Epileptogenic Foci on Subdural Recording in Intractable Epilepsy Patients with Temporal Dysembryoplastic Neuroepithelial Tumor

To investigate the epileptogenic foci in dysembryoplastic neuroepithelial tumor (DNT) in the temporal lobe, we studied extraoperative electrocorticography (ECoG) with subdural electrode arrays from nine patients with intractable epilepsy due to temporal DNT. Ictal onset zones and irritative zones were decided by the ECoG. The locations of these zones were compared to the location of the tumor. The number of ictal onset zone and irritative zone was 2.1 ± 0.93 and 2.9 ± 1.45 in a patient with a DNT. They were detected more frequently in the adjacent tissues of the tumor (88.9%) rather than within the tumor or in mesial temporal area (66.7%). Mesial temporal involvement was found in 6 patients (66.7%) as an ictal onset zone, and in 5 (55.6 %) as an irritative zone. The 7 patients (77.8%) had ictal onset zone in areas different from active irritative zone. The surgical outcome was better, when ictal onset zone was completely resected rather than partially removed. Temporal DNT can make multiple ictal onset zones and irritative zones in different regions including the mesial temporal area. Deliberate resection of epileptogenic foci, including all ictal onset zones and irritative zones, ensures excellent seizure control.

Key Words : Epilepsy, Temporal lobe; Brain Neoplasms; Neurosurgery

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INTRODUCTION

Dysembryoplastic neuroepithelial tumor (DNT) has been recognized as a cause of intractable complex partial seizures (1-4). DNTs have pathologic features, which are highly associated with cortical dysplasia in 69 to 100% of the cases (5-7). The cortical dysplasia has highly intrinsic epileptogenicity (8). DNT has the highest incidence in temporal lobe ranging from 62 to 94% (1, 5, 6, 9). In epilepsies with temporal lobe lesion, mesial temporal sclerosis can be coexisted in a range of 8 to 22% (10, 11). Coexistence of the dysplastic tissues and mesial temporal sclerosis in temporal DNT can cause temporal DNT enhance to have the potential of being highly epileptogenic in multiple areas.

DNT is usually detected by MRI, and its relationship to the epileptogenic foci can be determined by extensive interictal and ictal EEG recordings. The relationship of structural lesions to epilepsy is not always simple or clear-cut. Noninvasive recording and careful mapping show that a structural lesion is not the source of epileptic activity (12-14). Some studies about lesional epilepsies showed lateralization of epileptogenic foci to distant ipsilateral (15, 16) or even to contralateral regions (17). However, few studies have addressed a clear correlation between the lesion site and epileptogenic foci of the ictal onset zone as well as the irritative zone.

The surgical strategies applied to the temporal lesion remain controversial, although generally optimum seizure control in epilepsy surgery is achieved when the lesion is removed with the surrounding epileptogenic cortex (18, 19). The prognosis was excellent only after the resection of the DNT, as far as epileptic seizures were concerned (1, 2). En bloc resection of low grade tumor alone without the aid of electrophysiologic studies might result in good postoperative control of the patient's epilepsy (4, 17, 20, 21). However, the results in temporal lobe were somewhat different; only lesionectomy in the temporal lobe or partial removal of epileptogenic foci was disappointing (22, 23), and the electrophysiologic guided resection for temporal lobe tumors was superior to only lesionectomy (13, 19, 24). Furthermore, seizure control following temporal lobe surgery, guided by image analysis and electrocorticography (ECoG), can be achieved without complete removal of the lesion (19, 25, 26). In studies using ECoG, the correlation between DNT and epileptogenic foci is not sufficient because the epileptogenic foci has been evaluated mainly by the irritative zones. The clear relationship between the tumor and epileptogenic foci can be verified by analyzing the ictal onset zones as well as the irritative zones.

In this study, we investigated the relationship of DNT to the epileptogenic foci with regards to the ictal onset zones as well as the irritative zones using chronic subdural electrode recording. We also evaluated the outcome of the resection of the lesion-plus-epileptogenic foci, including the ictal onset zones and the irritative zones.

