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Surgical Treatment of Seizures in Malformations of Cortical Development (MCD)

대뇌피질 발달기형으로 인한 간질의 수술적 치료

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ABSTRACT

Object : Surgical treatment of cortical dysplasias (CDs) presenting with intractable seizures is challenging, because visualization/localization of the lesion is difficult, correlation with seizure foci needs comprehensive investigations, and the reported surgical results are not satisfactory. We report our result of surgical treatment of CD classified from the surgical point of view. ***Methods*** : Definition of CD was a visible dysplastic lesion on MRI or MRI-negative (normal MRI) case with pathological diagnosis of moderate to severe dysplasia. During the last 4.5 years, we had operated on 36 cases of intractable epilepsy with CDs. We divided the 36 cases into 4 groups ; Group A : diffuse bilateral hemispheric dysplasia, Group B : diffuse lobar dysplasia, Group C : focal dysplasia, and Group D : moderate to severe degree of cortical dysplasia with normal MRI. All but one patient in Group C were monitored at EMU using subdural electrodes for seizure localization and functional mapping. ***Results*** : The incidence of CD in the whole epilepsy surgery cases was 12.4%. Mean age was 21.3 years. Mean age at seizure onset was 8.5 years. Mean follow up period was 26.0 months. Twenty-six (72.2%) patients (20 and 6, respectively) belong to Engel Class I and II. There were 5, 9, 9, and 13 cases in Groups A, B, C, and D, respectively. Groups A and B had significantly lower age at seizure onset and significantly poorer surgical outcome compared to Groups C and D ($p<0.05$). If the outcome was compared on the extent of removal of CD, patients with completely removed CD had very significantly better outcome than those with partial removal ($p<0.001$). ***Conclusions*** : We conclude that intractable epilepsy with CD can be treated surgically with comprehensive preoperative approaches. Deliberate resective procedures aiming at complete removal of dysplastic tissue ensure excellent seizure control without permanent neurological deficit. (**J Korean Epilep Soc 4 : 101-107, 2000**)

KEY WORDS : Surgery · Malformation of cortical development · Seizure · Outcome.

Introduction

With the recent interest in epilepsy surgery and with the advent of high-resolution imaging tools such as MRI and PET, cortical dysplasia is known as a major cause of intractable epilepsy except for the hippocampal sclerosis and other structural lesions (tumors and vascular malformations). Its definition, however, is poorly systemized. Even though Mischel and Barkovich proposed pretty good classification schemes,[1][2] they are not widely accepted yet.

In contrast to tumors and vascular malformations, which are known to cause seizures by pressure or irritation to the adjacent cortex,[3][4] there are recent reports advocating that cortical dysplasia is intrinsically epileptogenic.[5-11] With the development of high-resolution MRI, PET, computerized video-EEG and surgical techniques assisted by modern tools, it became possible to localize the epileptogenic area in patients with intractable seizures with the apparently-normal brain and treat the intractable epilepsy by resective procedures. Practically,

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however, well-defined diagnosis of dysplasia is difficult, because the pathological features from these specimens usually show wide spectrum of dysplasias. Also, features of mild degree of dysplasia are frequently found in the specimen from epilepsy patients.

In this study, we analyzed the surgical result from the patients with the more evident cortical dysplasias, that is, cortical dysplasia which was visualized by MRI or moderate to severe dysplasia proven pathologically by the grading system of Mischel et al.[2]

Materials and Methods

1. Patient selection and classification

Thirty-six patients with cortical dysplasias were selected among 291 patients who were operated for intractable epilepsy in Samsung Medical Center between January 1995 and June 1999 (four and half years). Cases with mild degree of cortical dysplasia with no visible lesion on MRI were excluded (n=20) from this study because such findings are frequently found as a non-specific finding in the specimen from non-lesional epilepsy patients. We also excluded cortical dysplasias found in the anterior temporal lobe in patients with hippocampal sclerosis which is treated by anterior temporal lobectomy with amygdalohippocampectomy. We confined the definition of cortical dysplasia as a visible lesion on high-resolution MRI (which was proven pathologically as CD) or MRI-negative cases (no visible abnormality on high-resolution MRI) with pathological diagnosis of moderate to severe cortical dysplasia. Because the approaches for presurgical evaluation, surgical planning, and postsurgical outcome were different, we divided the 36 cases into 4 groups ; Group A : diffuse bilateral hemispheric dysplasia (bilateral diffuse dysplasia involving the whole hemispheres), Group B : diffuse lobar dysplasia (diffuse involvement of one lobe or plus its adjacent lobes with poor demarcation), Group C : focal dysplasia (focal nodular lesion involving one brain lobe which is usually well-demarcated), and Group D : moderate to severe degree of cortical dysplasia with normal MRI (normal MRI, but pathologically proven as moderate to severe cortical dysplasia). We followed Mischels classification for grading the degree of cortical dysplasia as follows : severe presence of balloon cells and/or neuronal cytomegaly (cytoskeletal abnormalities) ; moderate presence of PMG (polymicrogyria) and/or white matter neuronal heteropia, but not balloon cells or neuronal cytomegaly ; mild no evidence of balloon cells, neuronal cytomegaly, PMG or white matter neuronal heteropia[2]. The pathologist was blind for the information about each patient.

