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Incidence and Clinical Profile of Extra-medial-temporal Epilepsy with Hippocampal Atrophy

We tried to investigate the incidence and the clinical profile of intractable epilepsy with hippocampal atrophy and ictal onset zones located in areas other than the hippocampus (extra-medial-temporal epilepsy; EMTE). We included patients who had hippocampal atrophy confirmed by MRI but with extra-medial-temporal ictal onset zones as verified by invasive intracranial electrodes or video-EEG monitoring. The case histories, interictal EEG, ictal semiology, other MRI findings in addition to hippocampal atrophy, and results of ictal SPECT and PET scans were evaluated. Results were compared with those of surgically proven medial temporal lobe epilepsy with hippocampal atrophy recruited during the same period. 8.5% of the intractable epilepsy patients with hippocampal atrophy had extra-medial temporal epileptogenic zones. A history of encephalitis and hemiconvulsion-hemiparesis were significantly common in the EMTE group. Most of the interictal EEGs of EMTE patients showed extratemporal irritative zones. MRI, ictal SPECT, and FDG-PET seemed to be helpful at localizing the true epileptogenic zones. The predominant EMTE seizure type was focal motor seizure with secondary generalization. Some portion of intractable epilepsy patients with hippocampal atrophy had extra-medial-temporal epileptogenic foci and careful analysis of semiology and neuroimagings could yield clues to correct diagnosis.

Key Words: *Hippocampus; Atrophy; Extra-medial-temporal Epilepsy; Epilepsy, Temporal Lobe; Clinical Characteristics; Surgery*

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INTRODUCTION

Medial temporal lobe epilepsy (MTLE) constitutes the largest group of surgically remediable epileptic syndromes (1). Approximately 90% of patients with non-lesional temporal lobe epilepsy (TLE) have localization of the ictal onset zone in the amygdala or hippocampus (2). The hippocampus and parahippocampal regions are probably the minimal areas required for seizure generation in this epilepsy syndrome (3). The most effective treatment for intractable partial epilepsy of temporal lobe origin, is anterior temporal lobectomy with amygdalohippocampectomy (4-6). Atrophied hippocampi are highly epileptogenic. As a result, the detection of hippocampal atrophy by magnetic resonance imaging (MRI) may obviate unnecessary invasive studies and imply a good surgical outcome. The primary histologic alterations in mesial temporal sclerosis are cell loss and gliosis, which involve predominantly hippocampal formation (7-9). Correlated MRI findings of these histologic alterations were atrophy or signal changes of the hippocampus (10-12). There is now a consensus that MRI is a reliable indicator of hippocampal atrophy or sclerosis in the diagnosis of TLE. MRI features of hippocampal sclerosis may be identified with an accuracy approaching 90% by visual inspection of images and can also be measured by volumetric technique (11-14).

However, there may be some patients who have hippocampal atrophy but an epileptogenic zone outside the medial temporal area (extra-medial-temporal epilepsy; EMTE). To successfully treat these patients, it is very important to identify them accurately. In this study we have attempted to estimate the incidence of EMTE and to document their clinical characteristics.

MATERIALS AND METHODS

Patients

We retrospectively reviewed the records of patients who underwent presurgical evaluation and had hippo-

campal atrophy on MRI between 1994 and 1998. The evaluation included long-term video-electroencephalography (EEG) monitoring, MRI, positron emission tomography (PET), 2-hr interictal EEG, and ictal single photon emission computed tomography (SPECT) if possible. Inclusion criteria for the selection of EMTE were as follows; 1) definite evidence of hippocampal atrophy on MRI, and 2) extra-medial-temporal ictal onset zone confirmed by invasive monitoring or discrete extratemporal ictal onset EEG by scalp video-EEG monitoring. Discrete extratemporal ictal onset EEG was defined as the initial ictal rhythm of one electrode located over areas other than temporal lobe being greater by 200% in amplitude than the others. The diagnosis of hippocampal atrophy on MRI was made by visual analysis. We only included the patients with unequivocal hippocampal atrophy and increased signal on T2-weighted image. The invasive studies consisted of chronic implantation of grid and strip electrodes including two or three inferior temporal strips reaching the parahippocampal gyrus.

