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Ictal single-photon emission computed tomography with slow dye injection for determining primary epileptic foci in infantile spasms

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= Abstract =

Purpose : We investigated whether ictal single-photon emission computed tomography (SPECT) with prolonged injection of technetium-99m (99mTc) ethyl cysteinate dimer during repeated spasms can localize the epileptogenic foci in children with infantile spasms.

Methods : Fourteen children with infantile spasms (11 boys, 3 girls; mean age, 2.2±1.3 years) were examined. When a cluster of spasms was detected during video electroencephalography (EEG) monitoring, ^{99m}Tc ethyl cysteinate dimer was slowly and continuously injected for 2 minutes to determine the presence of ictal SPECT. For 7 children, the ictal and interictal SPECT images were visually analyzed, while for the remaining 7 children, the SPECT images were analyzed using the subtraction ictal SPECT coregistered to magnetic resonance imaging (MRI) (SISCOM) technique. Subsequently, we analyzed the association between the ictal SPECT findings and those of other diagnostic modalities such as EEG, MRI, and positron emission tomography (PET).

Results : Increase in cerebral blood flow on ictal SPECT involved the epileptogenic foci in 10 cases6 cases analyzed by visual assessment and 4 analyzed by the SISCOM technique. The ictal SPECT and video-EEG findings showed moderate agreement (Kappa=0.57; 95% confidence interval, 0.18-0.96).

Conclusion : Ictal SPECT with prolonged injection of a tracer could provide supplementary information to localize the epileptogenic foci in infantile spasms. (Korean J Pediatr 2009;52:804-810)

Key Words : Infantile spasms, Computed tomography, Single-photon emission

Introduction

Infantile spasms (IS) is an age-dependent devastating epilepsy that is characterized by clustering spasms, hypsarrhythmia on electroencephalography (EEG), and regression of psychomotor development[1, 2]. Although IS was classified as a secondary generalized epileptic syndrome characterized by generalized EEG abnormalities and its bilateral clinical manifestations[3], recent studies with positron emission tomography (PET) and single photon emission computed tomography (SPECT) revealed focal cerebral metabolic and perfusion abnormalities in several cases with spasms[4-7]. The focal abnormalities of cerebral metabolism and perfusion corresponding to EEG abnormalities in cryptogenic forms prompted the surgical removal of these regions[8].

Ictal SPECT has been considered a reliable tool for presurgical evaluation of epileptogenic foci in patients with intractable localization-related epilepsy[9]. Previous ictal SPECT studies in IS showed heterogeneous findings by visual assessment. Some children with IS had focal cortical hypoperfusion, whereas others showed hyperperfusion in the presumed epileptogenic focus[10]. Multichannel near-infrared spectroscopy (mNIRS), which can measure the real-time changes in regional cerebral blood volume, has also been applied to children with IS[11, 12] and a recent study showed a transient and rapid cortical hyperperfusion synchronized with each spasm and a gradual cortical hyperperfusion across the

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cluster of spasms[12]. Based on the findings of this mNIRS study, we hypothesized that the cumulative uptake of tracer during repetitive spasms might delineate the seizure focus more accurately. We applied prolonged injection of ^{99m}Tc-ethyl cysteinate dimer (ECD) during repeated spasms instead of the usual rapid shooting of the tracer. We determined whether ictal SPECT with prolonged injection of ECD during repeated spasms has clinical value in identifying the primary epileptogenic foci in children with epileptic spasms.

Materials and methods

A consecutive series of 14 children (11 boys and 3 girls) with epileptic spasms seen at our institute between October 2004 and July 2005 met the inclusion criteria. The onset age of spasms was three to 20 months (mean±standard deviation: 8.5±6.6 months). The mean duration of epilepsy was 17.9±14.7 months. Fourteen patients were divided into the symptomatic (8 patients) and cryptogenic (6 patients) group. Clinical data for all patients are provided in Table 1 and Table 2.