MATERIALS AND METHODS

Subjects

Subjects were selected from 21 patients who underwent epilepsy surgery due to DNT in the temporal lobe and intractable epilepsy. They were admitted in the epilepsy monitoring unit of Samsung Medical Center (Seoul, Korea) between February 1995 and November 1998. Among the 21 patients, nine patients who underwent intracranial video/ECoG recording with subdural electrode arrays were included in this study. The nine patients (4 women and 5 men) aged 12 to 44 yr underwent long term video/ECoG monitoring for 7.8±2.9 days. During the monitoring the patients had 8.2±5.2 epileptic seizures. Retrospectively, we reviewed their neuroimaging, extraoperative ECoG and surgical outcome. Their clinical findings are summarized in Table 1.

Long-term Electrocorticographic Monitoring with Subdural Electrode Arrays

Subdural electrodes plates (PMT Co., MN, U.S.A.) were positioned over the temporal region after presurgical evaluation, including interictal and ictal video/EEG monitoring (Vanguard system, Cleveland, OH, U.S.A.), brain-magnetic resonance imaging (MRI) and functional imaging studies. The functional imaging studies include positron emission tomography, ictal single photon emission computerized tomography, and intracarotid amobarbital testing. Each plate represented a sheet of Silastic embedded with 4 mm diameter stainless-steel electrode discs. The centers of the discs were 10 mm apart and the electrode wires were bundled into a Silastic-covered cable designed to exit through a subcutaneous tunnel, independent of the craniotomy incision. They contained 60 to 100 electrodes (mean: 74.4±12.2) per patient. We tried to cover the lesion of the MRI, the ictal onset zone of scalp EEG, and eloquent areas such as the speech area if the lesion was located in the dominant hemisphere. In all patients, the mesial temporal area was covered by subdural electrodes to detect the electrophysiologic mesial temporal involvement (a four by eight grid array in five patients, a four by five in one patient, and one by eight strip electrodes in three patients). After the insertion of electrodes, surgical complications such as subdural hematoma or abscess did not occur in all the patients but transient partial third nerve palsy occurred in one patient (patient 3). We analyzed the interictal and ictal epileptiform discharges during the video/ECoG monitoring. We considered the epileptogenic focus as the zone with maximum interictal epileptiform activity, or the zone with maximum ictal epileptiform discharges at ictal onset, which could be detected on the same or different areas.

We counted the number of frequency of interictal epileptiform discharges on daily sampled recording for more than 2 hr. We decided highly irritative zone as areas on the subdural electrodes, which had interictal epileptiform discharges with more than 10% of frequency.

We labeled ictal onset zones as the areas on the subdural electrodes, which had initial ECoG changes during the seizures.

Localization of Subdural Electrodes and Tumor

Subdural electrode positions were verified by skull radiography. For each patient, the location of electrode sites was determined by intraoperative photographs and schematic drawings, and was supplemented by postoperative skull radiography. To estimate the relation of the location of tumor to the electrodes, we measured the distance from the temporal pole to the tumor in the operative field and in T2 axial MR images (GE Medical Systems, Milwaukee, WI, U.S.A.), and the distance from the temporal pole to the grid and strip arrays on tumors in the operative field. In six patients with DNT in the lateral temporal areas, we also confirmed the location of the electrodes and dysmorphic cortical gyri on DNT by visual inspection on the exposed cortical surface, intraoperatively.