2. Preoperative investigations

All patients had longstanding history of intractable seizures which were resistant to appropriate medical treatment. Careful interview about seizure history and semiology, scalp EEG, MRI, interictal SPECT, PET and neuropsychological test were performed before admission. If these investigations show some clue of partial seizure, the patients were admitted to EMU for seizure monitoring. Ictal SPECT was performed at EMU whenever possible. Wada test was performed for speech and memory dominance from each hemisphere. We use a image analysis system for image fusion of ictal/interictal subtraction image or PET image on MRI or 3D-rendering of MRI image of each brain. After subdural electrode insertion, each patient were scanned on spiral CT for data acquisition for 3D-rendering of subdural electrode- covered brain. After these preoperative evaluations, surgical planning was performed in the Patient Management Conference where the neurologists, psychologists, technicians, nurses, and neurosurgeon discuss together. After insertion of subdural electrodes, the patients were observed closely at ICU for one day and transferred to EMU for seizure recording and functional mapping. It usually took 1 week.

3. Surgical techniques

All but one patient with focal cortical dysplasia located at mesial temporal region went through intracranial electrode insertion and monitoring before resective procedures. Even when the lesion was visible and EEG findings coincide with the approximate location of the lesion, we put subdural electrodes on and around the lesion to confirm the exact location of seizure onset and propagation and to determine the extent of resection after functional mapping. Functional mapping included brain stimulation, somatosensory and visual evoked potential. The extent of resection was determined as the areas of

brain region where the seizures were confirmed to originate, where the active interictal spikes were observed, and where there was no eloquent brain function confirmed by brain stimulation. Visible lesions were included in the resection margin as far as that area was not involved in the eloquent brain function. After the extent of resection was determined, subpial resection was performed depending on the sulcal/gyral pattern of subdural electrode-covered brain. If the interictal spikes were observed at the boundary of subdural electrodes, intraoperative electrocorticography was performed on those areas before resection. If the seizure onset was confirmed to originate at the boundary of the electrodes, we replaced the electrodes by revision procedure (2 cases). After resection, electrocorticography was performed using 1×8 strip and/or 4×5 grid at the resection margin in all cases. If active spikes were observed and that area was resectable (anatomically and functionally), further resection was performed in an effort to minimize postoperative seizure recurrence.

4. Statistical analysis

Data from each group were analyzed using a commercially available statistical software. Comparison between each group was performed as well as between the merged groups (Groups A plus B versus Groups C and D) because the firmer and the latter two groups were similar in clinical features.

Data are presented as mean standard deviations. Statistical significance was set at a probability value less than 0.05.