All patients underwent video-EEG monitoring, MRI, ictal and interictal SPECT. Video EEG was recorded for at least for 24 hours. The EEG parameters for localization in this study were classified as follows: focal polymorphic slowing, asymmetrical hypsarrhythmia, focal spikes, localized paroxysmal fast activity, spindle shaped fast activitiy, persistent localized brief electrodecrements, and amplitude attenuation. All patients underwent MRI on 1.5 Tesla scanners with sequences including T1 and T2 weighted images, fluid atte-

Table 1. Clinical Characteristics of Patients, Determined by Visual Analysis

Patient No.	Age /sex	Onset age (mo)	Freq. of spasms	Character of spasms	Video-EEG	Ictal/interictal SPECT	PET	MRI
1	M/5	3	7	asymmetric (Lt)	Lt.F	Lt.F, Lt. BG	Lt.F	Normal
2	M/3	20	9	symmetric	Rt.F	Rt.F, bilat. BG	Rt.F	diffuse atropy, ventriculomegaly
3	F/1	5	4	asymmetric (Lt)	Rt.O	Rt.O, bilat.BG	NS, CA	Normal
4	M/4	9	11	symmetric	no lat.	Rt.F	Rt.T, F	Normal
5	M/1	5	10	symmetric	Lt.TO	Lt TO	Not done	delayed myelination
6	F/3	2	7	asymmetric (Lt)	Rt.F	Rt.F, Rt.BG	Rt.H	Rt,F CD, schizencephaly
7	M/2	8	14	symmetric	Rt.F	Rt.F	Rt.F	Normal
8	M/2	7	9	symmetric	multi	Rt.F, Rt.P	Rt.F, Rt.P	Tuberous sclerosis (multiple tuber)
9	M/3	7	28	symmetric	Rt.F	Rt. F	No focal	Normal
10	M/1	6	10	asymmetric (Rt)	Lt.H	Rt.O	Lt.P,T,O>F	Lt. H CD
11	M/3	20	12	symmetric	Rt.F	Rt.F	Diffuse	Normal
12	F/3	20	17	symmetric	Rt.F	Rt,F, Rt.BG	Diffuse	diffuse atrophy
13	M/1	3	10	symmetric	Rt.TO	Rt. TO	Not done	PVL
14	M/1	3	26	asymmetric (Lt)	Rt. F.	Rt. P	Rt.T,P,O	Rt.F CD

1, 2, 8, 9, 11,12 : head drop, # 3, 4, 5, 6, 7,10, 13, 14: spasms
Abbreviations : Rt, right; Lt, left; F, frontal; O, occipital; P, parietal; muli, multifocal; TO, Temporo-occipital; BG, basal ganglia; Lat, lateralization; H, hemisphere; NS, nonspecific; CA, cortical atrophy; CD, cortical dysplasia

Table 2. Clinical Characteristics, Video-electroencephalography (EEG) and Magnetic Resonance Imaging (MRI) Findings, and Surgical Outcomes of Patients

Patient No.	Age sex	Video-EEG	SPECT (Visual/ SISCOM)	PET	MRI	OP	Pathology	Outcome (Engel's class)
1	M/5	Lt.F	Lt.F	Lt.F	Normal	Lt. F lobectomy	Calcification, NS	I
6	F/3	Rt.F	Rt.F/Rt.BG	Rt. H	Rt. F CD Schizencephaly	Rt. Hemispherotomy	Schizencephaly	I
7	M/2	Rt.F	Rt.F	Rt.F	Normal	Rt. F lobectomy	NS	I
9	M/3	Rt.F	Rt.F	no focal	Normal	Rt. F lobectomy	MD	I
11	M/3	Rt.F	Rt.F	Diffuse	Normal	Rt. F lobectomy	MD	I
12	F/3	Rt.F	Rt.F/Rt.BG	Diffuse	Diffuse atropy	Rt. F lobectomy	MD	I

Abbreviations : Rt, right; Lt, left; F, frontal; BG, basal ganglia; H, hemisphere; NS, nonspecific; NS, Nonspecific; CD, cortical dysplasia; MD, microdysgenesis nuation inversion recovery (FLAIR), fast inversion recovery for myelin suppression (FIRMS) and spoiled gradient echo (SPGR) in the coronal, axial and sagittal planes. Twelve patients were evaluated using [^{18}F] fluoro- deoxyglucose (FDG) PET scanning. All patients showed interictal PET study by processing the simultaneous EEG. We compared the ictal SPECT with interictal SPECT by visual inspection in 14 patients. We also performed a SISCOM analysis in seven out of 14 patients as described below.