Table 1. Summary of patients

No.	Age (yr)	Sex	Sz. onset (yr)	Sz. duration (yr)	Semiological Sz. classification	Surgery	Postop. f/u (months)	Outcome
1	37	M	17	26	Visual aura→Hypermotor Sz.→GTCS	ATL+AH+Basolat	33	IB
2	19	M	16	14	Abd. aura→Automotor Sz.	ATL+Lat	73	IIB
3	12	F	10	11	Lt. versive Sz.→GTCS	Basolat*	59	IB
4	30	F	11	19	Psychic aura→Automotor Sz.→GTCS	ATL+AH+Lat*	32	IIB
5	44	M	32	12	Psychic aura→Lt. clonic Sz.	ATL+AH+Basolat	60	IC
6	39	F	30	9	Automotor Sz.→GTCS	ATL+AH+Bas	28	IA
7	20	M	18	1	Dialeptic Sz.→GTCS	ATL+Lat	65	IA
8	23	F	18	5	Automotor Sz.	ATL+AH+Bas	71	IA
9	19	M	13	6	Abd. aura→Rt. versive Sz.	ATL+AH+Lat	39	IA
AVG±S.D	27.0±11.0		18.3±7.8	11.4±7.6			51.1±18.0	

*No.: Number of patient, Sz.: seizure, Postop. f/u: postoperative follow-up period, GTCS: generalized tonic-clonic seizure, Abd. aura: abdominal aura, Lt./Rt.: left/right, ATL: anterior temporal lobectomy, AH: amygdalohippocampectomy, Lat/Basolat/Bas: lateral/basolateral/basal temporal resection, Outcome: surgical outcome according to the Engel's classification, *: partial removal.

In two patients, the location of the electrodes and tumor could also be confirmed by localizing the subdural electrodes with MRI-CT coregistration, extraoperatively. The image-processing procedures were performed with Analyze 7.5 software (Biomedical Image Resource, Mayo Foundation, MN, U.S.A.) and the Sun Ultra 1 creator workstation (Sun Microsystems, Mountain View, CA, U.S.A.) in our neuroimaging laboratory. The methods were previously described (27). We evaluated the location of the ictal onset zones, the highly irritative zones and a tumor on the schematic brain map of each patient considering the electrodes as a landmark. The illustrative maps of patient 8 and 9 were shown in Fig. 1.

We divided the location of the electrodes into three broad categories according to the relationship of the structural lesions to epileptogenic foci. The first category included subdural electrodes with epileptogenic foci exclusively within the region of the DNT. The second category included subdural electrodes with epileptogenic foci beyond the border of the structural lesion. The third category consisted of subdural electrodes

within the mesial temporal area. We determined that the mesial temporal area was electrophysiologically involved if the ictal onset zones or the irritative zones were located within two electrode-distance from the most medial contacts.

