient F5, brain MRI showed polymicrogyria involving both sylvian fissures with right-sided predominance. The interictal EEG revealed an epileptic focus on the lateral side of the right temporal lobe. In this patient, lateralization was concordant, but localization was partially concordant. Overall, both lateralization and localization were fully concordant in 2 (40%) of the 5 patients with frontal lobe epilepsy. Complete/partial concordance was noted in 3 (60%) of the 5 patients.

Four patients had parieto-occipital lobe epilepsy (Table 1). The mean age at epilepsy

onset was 6 years and 7 months. The mean age at IMZ-SPECT study was 10 years and 6 months. In Patient O4, although right parieto-occipital epileptic foci were estimated, IMZ-SPECT showed two independent foci involving not only the right parieto-occipital region but also the left posterior central region independently; therefore, the localization was partially concordant. Overall, both lateralization and localization were fully concordant in 2 (50%) of the 4 patients with parieto-occipital lobe epilepsy. Localization alone was partially concordant in 2 (50%) of the 4 patients.

Effect of benzodiazepines on the detection rate

Ten of 21 patients received benzodiazepine agents (clobazam: 8 patients, clorazepate: 1, and clonazepam: 1) (Table 1). Localization of the estimated epileptic focus and that of the lesion site visualized on IMZ-SPECT were concordant in 7 (70%) of 10 benzodiazepine-treated patients and in 8 (73%) of 11 non-benzodiazepine-treated patients. There was no significant difference between the two groups ($P>0.05$).

Discussion

Functional neuroimaging studies to investigate epileptogenic brain lesions include cerebral blood flow SPECT, FDG-PET, and IMZ-SPECT. The sensitivity of cerebral blood flow SPECT differs markedly between ictal and interictal studies. A meta-analysis of cerebral blood flow SPECT findings obtained in patients with intractable focal epilepsy

showed that the sensitivity of this procedure for detecting the epileptic focus was 44% in interictal, 75% in postictal, and 97% in ictal studies [10]. The sensitivity of ictal SPECT studies has been reported to be 90% or higher, suggesting its usefulness [8-12]. However, timely injection during the ictal phase remains the main limitation of SPECT in children with epilepsy [22]. It is necessary to infuse a tracer immediately after seizure onset. If the tracer is not infused within 20 seconds, the sensitivity may reduce markedly [23]. In addition, SPECT must be conducted in a shielded room. Therefore, hospitals that can perform this study are limited.

FDG-PET is particularly useful in patients with medial temporal lobe epilepsy. The sensitivity of this procedure for detecting hypometabolism of the temporal lobe in the interictal state is high, ranging from 80 to 90% [2, 3, 7, 9]. This method provides reliable information for lateralizing the epileptogenic temporal lobe in "MRI-negative" cases, with a yield ranging from 45 to almost 90 percent [2-7]. The sensitivity improves when seizures are frequent or when imaging is performed immediately after seizure onset [24]. However, FDG-PET devices are expensive, and only a limited number of hospitals are equipped with them.

Benzodiazepine receptors (BZRs) comprise a complex conjugated with γ -aminobutyric acid (GABA) receptors and Cl⁻ channels, and are involved in GABA-agonistic inhibitory neurotransmission. It is known that BZRs are reduced in the epileptic

focus [14]. Late IMZ-SPECT images obtained 3 hours after intravenous injection of ¹²³I-*iomazenil* reflect the distribution of central BZRs [25]. According to previous studies, the distribution of BZRs at the epileptogenic site was reduced not only in an experimental animal epilepsy model [15], but also in a resected section of the human epileptogenic tissue, which was reflected by a decrease in IMZ-uptake [14, 26]. McDonald et al. [26] showed that GABA/BZR affinity was reduced in CA1 and CA4 regions in hippocampal specimens resected from patients with intractable temporal lobe epilepsy. Theoretically, this procedure may be the most sensitive method for detecting epileptogenic lesions.

In this study, the sensitivity of IMZ-SPECT examination in detecting the epileptic focus in children with temporal lobe epilepsy reached 75%, and the detection rate was similar to that previously reported [27]. The results suggest the usefulness of IMZ-SPECT in children with temporal lobe epilepsy, as demonstrated in adults. As the sensitivity of interictal cerebral blood flow SPECT studies has remained low, IMZ-SPECT should be used in patients with intractable focal epilepsy of suspected temporal lobe origin. As for frontal and parieto-occipital lobe epilepsies, the concordance rates were 40 and 50%, respectively, which were much lower than that for temporal lobe epilepsy. This is consistent with the results of several previous FDG-PET and cerebral blood flow SPECT studies in patients with extra-temporal lobe epilepsy, in which the detection rates were as low as 50 to 60%

[28, 29]. However, the number of patients with extra-temporal lobe epilepsy in this study was too small to make meaningful comparisons with other neuroimaging modalities.

In this study, partial concordance in localization was noted in 5 patients who showed 3 independent lesions on IMZ-SPECT. In particular, 4 of them had extra-temporal lobe epilepsy; epileptic foci were also present in the contralateral hemisphere in all patients. In these cases, it is difficult to estimate whether the epileptic focus is actually multifocal, or comprises a network of epileptic foci emanating from the original focus.

The epileptogenic zone indicated by a decrease in IMZ-uptake is generally smaller than that detected in FDG-PET/cerebral blood flow SPECT study [27]. In our study, an epileptic focus detected by IMZ-SPECT involved two adjacent lobes in only 3 of the 12 children with temporal lobe epilepsy. Kaneko et al. [18] reported that in 7 adults with intractable temporal lobe epilepsy, IMZ-SPECT facilitated the visualization of more localized lesions without involving other regions as compared to cerebral blood flow SPECT and FDG-PET. In their study, IMZ-SPECT more accurately detected the epileptogenic focus than cerebral blood flow SPECT in 5 of the 7 patients and FDG-PET in 4 of the 7 patients.

Tanaka et al. [16] performed IMZ-SPECT, FDG-PET, and ictal/interictal cerebral blood flow SPECT in 10 patients with intractable epilepsy (temporal lobe epilepsy: 9, frontal lobe epilepsy: 1), and reported that the sensitivity/specificity of these procedures were

90/80, 100/30, 80/60, and 50/83%, respectively. Matsuda et al. [17] reviewed 126 patients with intractable focal epilepsy who underwent epilepsy surgery (temporal lobe epilepsy: 85, frontal lobe epilepsy: 32, occipital lobe epilepsy: 2, parietal lobe epilepsy: 1, and multilobar epilepsy), and reported an 80.2% detection rate of the primary epileptogenic focus for IMZ-SPECT, higher than that for cerebral blood flow SPECT (62.7%). On the other hand, IMZ-uptake may not be uniform in patients receiving benzodiazepines due to their biochemical nature, making it potentially difficult to interpret IMZ-SPECT findings [21]. In our study, there was no significant difference between the benzodiazepine-treated and non-benzodiazepine-treated groups.

A limitation of this study was the method in which we estimated the true epileptic focus based on the concordance of two or more reliable information sources among seizure semiology, interictal/ictal EEG and brain MRI examinations, and we evaluated the MRI as well as IMZ-SPECT findings based on visual analysis by one or two experienced radiologists. In addition, the number of patients was too small to perform statistical evaluation. These limitations lowered the validity of this study.

In conclusion, as IMZ-SPECT appears to be a more useful tool to detect epileptic foci than cerebral blood flow SPECT in children with intractable focal epilepsy. It is necessary to accumulate data of larger subsets of patients, and determine the indications and limi-

tations of this method, especially in those without MRI lesions.

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