1. Single photon emission computed tomography

Dual-headed SPECT cameras were applied to seven patients, and brain SEPCT studies were performed with ceraSPECT in the other seven patients because of a transition from dual-headed SPECT to ceraSPECT cameras at our hospital during that time. Dual headed SPECT The planes were obtained using the ADAC Dual Head VERTEX EPIC gamma camera (®Adac Laboratories, Milpitas, CA). CeraSPECT Brain images were obtained using a brain-dedicated annular crystal gamma camera (Digital Scintigraphic Incorporation, Waltham, Mass.) equipped with low-energy, high-resolution parallel-hole collimators. The full-width at half-maximum (FWHM) of a high-resolution collimators is typically 7.5 mm at the centre of rotation (COR) and 5.8 mm at the peripheral regions 9 cm from the COR. SPECT studies were acquired for 20 minutes in a 128×128 matrix with 3° of angular increment. SPECT was performed in a silent room following intravenous injection of 10 MBq/kg of 99 m Tc ECD (BARC, Mumbai, India).

All patients except two patients (#1, 4) took small amounts of sedative medications with chloral hydrate (10 mg/kg) during scanning. Ictal SPECTs were obtained by prolonged continuous slow injection of ECD when the observer detected the first ictal spasm of a cluster. Prolonged continuous slow injection means infusion at a regular velocity throughout two minutes from the first repetitive spasms by continuous injection (Fig. 1).

All patients underwent ictal and interictal SPECT studies at an interval of less than two week. In seven patients with IS, SISCOM images were constructed by using a Unix based workstation with image-analysis software packages (ANALYZE 7.5 AND Analyze/AVW; Biomedical Imaging Resource, Mayo Clinic Foundation, Rochester, MN, U.S.A.). The results were interpreted by radiological specialists who remained blind to the clinical and EEG findings of each patient.

Statistical analysis The concordance between ictal SPECT and video-EEG, FDG-PET, and brain MRI was presented by Cohens kappa (*k*) score and 95% confidence interval (CI). Agreement was considered poor when the k score was <0.2, fair when it was between 0.2 and 0.39, moderate when it was between 0.4 and 0.59, substantial when it was between 0.60 and 0.79, almost perfect when it was between 0.8 and 1.0. The significance level for all tests was set at *P*-value <0.05.

Results

Eight patients evolved into Lennox-Gastaut syndrome, and none of the patients had partial seizures. The age of children at SPECT study ranged from one to five years. The mean frequency of spasms within a cluster of spasms was 12.4±6.9. The mean duration of a cluster was 250±112 seconds (range: 125 to 456 seconds). The mean interval between spasms was 24±13 seconds (12 to 56 seconds).

The brain region showing the increase cerebral blood flow involved the epileptogenic foci of EEG in 10 cases (six cases in visual assessment and four cases in SISCOM) (Table 3). There were also the increase of blood flows in basal ganglia in five cases (#1,2,3,6,12) (Table 1, Fig. 2, 3). In the seven

Table 3. Concordance Rates between Single-photon Emission Computed Tomography (SPECT) and Video-electroencephalography (EEG), Positron Emission Tomography (PET), and Magnetic Resonance Imaging (MRI) in the 14 Patients with Infantile Spasms

Side by side (cases 1-7)	Video EEG (N=7)	PET (N=6)	MRI (N=7)
Ictal SPECT			
Concordance	6 (86%)	4 (67%)	1 (14%)
Discordance	1 (14%)	2 (33%)	6 (86%)
Siscom (cases 8-14)	Video EEG (N=7)	PET (N=6)	MRI (N=7)
Ictal SPECT			
Concordance	4 (57.1%)	2 (33%)	1 (14%)
Discordance	3 (42.9%)	4 (67%)	6 (86%)
Total (case 1-14)	Video EEG (N=14)	PET (N=12)	MRI (N=14)
Ictal SPECT			
Concordance*	10 (71.4%)	6 (50%)	2 (14%)
Discordance	4 (28.6%)	6 (50%)	12 (86%)