Surgical Procedures

Wide craniotomy centered over the region of interest and the wide coverage of subdural electrodes obviated any incorrect placement of electrodes. The extent of resection was determined to be the areas of brain region, in which the ictal onset zones, the highly irritative zones and tumor were located. The eloquent area by direct electrical cortical stimulation on each subdural electrode during the long term monitoring was not resected. In two patients, the extent of resection did not fully include those areas (only an irritative zone in patient 2, an irritative zone, an ictal onset zone and posterior part of the tumor due to Wernicke's area in patient 4). In six patients who had the electrophysiologic involvement of mesial temporal region,
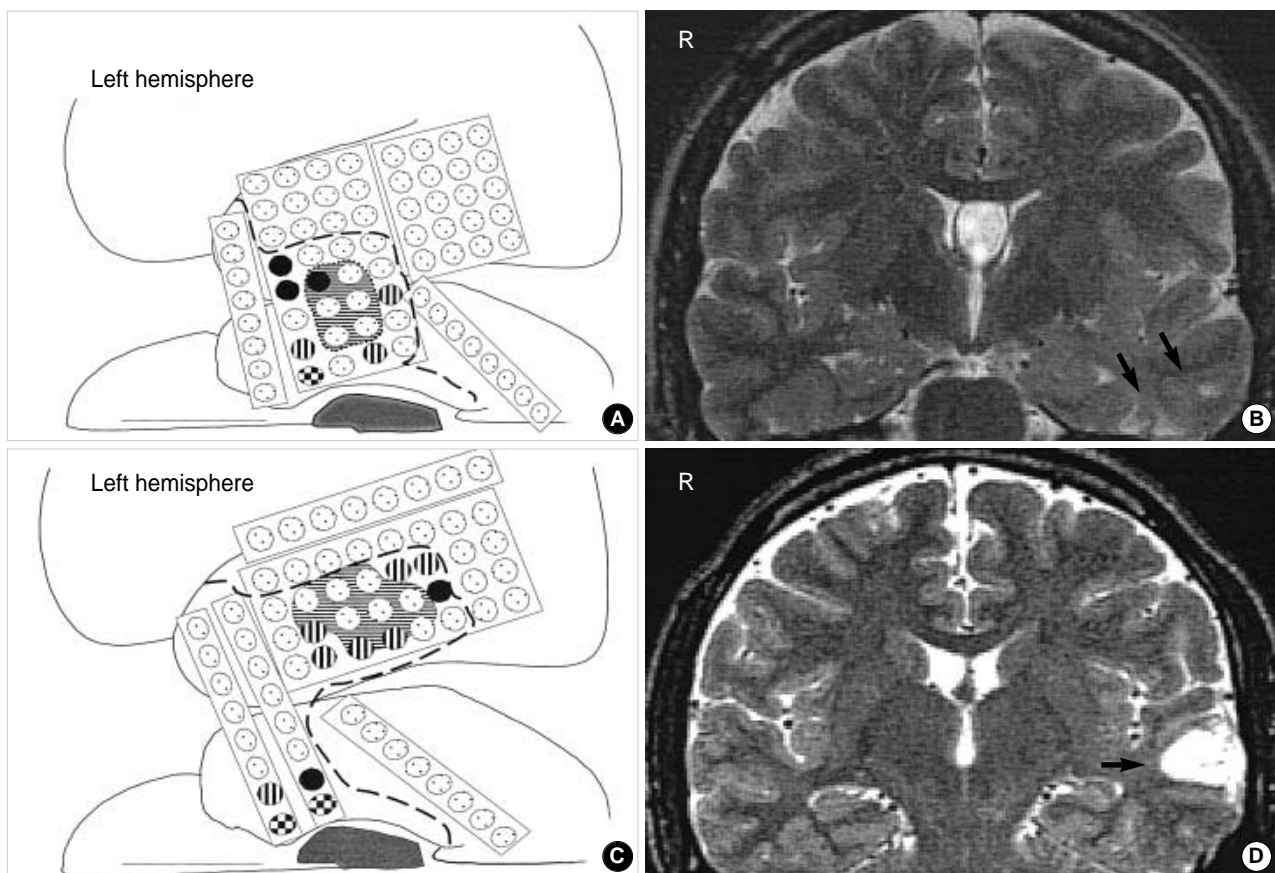

Fig. 1. The schematic map of the illustrative cases. (A) The ictal onset zones (the electrodes filled with black or checkerboard patterns) and highly irritative zones (electrodes filled with horizontal lines or checkerboard patterns) of the patient 8 are shown in perilesional, intralesional and mesial temporal areas. The circles with checkerboard patterns are electrodes with both ictal onset zone and highly irritative zone. Closed thin interrupted lines filled with vertical lines mark the extent of tumor. The margin of resection is a thick interrupted line. (B) T2-weighted MRI of patient 8 shows the lesions (arrows) in left basal and inferior temporal region. (C) The ictal onset zones and irritative zones of patient 9 are located at the perilesional and anterior mesial temporal areas. (D) T2-weighted MRI of patient 9 reveals the lesion (arrow) in left middle temporal area.