The patients' clinical histories were analyzed, and the presence of possible risk factors including febrile convulsion, age at onset, main seizure type, characteristics of aura, seizure frequency, and neurologic deficit were noted. The results of PET and ictal SPECT, additional findings on MRI other than hippocampal atrophy, spike distribution of interictal EEG, characteristic semiology on video-EEG monitoring were also analyzed (15). The diagnoses of epileptic syndromes (frontal lobe epilepsy, lateral temporal lobe epilepsy, occipital lobe epilepsy, and parietal lobe epilepsy) were made on the basis of presurgical evaluation results.

MRI

Standard MR imaging was performed on a 1.0-T or a 1.5-T unit with conventional spin-echo T1-weighted sagittal and T2-weighted axial and coronal sequences. To evaluate the hippocampus, T2-weighted fast spin-echo sequences with 3-mm thick sections and T-1 weighted 3D magnetization prepared rapid acquisition with gradient-echo sequences and 1.5-mm thick sections were obtained in the oblique coronal plane of the temporal lobe. The angle of oblique coronal imaging was perpendicular to the long axis of the hippocampus.

Video-EEG monitoring

Ictal scalp recordings were obtained using a full complement of scalp electrodes placed according to the International 10-20 system with additional anterior temporal electrodes (T1 and T2). Video-EEG monitoring was performed under the withdrawal of antiepileptic drugs except phenobarbital. Bipolar and referential montages were selected. The mean number of seizures we picked up during video-EEG monitoring was 3.7 ± 2.5.

PET

Axial raw data were obtained on a PET scanner 60 min after intravenous injection of ^{18}F-fluorodeoxyglucose (FDG) (370 MBq) during the interictal period. Acquisition time was approximately 20 min. Axial images were reconstructed with a Shepp-Logan filter (cutoff frequency, 0.35 cycles per pixel) and realigned in the coronal and sagittal planes. Spatial resolution was $6.1\times6.1\times4.3$ mm.

Interictal and Ictal SPECT

Ictal SPECT was performed during video-EEG monitoring. ^{99m}Tc was mixed with HMPAO and injected as soon as a seizure started. The brain SPECT image was acquired within 2 hr of injection, using a triple head rotating Gamma camera (Prism 3000, Picker, U.S.A.) with a high-resolution fan beam collimator, a brain perfusion SPECT was acquired with a step and shoot method at 3-degree intervals using a 128×128 matrix. The whole acquisition lasted 15 min. Interictal and ictal SPECT images and PET were reviewed by one experienced physician who was unaware of the clinical history or the results of the other presurgical evaluations. Coronal, sagittal and transaxial images were analyzed. The results of interictal SPECT were considered in the interpretation of ictal SPECT.

All clinical and neuroimaging findings of these patients were compared with those of 87 surgically proven MTLE patients recruited during the same period. MTLE patients were selected when they had excellent surgical outcome (free of disabling seizures) after standard anterior temporal lobectomy with amygdalohippocampectomy and unilateral hippocampal sclerosis on MRI. All patients had been followed up for more than one yr after operation. Chi-square test was used to test statistical significance.

RESULTS

Clinical features

We identified 247 refractory epilepsy patients with hippocampal atrophy who underwent video-EEG monitoring during the study period. Twenty-one patients who met the criteria of EMTE were included in the analysis. The mean age was 26.5 ± 8.2 yr and the mean age at onset of epilepsy was 8.9 ± 6.7 yr. A history of febrile convulsion was reported in ten patients. Mental retarda-