Abbreviations : N, number of patients
*k=0.571, CI (0.18-0.96), *P*<0.05

patients using dual headed SPECT, we compared ictal SPECT with interictal SPECT by visual inspections (Fig. 2). Ictal SPECT findings showed high concordance to the epileptogenic lesion on EEG (6/7, 86%) while FDG PET revealed the concordance in 67% (Table 3, Fig. 2). In patients studied with SISCOM, ictal SPECT showed 57.1% concordance for epileptogenic lesions on EEG and 33.0% concordance on FDG PET (Table 3, Fig. 3). A moderate agreement among ictal SPECT and the patterns of localization on video-EEG findings was observed (k=0.57, 95% CI (0.18–0.96, P< 0.02)).

Among the ten patients with concordance between EEG and ictal SPECT, six patients underwent epilepsy surgery with at least 12 months of postsurgical follow-up. The other patients had their conditions controlled by ketogenic diet or antiepileptic drugs. Histopathologic findings confirmed microdysgenesis or schizencephaly in four patients who had good surgical outcomes, and calcification or normal morphology in the others (Table 2).

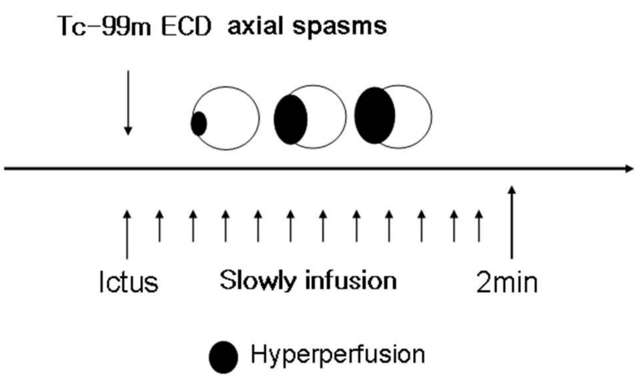

Fig. 1. Protocol of slow infusion of ^{99m}Tc ethyl cysteinate dimer.

Discussion

Our findings showed ictal perfusion changes were observed in focal epileptogenic lesions with the prolonged injection of tracer during repeated spasms in a cluster. Regardless of the difficulty of ictal SPECT in IS, ictal SPECT under prolonged injection of tracers showed high concordance rate (10/14, 71.4%) with video EEG findings.

Although ictal SPECT has recently come to be considered a reliable tool for presurgical detection of epileptogenic foci in patients with intractable localization-related epilepsy, ictal SPECT studies have limitations for various reasons. The first reason is the heterogeneity of the ictal findings in IS[10]. Haginoya et al.[10, 13] reported two distinct patterns of focal cortical hyperperfusion and diffuse pattern that probably included patients with diffuse cortical hyperperfusion and those with no changes in ictal SPECT findings in IS. They offered two possible explanations for this phenomenon. One is that the two patterns of ictal SPECT reflect the differences in blood flow because of frequency and interval between each tonic spasms. If tonic spasms are actually clusters of