Table 2. Summary of extraoperative electrocorticography

No.	Duration of LTM (days)	Seizure frequency			Irritative zones			Ictal onset zones		
		SPS	CPS	SGTCS	within tumor	around tumor	in mesial	within tumor	around tumor	in mesial
1	10	0	17	3	1*	3*	1*	1*	2*	1*
2	7	5	6	0	1*	4	0	1*	1	0
3	4	0	4	2	0	3	0	0	1	0
4	6	0	9	1	0	2*	1*	1	1*	1*
5	9	0	4	0	1	0	0	0	1	1
6	6	0	6	2	0	0	1*	0	0	1*
7	13	0	4	4	0	2*	0	0	2*	0
8	5	0	3	0	1*	1	1*	1*	0	1*
9	10	1	3	0	1	1*	1*	0	1*	1*
AVG±SD	7.8±2.91	0.7±1.66	6.2±4.47	1.3±1.50	0.6±0.53	1.8±1.39	0.6±0.53	0.4±0.53	1.0±0.71	0.7±0.50

LTM: long term monitoring, SPS: simple partial seizures, CPS: complex partial seizures, SGTCS: secondarily generalized tonic-clonic seizures, in mesial; in mesial temporal area, AVG±SD; average±standard deviation.
*: the number of epileptogenic foci including the areas, which were both irritative zone and ictal onset zone.

Table 3. Comparison of the extent of irritative zones and ictal onset zones in adjacent and remote areas regarding the direction from the DNT (in cm)

Direction	Irritative zone		Ictal onset zone	
	Maximum	AVG±SD	Maximum	AVG±SD
Anterior	3	1.3±0.94	4	1.1±1.20
Posterior	3	0.7±0.94	3	0.6±0.96
Superior	2	0.6±0.83	1	0.3±0.47
Inferior	3	0.7±1.05	2	0.4±0.68

*Maximum: the maximal distant of the epileptogenic foci from the tumor on each direction. AVG±SD: average±standard deviation.

hippocampectomy was also performed.

Surgical Outcome

The mean postoperative follow-up period in all patients was 51.1±18.0 months. We evaluated the surgical outcome according to Engel's classification. We also evaluated the results of epilepsy in remission without antiepileptic drugs.

RESULTS

Electrocorticography

The interictal epileptiform discharges were frequently detected and the onset zone of ictal recordings in all seizures were clearly localized on each inserted electrode in all patients. The average numbers of recorded ictal ECoG were 0.7±1.7 in simple partial seizures, 6.2±4.5 in complex partial seizure, and 1.3±1.5 in secondarily generalized tonic clonic seizure. In two patients, simple partial seizures such as abdominal aura showed definite ictal ECoG changes. The seizures originated from the different epileptogenic focus could be recorded. When we evaluated the numbers of different epileptogenic foci, multiple ictal onset zones and irritative zones were observed in all

patients. The number of the ictal onset zones in a patient with a DNT ranged from 1 to 4 (average: 2.1±0.9) and the irritative zones from 1 to 5 (average: 2.9±1.5). The ictal onset zones were more frequently seen in the perilesional area (1.0 ±0.7) than the intralesional region (0.4±0.5). The highly irritative zones were also more frequently observed in the perilesional area (1.8±1.4) than intralesional region (0.6± 0.5) (Table 2). The ictal onset zones in the mesial temporal area were seen in six patients (66.7%). Among them four patients had mesial temporal ictal focus on electrodes remote from the tumor and two patients on electrodes near the tumor. Irritative zones in the mesial temporal area were observed in five patients (55.6%). Among them three patients had mesial temporal interictal focus on electrodes remote from the tumor and two patients on electrodes near the tumor.

Relationship of the Ictal Onset Zones with the Irritative Zones

Comparing the location of the ictal onset zone with that of the irritative zone, the ictal onset zones were located on electrodes entirely different from the irritative zones in 2 patients, partially different in 3, and completely overlapped in 4 (Table 2). This discrepancy was seen more frequently in the perilesional area (4 patients) than in the intralesional area (2 patients). In regards to the electrophysiologic involvement of mesial temporal regions, 4 patients had the irritative zones and the ictal onset zones on the same electrode, 1 had them on different electrodes, and 1 had only ictal onset zone.

The Relationship of Epileptogenic Foci with Tumor

Analyzing the distance of epileptogenic foci from the tumor, the irritative zones were found within 3 cm to the margin of the tumor. The ictal onset zones were observed within 4 cm to the margin of the tumor. The anterior extent of the irritative zone (1.3±0.9 cm) and ictal onset zone (1.1±1.2 cm)

was longer, rather than the other extent of them (Table 3).