tion (IQ <70) was also found in ten of 21 patients. The mean frequency of seizures was 4.8±4.9 per month. Possible causes of epilepsy other than febrile convulsion were reported in ten patients, and they were as follows: encephalitis in five, hemiconvulsion-hemiparesis in four, and head trauma in one. Aura were present in thirteen patients; affective symptoms in five, visual hallucinations in three, somatic sense in two, dizziness in one, headache in one, and olfactory hallucination in one. The epileptic syndromes consisted of eight frontal lobe epilepsies (FLE), four occipital lobe epilepsies (OLE), three lateral TLE (LatTLE), one parietal lobe epilepsy (PLE), and five multifocal epilepsy cases. Eight patients showed abnormal neurologic status. Four patients had hemiparesis, two had visual field defect, and two had hemiparesis with homonymous hemianopsia.

Interictal EEG

Interictal EEG recordings were characterized by the presence of interictal epileptiform discharges (IEDs) from areas other than the anterior temporal area. Seven cases had multifocal IEDs, including anterior temporal sharp waves. Ten showed IEDs exclusively in areas other than the anterior temporal region (one parietal, one occipital, three posterior temporal, and five frontal areas). Three cases had IEDs only in the anterior temporal area. One had no IEDs on scalp EEG.

MRI

In addition to hippocampal atrophy, eight patients had hemiatrophy ipsilateral to the hippocampal atrophy (Fig. 1). Additional focal cerebromalacia were also found in two cases (one in the frontal and one in the occipital lobe).

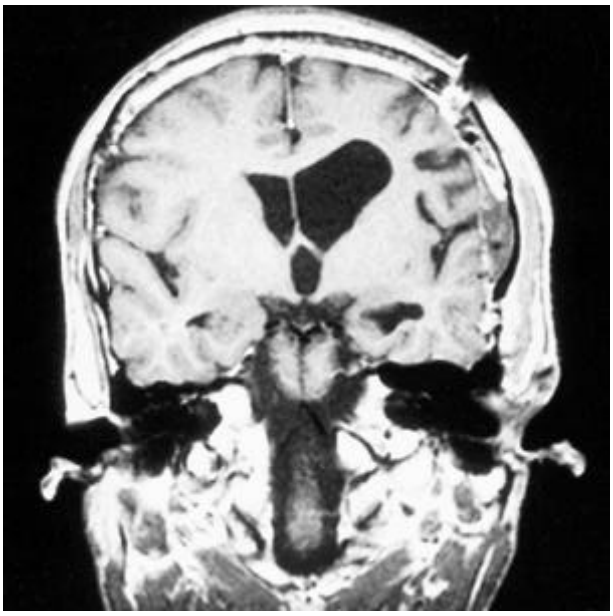

Fig. 1. The left hemispheric atrophy and hippocampal atrophy.

PET

FDG-PET was performed in all patients. Hypometabolism confined to the ipsilateral temporal lobe was observed in six cases. Two patients with normal MRI except hippocampal atrophy had focal hypometabolism in areas other than the temporal lobe (one in the frontal and the other in the occipital lobe) (Fig. 2) and one had multifocal hypometabolism. Hemihypometabolism was found in eight patients who had hemiatrophy on MRI. Four had normal metabolism.

Ictal SPECT

Ictal SPECT was performed in 20 cases. The mean injection delay was 32.0±11.9 (range: 14-52) seconds. Hemihyperperfusion was found in four cases, and focal temporal hyperperfusion in six cases. Focal hyperperfusion in areas other than the temporal lobe was observed in three cases of frontal lobe epilepsy (FLE), three of occipital lobe epilepsy (OLE), and one of multifocal epilepsy (Fig. 3). Three of seven patients who showed extratemporal hyperperfusion had normal MRI except hippocampal atrophy. We could not find any change of perfusion in three patients.

Video-EEG monitoring

The most common seizure type, as confirmed by video-EEG monitoring was focal clonic seizure followed by secondary generalized tonic-clonic seizure (7 cases). Automotor seizure characterized by brief loss of consciousness and automatism was observed in only six cases. Two patients with automotor seizures also had preceding visual hallucinations. Three of four patients with occipital lobe epilepsy had automotor seizures (Table 1).