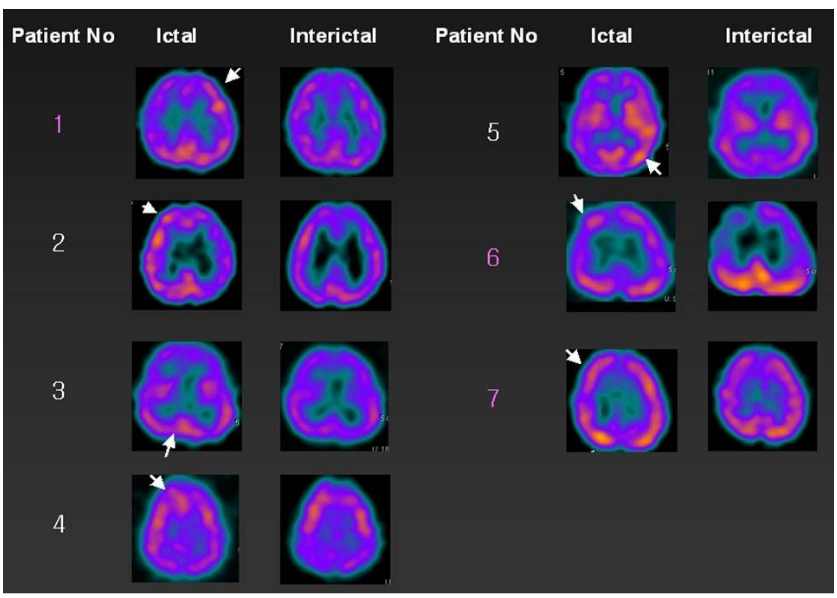

Fig. 2. Visual analysis of interictal and ictal single-photon emission computed tomography (SPECT) images of patients with infantile spasms.

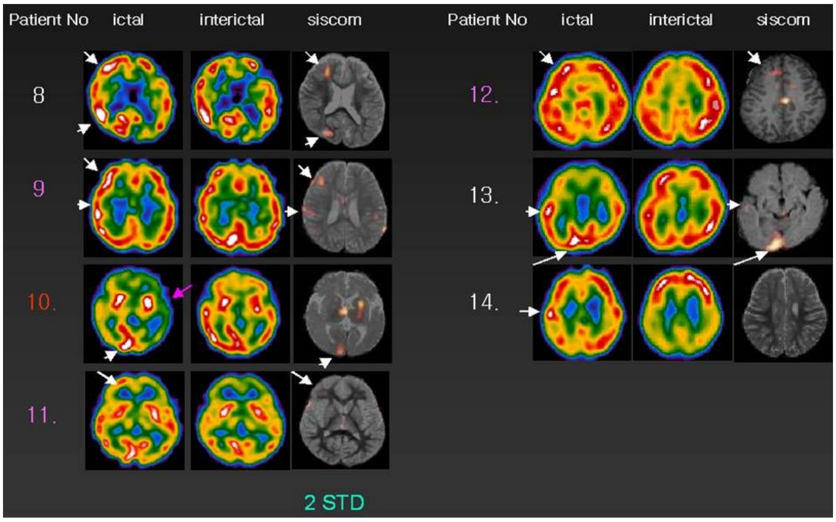

Fig. 3. Visual analysis of single-photon emission computed tomography (SPECT) images and analysis using the subtraction ictal SPECT coregistered to magnetic resonance imaging (SISCOM) technique for 7 patients in each case.

individual seizures, we would not be able to determine whether an ictal study is ictal or not. The other possibility is that the tonic spasms observed on IS is not always due to a single neurophysiological process. Diverse brain lesions were associated with IS and might explain the diversity of ictal SPECT patterns among patients with IS[10, 13]. The second reason is the unknown pathophysiologic mechanisms, although Chugani et al.[5, 6] suggested that pathology in the cortex plays an important role in the pathogenesis of the tonic spasms and suppose the hypothesis between the cortico-subcortico interrelationship in patients with IS. Asano et al.[14] hypothesized that spasm-associated fast-wave bursts might be derived from a cortico-subcortico-cortical pathway. We also saw the increase of blood flow in the basal ganglia as well as cortical lesions, which was associated with cortico-subcortico pathway in five patients (#1, 2, 3, 6, 12). The third reason is that it is very difficult to obtain a real ictal SPECT in IS because of the insufficient time resolution of SPECT for rapidly progressing and repeatedly occurring spasms. The results from secondarily generalized seizures are not as good because those seizures show more wide spread ictal discharge

Haginoya et al.[11] reported heterogeneous cerebral blood volume (CBV) during tonic spasms with mNIRS showed a remarkable increase and no substantial changes. Munakata et al.[12] reported transient increases that were synchronized with spasms, a gradual increase during an ictal event that fluctuated in synchrony with spasms, and a combination of transient and gradual increases in the heterogenous regional changes in CBV during ictus were observed in ictal events in patients with IS by using mNIRS. Although the pathophysiologic basis for the gradual increase in CBV during a cluster of spasms remains unknown, one possible explanation is that gradual increases in CBV may be indicative of the presence of an epileptogenic area that is activated subclinically before spasms, which subsequently dominates the entire ictal event. The progressive increase in CBV may result from frequent periodic or sustained cortical discharge, which might in turn cause an accumulation of blood[12].