Surgical Outcome

Patients' outcomes delineated by Engel's classification are summarized in Table 1. After the surgery, seven patients were categorized to Class I. When the ictal onset zones were completely resected, the surgical outcome was better than when those were incompletely removed. In six patients among the seven patients in Class I, antiepileptic drugs were successfully tapered off.

DISCUSSION

Electrophysiologically single tumor can make multiple epileptogenic foci which are within, around or remote from itself. The foci can be made in contralateral hemisphere. Awad et al. (28) reported that intractable lesional epilepsy patients had more frequently contiguous foci around the area of lesion (61.7 %), rather than noncontiguous foci remote from the area of lesion (38.3%). Regarding the brain tumor, Awad et al. (28) also reported that tumors were never associated with a seizure focus exclusively within the region of known structural lesions, and that malignant neoplasms were not associated with a focus remote from the lesion. These findings support that the epileptogenic foci can be made by the effects of lesions on the normal brain by several mechanisms. The effects depend on several factors including the biology, location, and structure of the tumor. Regarding DNT, histologic study shows that DNT has multinodular architecture, mainly in the cortex, and is composed of oligodendrocytes, astrocytes, neurons, and the glioneuronal elements (29). This cortical structural abnormality that disrupts normal neuronal circuitry becomes an epileptogenic focus. Neuronal cells in the lesion may also secrete neurotransmitters or express receptors. Wolf et al. (30) demonstrated that neurons in DNT are variably immunoreactive for subunit 1 of the N-methyl-d-aspartate receptor, the alpha-a subunit of the gamma-amminobutyric acid, glutamate decarboxylase, somatostatin, tyrosine hydroxylase, and the calcium-binding protein calretinin, suggesting a high degree of differentiation and a possible neurochemical function. Regarding DNT in our series, the tumor has epileptogenic foci including the irritative zone or the ictal onset zone within itself in 77.8% of patients. These findings suggest DNT can have intrinsic epileptogenicity. DNT also is usually found in association with contiguous areas of cortical dysplasia, which may itself be associated with epilepsy (29). The cortical dysplasia can cause the DNT to enhance its power to make an epileptogenic foci in contiguous area around tumor. In our series, temporal DNT had the most frequent epileptic lesions in the neighboring tissues of the tumor, indicating the widespread epileptogenicity beyond visible tumor. To know the exact epileptogenecity of the cortical dysplasia in DNT, the correlation of pathological and electrophysiolgical mapping is needed. And the comparison of the extent of epileptogenic focus in contiguous area around the tumor between DNT and the other tumor could be helpful. But the pathological mapping were not involved in our study and the extent of surrounding epileptogenic foci by chronic electrocorticographic recording on subdural grid arrays were not reported yet.

In our study, temporal DNT has tendency to make more extensive foci in anterior direction. The temporal lobe has inferior longitudinal fascicles in the subcortical area, which extends horizontal to the temporal axis. Ventromedial temporal area has prominent parts of largely subcortical amygdala and hippocampal formation, which have extensive feedback projections to anterior temporal area. These connections can be related with the findings that anterior part of temporal lobe can be more vulnerable to have epileptogenicity than posterior and superior part of the temporal lobe.

The epileptogenic foci in the mesial temporal region may also be related to secondary epileptogenesis, although whether temporal lesions contribute to independent hippocampal epileptogenesis remains unsolved. The evidence supporting secondary epileptogenesis includes studies showing independent mesiotemporal discharges identified by electrocorticography in patients with low-grade temporal gliomas by Berger et al. (20) and temporal arteriovenous malformation by Yeh et al. (31). In our study, temporal DNT can make the mesial temporal area become epileptogenic foci in 66.7% of the cases. Mesial temporal area can be more highly involved when the tumor is located in the basal temporal area rather than in the lateral temporal area. In a pathological study of temporal lobe lesions in intractable epilepsy patients, hippocampal cytoarchitecture had increased vulnerability to proximal lesions (32).