Comparison between EMTE and MTLE

Automotor or psychomotor seizure, which was most commonly encountered in MTLE (92.3% in our series) was observed in only 28.6% of the EMTE cases ($p<0.0001$) (Table 2). The mean age at onset and the incidence of febrile convulsion were not significantly different. A history of encephalitis or hemiparesis-hemiconvulsion was more common in the EMTE group ($p<0.05$). Interictal epileptiform discharges observed in areas other than the anterior temporal region were significantly com-

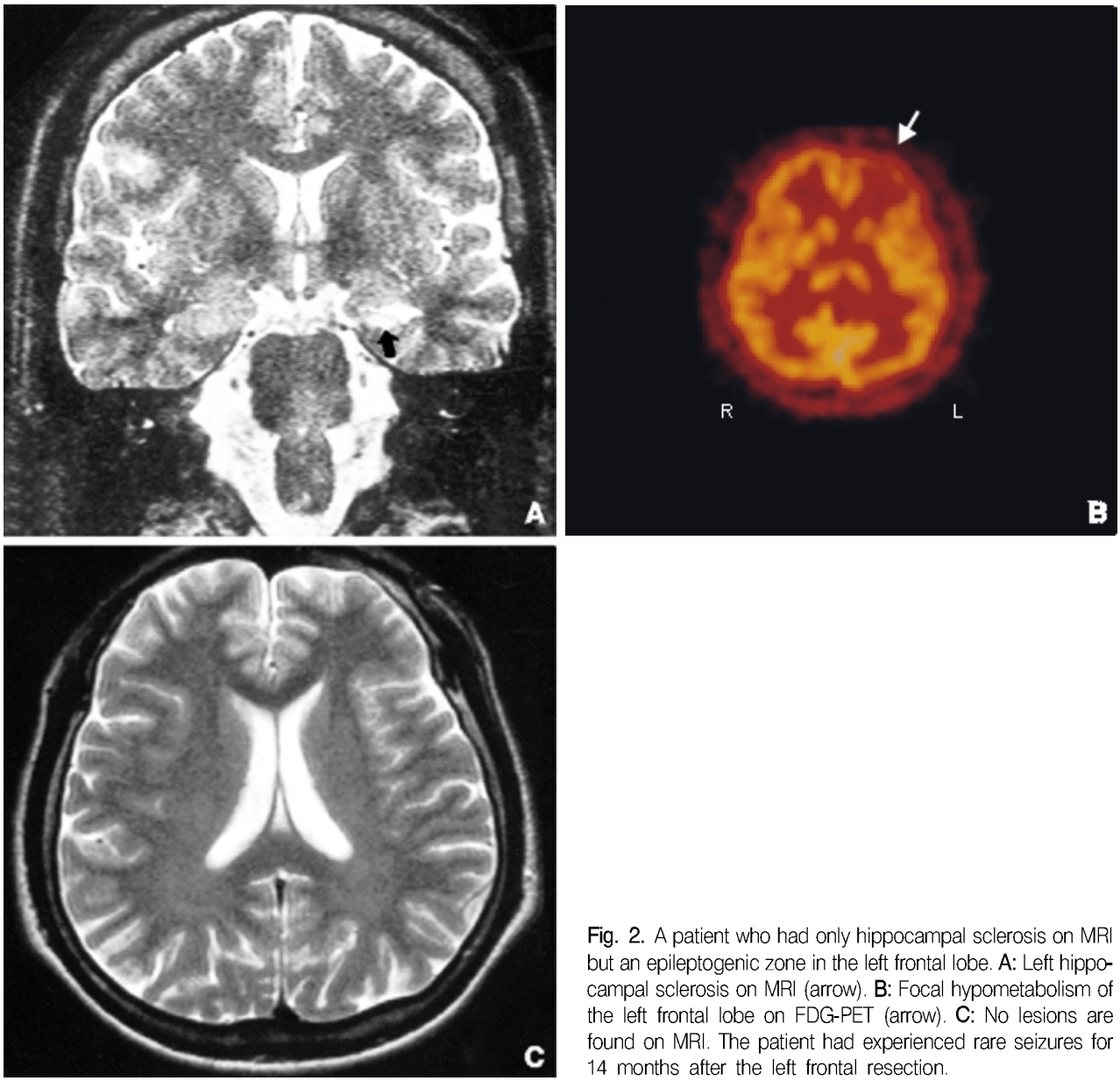

Fig. 2. A patient who had only hippocampal sclerosis on MRI but an epileptogenic zone in the left frontal lobe. **A:** Left hippocampal sclerosis on MRI (arrow). **B:** Focal hypometabolism of the left frontal lobe on FDG-PET (arrow). **C:** No lesions are found on MRI. The patient had experienced rare seizures for 14 months after the left frontal resection.

mon in the EMTE group ($p<0.0001$). Presence of lesions other than hippocampal atrophy was also common in EMTE patients ($p<0.01$). More widespread or focal hypometabolism in areas other than temporal lobe was frequently seen in the EMTE group ($p<0.0001$). Extratemporal hyperperfusion was also more frequently encountered in EMTE ($p<0.0001$).

Surgery

Operations were performed in 15 cases. The resected areas were the frontal lobe in five, the occipital lobe in four, the parietal lobe in three, and the posterior temporal area in two cases. Functional hemispherectomy was performed in one patient who had frontal lobe epilepsy and nonfunctioning hand. The mean follow-up period was 2.6 yr (12 months-4.5 yr). Seven cases were free from seizure and four cases had worthwhile improvement (seizure reduction >90%). The seizure reduction did not reach 90% in four cases.

DISCUSSION

There are two possible hypotheses for the extrahippocampal epileptogenic zone in the patients with hippocampal atrophy. The pathogenesis of hippocampal atrophy or sclerosis has been the subject of controversy (16). Current concepts of the pathogenesis began with a surgical series of patients with TLE (17-19). These studies cor-