Results

Information of the 36 patients is summarized in Table 1. The incidence of cortical dysplasia from 291 patients of epilepsy surgery cases was 12.4%. If we include the 20 patients with mild cortical dysplasia without visible lesion on MRI, the incidence is 19.2%. There was each case of mild degree of CD in Groups B and C (Case 8 and 16, Table 1). Mean age of total patients was 21. 3 years (1 to 58 years). Male to female ratio was 24 : 10. Mean age at seizure onset was 8.5 years. As was mentioned above, all but one patient with mesial temporal dysplasia (Case 20) went through intracranial recording using subdural electrodes. Total removal was impossible in Group A by its definition that whole bilateral hemispheres are involved. Gross total removal of diffuse lobar cortical dysplasia was performed in 3 patients (Cases 10, 13, and 14 in Table 1) of Group B. Gross total removal was possible in all but 2 cases (Cases 21 and 22 : difficult access of the lesion located at the mesiobasal aspect of occipitotemporal area, subdural empyema, respectively) in Group C. We could regard that total removal was performed in all cases of Group D because there was no visible lesion on MRI. The demographic data did not show any statistical difference between groups. If the Groups A and B are merged and compared to the merged Groups C and D by 2×2 table, mean age in Groups A and B also seemed to be lower than Groups C and D, but there was no statistical significance ($p=0.09$). Age at the onset of seizure was significantly lower in Groups A and B (6.4 and 2.9 years, respectively) compared to Groups C and D (10. 7 and 11.8 years) ($p<0.05$). The mean IQ in Group A and B were 66.0±22.6 and 73.5±13.0, respectively compared to Groups C and D (97.0±24.4 and 95.8±24.5, respectively). Though these difference did not reach statistical significance ($p=0.08$, Pearson Chi-square test), there was a tendency that patients in Groups A and B had lower intelligence than the patients in Groups C and D who had almost normal IQ. Except for two patients with FS.

There were three and one case of transient and permanent hemiparesis after resection, respectively. Also, there was each case of subdural electrode- associated subdural empyema, which hindered complete resection of focal cortical dysplasia (Case 21) and epidural hematoma which was removed during resective procedure. Two cases (Cases 2 and 9) were reoperated due to recurrence of seizures. However, they still remain in Class IV and III, respectively.

Discussion

1. Definition and terminology of CD

Cerebral neocortical malformation is a disorder derived from a defect of neuronal migration with subsequent disruption of the normal cortical lamination and abnormal

Table 1. Summary of 36 patients with four types of cortical dysplasia. Abbreviations : PR : partial removal, GTR : Gross total removal, F : frontal, T : temporal, P : parietal, O : occipital

Group	Case No.	Sex	Age	Onset age	Location	Extent of removal	Pathology (Grade of CD)	Follow up period (mos)	Outcome
A	1	M	26	10	Lt. F-T	PR	Mod	56	III
	2	M	13	1	Rt. F	PR	Sev	40	IV
	3	M	10	9	Lt. F-T	PR	Sev	19	III
	4	F	11	9	Lt. F-T-P	PR	Mod	15	III
	5	F	22	3	Rt. F-P	PR	Mod	10	I
B	6	M	8		Lt. F	PR	Sev	43	IV
	7	M	2	1	Lt. F-P	PR	Sev	37	IV
	8	F	38	4	Rt. F-P-T	PR	Mild	36	II
	9	M	22	5	Lt. T-O	PR	Sev	20	III
	10	M	5	1	Lt. T-O	GTR	Sev	20	I
	11	M	24	6	Lt. T-O	PR	Mod	10	II
	12	M	21	5	Lt. T-P-O	PR	Sev	10	II
	13	M	6	1	Lt. F-P	GTR	Sev	6	I
	14	M	1	0	Lt. T-O	GTR	Sev	5	I
C	15	M	35	7	Lt. F	GTR	Mod	55	I
	16	M	41	16	Lt. P	GTR	Mild	49	I
	17	M	17	8	Lt. T-P	GTR	Mod	45	I
	18	F	22	5	Lt. F-P	GTR	Sev	41	I
	19	M	33	20	Rt. T	GTR	Mod	33	I
	20	F	58		Lt. T	GTR	Mod	28	I
	21	M	18	6	Lt. F-P	PR	Mod	21	III
	22	M	23	13	Lt. T-O	PR	Sev	17	II
	23	M	9		Rt. T-O	GTR	Sev	10	I
D	24	M	24	13	Rt. F	GTR	Sev	56	I
	25	F	8	3	Lt. F	GTR	Sev	50	II
	26	M	23	10	Lt. F-T-P	GTR	Mod	32	II
	27	F	19		Rt. F	GTR	Mod	31	I
	28	F	17	7	Lt. F	GTR	Sev	28	I
	29	M	27	7	Lt. F-P	GTR	Sev	25	I
	30	F	42	31	Lt. F	GTR	Sev	17	I
	31	M	18	9	Rt. F	GTR	Mod	17	I
	32	M	14	9	Rt. T	GTR	Mod	17	III
	33	F	33	29	Rt. T-O	GTR	Mod	12	I
	34	M	25	7	Lt. T-O	GTR	Mod	8	III
	35	M	47	15	Lt. F-P	GTR	Mod	8	I
	36	M	6	2	Lt. T-P	GTR	Sev	8	I