Interestingly, our study suggests that if interictal epileptiform discharges are seen in the mesial temporal area, the ictal onset zone will also be located in the mesial temporal area. Therefore, intraoperative ECoG in mesial temporal structure can give helpful information in determining whether an ictal onset zone can be made in that area. However, considering the ictal onset zones on the neocortical regions as well as the mesial areas, 44.4% of patients in our study had ictal onset zones different from the irritative zones. These findings indicate that the discrepancy between the ictal onset zone and the irritative zone can be higher in neocortical temporal area than in mesial temporal region.

Many electrophysiologic studies on DNT have been based on intraoperative ECoG where the extent of resection cannot include ictal onset zones, although generally, ictal onset zones are more important than irritative zones as regions that need to be removed in epilepsy surgery (12, 34, 35). Subdurally recorded interictal epileptiform discharges can be more helpful than ictal discharges in planning the extent of resection because seizures usually arose from small areas within the larger total area of interictal epileptiform discharges (23). However, in our study, the ictal onset zones and the irritative zones

were formed in different temporal area, especially in neocortex. Therefore, the neocortical ictal onset zone can be omitted more highly than the mesial ictal focus, if the tailored resection of a temporal DNT is based only on the intraoperative ECoG.

It remains debatable whether the resection should be limited to the lesion alone or whether a more extensive resection should be done. In surgical outcome of our study, the complete removal of ictal onset zones can give significantly better results than the partial removal. With more extensive resection by en bloc anteromesial temporal resection (36), the seizure-free rate was 81% (33). However, the uncertainty of the role of hippocampus in the generation of seizures in these patients is added to concerns regarding neuropsychologic sequelae, especially to memory function, in resecting healthy hippocampus. The extent of the resection can be appropriately determined depending on how much we know regarding electrophysiologic epileptogenic foci and lesional data. If the considerately decided hippocampectomy is performed in the patients, it can help the epilepsy surgery produce with better outcome and obviate postoperative neuropsychologic sequelae.

The presented data indicate that chronic temporal lobe epilepsy related to a DNT can be safely treated by the resection of seizure foci and tumor. Seizure control in our patients was similar to that of other series showing lesion excision resulting in 80 to 90% seizure free outcome and 91 to 95% good outcome (4, 12, 17, 28). Discontinuation of antiepileptic drugs after successful epilepsy surgery has not been reported in patients with DNT. Generally previous studies have reported that 25 to 67% of patients discontinued Antiepileptic drug (AED) treatment after epilepsy surgery (37, 38). In our study, 85.7% of patients in Engel's class I has successfully tapered antiepileptic drugs off, although the case is small and the follow-up period is short. The resection of the epileptogenic foci after detailed electrophysiologic studies in temporal DNT could help to discontinue the use of antiepileptic drugs after successful epilepsy surgery.

Whether extensive invasive studies are needed in all patients with temporal DNT should be evaluated. In extraoperative ECoG, ictal recording can be obtained in addition to precise evaluation of functional mapping, as well as interictal epileptiform discharges. However, the cost and the risks of extraoperative ECoG should also be considered. Although chronic subdural recording including mesial temporal area should be prudently decided in temporal DNT, extraoperative ECoG will be helpful in disclosing epileptogenic foci of DNT completely, and deliberate resection of areas with ictal onset zones, highly irritative zones, and visible tumor after considering eloquent area will give good surgical outcome including discontinuation of antiepileptic drugs.

Temporal DNT can have not only intrinsic epileptogenecity but also widespread surrounding epileptogenic foci including the mesial temporal area. Electrophysiologically the ictal focus can be different from the interictal focus and the extent of epileptogenic focus can be more preponderence in the ante-

rior direction. Deliberate resection of epileptogenic foci including all ictal onset zones and irritative zones ensures excellent seizure control.

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