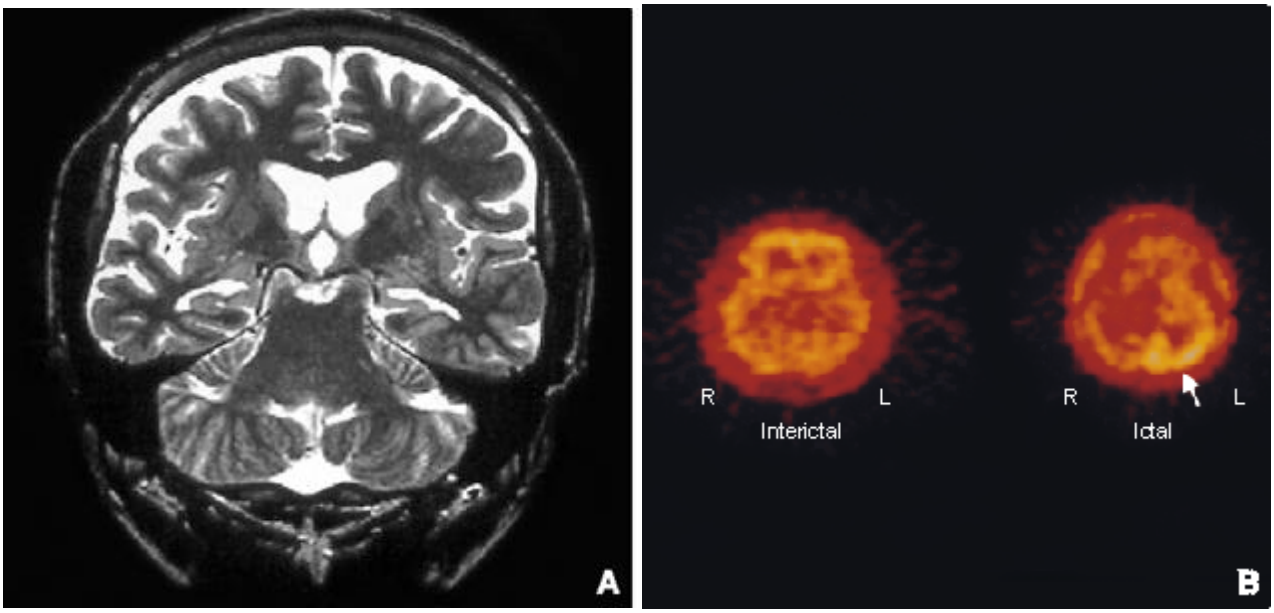

Fig. 3. A patient who only had hippocampal sclerosis on MRI but with an epileptogenic zone in the left occipital area. **A:** Left hippocampal sclerosis on MRI. **B:** Focal hyperperfusion of the left occipital lobe on ictal SPECT (arrow). The patient had been free from seizure for one yr after the left occipital lobectomy.

Table 1. Seizure types according to epileptic syndromes

Seizure type	FLE (n=8)	OLE (n=4)	LatTLE (n=3)	PLE (n=1)	Multifocal (n=5)
Focal clonic → GTCS	3		1	1	2
Automotor		3	1		2
Versive	1	1	1		
Hypermotor	2				
Sudden GTCS	1				1
Brief tonic (SSMA)	1				

FLE, frontal lobe epilepsy; OLE, occipital lobe epilepsy; LatTLE, lateral temporal lobe epilepsy; PLE, parietal lobe epilepsy; Multifocal, multifocal epilepsy; n, number of patients; GTCS, generalized tonic-clonic seizure; SSMA, supplementary sensorimotor seizure

related pathology with clinical history and found that hippocampal sclerosis was probably a chronic pathology associated with a prior cerebral injury, such as a seizure early in life, and became an epileptogenic zone later in life.

However, limbic structures are vulnerable to many kinds of insults. Hippocampal damage can be induced by a variety of toxic, metabolic and hypoxic disturbances (20) and these do not necessarily produce medial TLE. Diffuse insults can cause hippocampal damage while render areas other than hippocampus as epileptogenic zones. These insults may be severe enough to cause hemiatrophy or cerebromalacia. Or these insults may be so mild as to make a cryptic lesion such as focal neuronal loss or gliosis in addition to hippocampal atrophy. It might be implicated that our cases had relatively frequent relevant past medical history, which suggested diffuse brain injury such as encephalitis or hemiconvulsion-hemiparesis syndromes. Other structural abnormalities found on MRI, abnormal neurologic status, and interictal epileptiform discharges not confined in the temporal area, also suggest widespread initial damage and the presence of non-medial epileptogenic foci.

Another hypothesis is that repeated seizures from the hidden pathology other than hippocampus may cause hippocampal atrophy. Hippocampal sclerosis has been regarded to be the cause and consequence of epilepsy (21). Quantified hippocampal pathology techniques have shown that repeated seizures can contribute to hippocampal neuronal loss (22). There was also evidence consistent with the idea that repeated complex partial seizures for more than 15 to 20 yr could be linked with hippocampal neuronal damage (23).

Our cases might be regarded as having characteristics of dual pathology, that is, hippocampal sclerosis as well as defined extrahippocampal structural abnormalities. Structural abnormalities usually mean a tumor or cortical dysplasia (24-26). However, several studies also included

Table 2. Comparison of clinical characteristics and neuroimaging findings of EMTE and MTLE