Table 2. Outcome of seizure control in each group

Group	Engel class			
	I	II	III	IV
A	1		2	2
B	3	3	1	2
C	7	1	1	
D	9	2	2	
Total	20	6	6	4

Table 3. Seizure outcome according to the exent of resection

		Engel class			
		I	II	III	IV
Partial removal	Group A (n=5)	1		2	2
	B (n=6)		3	1	2
	C (n=2)		1	1	
	D (n=0)				
Cross total removal	Group A (n=0)				
	B (n=3)	3			
	C (n=7)	7			
	D (n=13)	9	2	2	

neuronal and glial cells in the cerebral mantle. Although these disorders have been called cortical dysplasia, neuronal migration disorders (NMDs), dysgenesis of cerebral cortex, microdysgenesis, or abnormalities of cell migration, it is clear that the most common form of these disorders involve abnormal cell formation in the germinative zone or abnormal cortical organization.[13-15] While the definition and nomenclature of these pathological

conditions are somewhat confusing, we prefer to use the term cortical dysplasia to include the full range of NMDs as a spectrum of pathologic changes reflecting disturbances of normal developmental process, though cortical dysplasia has been considered as a subtype of this group of disorders.[2] In this study, we excluded the subgroup of patients with mild degree of cortical dysplasia with no visible lesion on MRI, which might be merely a nonspecific pathological change associated with longstanding seizures, instead of being a true developmental anomaly. A clearer and more concrete definition, nomenclature and classification of these developmental disorders need to be established in the future.

2. Considerations in the surgery of CD

With the advent of modern imaging and EEG techniques and with the increasing number of epilepsy surgery cases, it became evident that cortical dysplasias are much more common than previously estimated in patients with drug-resistant intractable seizures.[14)16 19)] The reported incidence of cortical dysplasia in intractable partial epilepsy patients is between 2±5%[20)21)] and 15±50%,[18)] getting more frequent in the more recent series. The incidence of cortical dysplasia is 12.4% in our series where the mild degree of cortical dysplasia without MRI-visible lesion (20 cases), and the so-called dual pathological lesions from neocortical temporal lobe tissue from hippocampal sclerosis were excluded.[22)] We, of course, admit that grouping into 4 groups as in this study is quite arbitrary for classification of cortical dysplasia. However, this kind of grouping was very practical because Groups A, B, C and D could be a spectrum of degree of cortical developmental anomaly from the more severe and diffuse dysplasia to the more focalized and milder degree of dysplasia as was seen in our clinical data. Mental retardation and developmental delay were more prominent in Groups A and B compared to the Groups C and D. Seizures were severer in frequency and disabling nature (generalization) in the former groups than the latter groups though the data are not shown in this paper. Also, the difficulty in surgical planning and surgical outcome showed a tendency of spectrum from Group A to D.

Though it is generally agreed that intractable partial seizures with cortical dysplasia is a good candidate for surgery, most of the reports about the surgical treatment are resection of the visible lesion with occasional use of electrocorticography or more rare use of intracranial recordings using subdural electrodes.[10)23-25)] Simple lesionectomy as in the cases of localized tumors or vascular malformations might be a feasible surgical option as far as the lesion is completely removed. However, we realized that the satistactory complete removal of the CD is difficult because demarcation of the lesion is very poor even in focal dysplasia as in Goup C, and the seizure onset is not esssentially from the lesion itself, but also from around the lesion which can be proven from the subdural electrodes. We think that we could accomplish good surgical outcome by removing the dysplastic tissue as completely as possible including the surrounding epileptogenic regions. The pathological substrate of these surrounding epielptogenic regions might be the microscopic dysplastic tissue which is hardly visualized by high-resolution MRI or other functional imaging tools. Dependence upon the interictal spikes from electrocorticography might be another option, but interictal spikes do not essentially show the epileptogenic area.[26)27)] Though the intracranial recording is an invasive procedure, carefully planned insertion and recording from comprehensive preoperative investigations could minimize the complications of this invasive procedure and ensure the excellent outcome. We think that the use of subdural electrodes also contributed in the complete removal of cortical dysplasia in the gross total removal cases of Groups B and C because the resection margin was always beyond the MRI-visible margin of the lesion. Identification and resection of the epileptogenic area would have been impossible without subdural electrodes in Group D. Without subdural electrodes, gross total removal might have been impossible even in Group C because gross appearance on the cortical surfaces are normal in most cases. Though there is some difference in gross appearance and consistency between normal brain tissue and dysplastic tissue, definition of resection margin by such difference was impossible even when the lesion was very focal and well-demarcated on MRI. Although the most active epileptogenic region was resected after the com-

prehensive recording procedures, the outcome in Group A is poor, four of 5 patients belonging to Class III and IV. We think that the remaining tissue might have resumed epileptogenesis. We infer the similar phenomenon in Class III and IV of Group B (3 cases) where total removal was practically impossible because of the extensiveness of the large lobar lesions.