Recently, Mori K et al.[17] reported the increase of regional cerebral blood flow (rCBF) during ictus and decrease of during the interictal period in the areas that coincided with focal cerebral lesions recognized by CT/MRI in the three patients with IS.

Maximal activity of [^{99m}Tc] ECD is reached 1 min after administration and then [99mTc] ECD is retained in the brain after an enzymatic conversion to ionized acid compounds for 6 to 8 hours[18]. Based on these reports, we hypothesized that ictal perfusion changes increased in the focal epileptogenic lesion, in which the continuous infusion of tracer could help CBV accumulate better than the rapid shooting of tracer. There might be increased CBV during spasms in our patients and those factors might reveal big changes between interictal and suspected ictal stage SPECT. Remarkably, Our ictal SPECT using prolonged infusion of tracer showed better localized epileptogenic areas than previous studies and supported by our surgical outcome based on SPECT finding and other diagnostic methods.

There were discordances between ictal SPECT and video-EEG findings because EEG showed no localization or multi-foci in four patients. Avery RA et al.[19] revealed the decrease of cerebral blood flow during seizures with ictal SPECT injections. If the ictal blood flow of the patient might be decreased during spasms of long duration, there might be no differences between the ictal and icterictal blood flows.

When we consider the various hypotheses of the pathomechanisms of epileptic spasms, our data disclosed high concordances between the ictal SPECT and video-EEG findings. Based on the post operative results of six patients, ictal SPECT and video-EEG might be highly sensitive tools to determine the epileptogenic cortical pathology in IS including epileptic spasms. However, caution should be recommended when interpreting the results of the present study, because the number of patients was relatively small.

한 글 요 약

영아연축에서 추적자의 느린 점적주사를 이용한 발작기 SPECT

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목 적 : 영아연축은 이차성 전신간질중의 하나로 간질 병소를 발견하기 힘든 질환중의 하나이다. 이에 저자들은 ^{99m}Tc-ECD 추적자의 느린 점적 주사를 이용한 발작기 SPECT를 통하여 영아 연축 환아에서 간질 병소를 찾아보고자 하였다.

방 법 : 2005년 3월부터 2007년 2월까지 연세대학교 의과대학 소아과에 내원한 영아 연축 14명의 환아를 대상으로 첫 연축이 발생하는 시점에 ^{99m}Tc-ECD 를 2분에 걸쳐 천천히 같은 속도로 주입하였다. 발작간기와 발작기 간의 SPECT 의 차이를 비교하였으며 객관적인 비교를 위하여 SISCOM기법을 사용하였다. 또한 간질 병소를 발견할 수 있는 진단기법인 뇌파, 자기공명영상, 양전자단층촬영(PET) 등과 비교 분석하였다.

결 과 : 전체 14례의 추적자의 느린 점적 주사를 이용한 발작기 SPECT 중 10례에서 간질 병소의 혈류가 증가하였다. 비디오 뇌파와 발작기 SPECT에서 간질병소의 일치율은 Kappa=0.57, 95% confidence interval: 0.18-0.96로 높게 나왔다. 이 중 6례에서 발작기 SPECT와 비디오 뇌파에 근거하여 간질 수술을 시행하였으며 수술적 예후가 Engle class I으로 좋은 결과를 보였다.

결 론 : 추적자의 느린 점적 주사를 이용한 발작기 SPECT는 간질 병소를 찾기 어려운 영아 연축 환아에서 간질 병소를 찾아내는데 중요한 역할을 하는 것을 알 수 있었다. 그러나 보다 큰 규모의 전향적인 연구가 필요할 것으로 사료된다.

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