	Extra-medial-temporal lobe epilepsy (n=21)	Medial temporal lobe epilepsy (n=87)
Mean age (yr) (Mean±SD)	26.5±8.2	28.4±9.1
Age at onset (yr) (Mean±SD)	8.9±6.7	12.8±7.6
History		
Febrile convulsion	47.6%	65.5%
Encephalitis	23.8%	9.0%
Hemiparesis and hemiconvulsion	19.0%	5.7%
Semiology of seizure		
Focal clonic → generalized tonic-clonic seizure	33.3%	0%
Automotor	28.6%	92.0%
Versive	14.3%	2.3%
Hypermotor	9.5%	5.7%
Sudden generalized tonic-clonic seizure	9.5%	0%
Brief tonic (supplementary sensorimotor seizure)	4.8%	0%
Interictal sharp waves		
Other than anterior Temporal	81.0%	6.9%
Anterior Temporal only	14.3%	85.1%
Normal	4.7%	8.0%
MRI		
Hippocampal atrophy only	52.4%	83.9%
Presence of other lesion	47.6%	16.1%
PET	(n=21)	(n=80)
Hemihypometabolism	38.1%	5.0%
Extratemporal focal hypometabolism	14.3%	5.0%
Temporal hypometabolism	28.6%	83.7%
Normal	19.0%	6.3%
Ictal SPECT	(n=20)	(n=72)
Extratemporal focal hyperperfusion	35.0%	5.6%
Temporal hyperperfusion	30.0%	88.8%
Hemihyperperfusion	20.0%	5.6%
Normal	15.0%	0%

SD, standard deviation

microscopic lesions such as heterotopias or microdysgenesis and have found an incidence of dual pathology in more than 30% of cases (26, 27). Even if the temporal specimens contain more than one pathology, it is not clear how these different temporal abnormalities contribute to the generation of seizures. Current electrophysiologic evidence suggests that the hippocampus is the most frequent first site of ictal onsets, even in patients with extrahippocampal mass lesions (21, 24, 28). The characteristics of our cases are somewhat different from those of dual pathology in that we selected patients with hippocampal atrophy who had a clear-cut extrahippocampal ictal onset zone. Furthermore, our cases did not have any discrete pathologic lesions on MRI, such as a mass lesion or focal cortical dysplasia.

MTLE has a relatively characteristic clinical ictal semiology (3, 29). Auras are frequent and often consist of visceral sensation, or fear, or other vegetative autonomic symptoms and psychic phenomena. These auras are usually followed by a motionless stare with progressive clouding of consciousness and oroalimentary or hand automatisms. These seizures can be classified as the automotor or the psychomotor type (15). 92.3% of our MTLE series had these kinds of seizures. However, ictal semiology confirmed by video-EEG monitoring showed that 76.2% of the EMTE patients had different types of ictal semiology. Three of four patients with occipital lobe epilepsy had automotor seizure resembling MTLE. However, three of four occipital lobe epilepsy patients also had visual hallucination as aura. Careful history taking of ictal semiology or video-EEG monitoring can provide a clue for correct diagnosis.

The diagnostic role of ictal SPECT and FDG-PET in MTLE is well known. The localizing value of ictal SPECT has been shown to be up to 94% (30). Lateral as well as medial temporal hyperperfusion is a typical pattern of ictal SPECT in MTLE. A distinct metabolic pattern is usually seen interictally in FDG-PET in 86% of patients with TLE (31). It is a widespread but particularly marked lateral temporal hypometabolism interictally (32). False-

positive results are known to be rare (33). As shown in our results, focal hypometabolism of FDG-PET in areas other than the temporal area or focal extratemporal hyperperfusion can be a clue to the diagnosis of extramedial temporal epileptogenic foci.

We included cases in which ictal onset zones were confirmed by invasive study or discrete ictal EEG onset of scalp EEG. It seems ideal to include only surgically proven cases with good outcome. However, the ictal EEG patterns of MTLE have been well known and dicrete ictal onset (onset at the only one electrode) outside the temporal areas has never been reported in MTLE (34-36). As a result including these patients in our study seems not illogical.

Our results indicate that some portion of intractable epilepsy patients with hippocampal atrophy have extramedial-temporal epileptogenic foci and careful analysis of history, semiology, PET, ictal SPECT, and MRI yield clues to correct diagnosis. While patients with hippocampal atrophy often proceed to epilepsy surgery without further invasive monitoring, our results demonstrate that there is a group of patients in whom such a procedure is not the proper management.

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