3. Surgical outcome

This series has the advantage of homogeneity of patients who were operated by one neurosurgeon (S-C H.) during the recent short period, with a protocol of updated preoperative investigations, with the same equipment for the epilepsy surgery (state-of-the-art high resolution MRI, PET, computer video-EEG, etc.). Most strikingly, we went through extensive coverage of subdural elctrodes on the suspected areas of the brain. We had analyzed the visible lesion with high-resolution MRI, monitored seizure onset and propagation with wide coverage of suspected region by subdural electrodes (except for only one case with mesial temporal lesion), and correlated the data using the image fusion techniques. We think that the excellent result of our series is due to these comprehensive preoperative investigations and attempted radical resection of the lesions. Even with this relatively aggressive preoperative work up and wide resection of epileptogenic regions, the outcome from the partial resection group is not satisfactory. We had, of course, monitored sufficiently the stereotypic epileptogenic area before resection. The extent of resection was wide enough to include the surrounding irritable but non-eloquent region as well as focal or multifocal epileptogenic area confirmed by seizure propagation, electrocorticography-guided interictal spikes, and functional mapping. We hesitated to operate in patients with diffuse dysplasia cases, because the scalp EEG showed multiple seizure onset from diffuse areas of the brain. Surgical outcome was poor in patients whose dysplastic tissue was resected partially because of the difficulty in surgical access or worry about affecting the eloquent region. The opposite was true in patients whose dysplastic tissue was resected extensively, or gross-totally, mainly at the recent period after the experience of the poor result of the partially-resected cases. This phenomenon also supports the fact that the dysplastic tissue is intrinsically epileptogenic. Epileptogenic and adjacent irritable areas were deliberately resected using extensive coverage of subdural electrodes and seizure monitoring in all cases of Engel Class III and IV from Groups A and B.

Most of such cases had remained seizure free immediately after surgery. Though the data are not shown in this manuscript, their seizures recurred after several months. So, we postulate that the "silent areas" of CD which had been left intact in partially resected cases take over epileptogenic activity after some interval of seizure-free period because of its intrinsic epileptogenicity.[5,11]

Previous reports about surgical outcome of cortical dysplasia show wide variation.[20,24,25,28-30] Some authors reported better outcome in cortical dysplasia located in the temporal lobe,[20,29] but such finding was not found in our series. These variations in surgical outcome might be due to difference in patient selection, surgical methods, and insufficient number of patients. But the most important factor would be the wide spectrum of cortical dysplasias. Though the reported surgical outcome is generally poor,[18,20,28,29] we strongly believe that the surgical outcome can be improved by comprehensive preoperative investigation for the accurate localization of seizure onset, meticulous brain mapping, and attempted radical resection of the pathological regions of the brain. Grouping into 4 groups as in this study would improve the surgical outcome by improving the patient selection criteria. For example, patients with Group A and extensive form of Group B features would not benefit by resective procedures despite extensive and laborious preoperative investigations. Rather, these patients would benefit by callosotomy or hemispherectomy procedures if the seizures are medically intractable. Instead, the intractable epilepsy with well-defined and completely resectable cortical dysplasias as in Group C, D, and part of Group B can be cured by surgery after the comprehensive preoperative investigations.

Conclusions

We conclude that intractable epilepsy with CD can be treated successfully by surgery. Patient selection depend-

ing on the extent of lesion is very important. Comprehensive preoperative evaluation for the localization of seizure onset and functional mapping with correlation of the dysplastic lesion is mandatory. Because CD can be intrinsically epileptogenic, deliberate resective procedures aiming at complete removal of dysplastic tissue ensures excellent seizure control without significant neuropsychological problems. A clearer and more concrete definition of CD needs to be established in the near future.

중심 단어 : 수술 · 대뇌피질 발달 기형 · 간질 · 결과.

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