Clinical outcome following medical treatment of cavernous malformation related epilepsy

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Clinical outcome following medical treatment of cavernous malformation related epilepsy

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This certifies that the Master's Thesis of
Yoonju Lee is approved.

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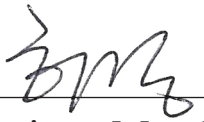

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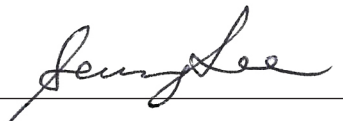

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<ABSTRACT>

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Purpose: The study was conducted to assess the long-term outcome of antiepileptic drug (AED) treatment in drug-naïve patients with cavernous malformation related epilepsy (CRE)

Methods: This is a retrospective, single-center, long-term observational study. Study included patients presented to the epilepsy clinic between 2000 and 2011 with previously untreated seizures related to MRI-proven, cavernous malformation (CM). All patients were followed-up for at least two years. Previous history of surgical or AEDs treatment, lack of EEG examination, no or only a single previous seizure were exclusion criteria. Seizure outcome was assessed on annual basis and patients were divided into two groups according to the success (Group 1) or failure (Group 2) to achieve terminal 1-year seizure remission (1-year TSR). Drug resistant epilepsy

(DRE) was defined as two or more seizures per year after trial of two appropriate AEDs. Patients who had only one seizure during the previous one year were assigned as “epilepsy with rare seizure (ERS)”.

Results: A total of 34 drug-naïve patients (male 20) were included to the study. Mean duration of follow up was 5.88 ± 3.15 years. Pre-treatment baseline mean and median seizure frequencies were 4.93 ± 12.63 and 0.85 (1.92) episodes per month, respectively. 1-year TSR was achieved in 22 of 34 (64.7%) patients, nine (26.5%) patients were diagnosed as DRE, and three (8.82%) patients were as ERS. 1-year TSR was achieved in 18 of 34 (52.9%) patients by the first drug regimen and in additional four (11.8%) patients by the second drug regimen. Among 16 patients who failed to achieve 1-year TSR by the first drug monotherapy, three patients were ERS and did not undergo second drug trial. None of nine patients who failed to first two drug regimens did achieve 1-year TSR. Univariate analysis of multiple clinical variables disclosed that the location of CM in the temporal lobe was the only prognostic factor predicting a poor seizure outcome ($p = 0.012$).

Conclusion: 1-year TSR was achieved in 64.7% of newly diagnosed patients with CRE in a long-term AEDs therapy. Failure to achieve seizure-freedom after adequate trials of two AEDs is strongly recommended as criteria for their referral to surgical treatment. However, for patients with temporal lobe CRE, a presurgical evaluation may be considered appropriate once they failed to an adequate trial of the first drug.

Key words: cavernous malformation, epilepsy, medication treatment

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INTRODUCTION

Cavernous malformation (CM) is the second most common type of vascular malformation. An epileptic seizure is the most common presenting symptom of CM, which is followed by focal neurological deficits, acute hemorrhage, and headache.[1] Supratentorial location, cortical involvement and archicortical and mesiotemporal location are established risk factors of cavernous malformation related epilepsy (CRE).[2]

A prospective population-based registry reported that 5-year risk of first-ever seizure after the presentation of incidental CM was 4%, while 5-year risk of epilepsy (or second seizure) after first-ever seizure in patients with CM was 94%, which has provided a strong evidence for starting antiepileptic drug (AED) therapy in patients with a single seizure related to CM.[3] In this study, 2-year seizure remission rate by AED therapy at 5-year follow-up period was 47%, which was lower than the 2-year seizure remission rate (68%) from a population-based study in

UK.[4] On the other hand, a large outpatient clinic database found that the seizure-free rate (SFR) in patients with vascular malformation related epilepsy was 50%, which was better than that of patients with normal MRI (42%), due to head trauma (30%), cortical dysplasia (24%), and hippocampal sclerosis (11%).[5] However, long-term outcomes of AED therapy in a pure group of CRE have not been adequately investigated yet, thus any evidence-based guidelines for the management of newly diagnosed patients with CRE are not available yet.

Surgery of patients with CRE was associated with 70% to 84% of Engel Class-1 outcome with earlier surgical intervention being a favorable prognostic factor.[6-9] However, a meta-analysis of surgical outcomes in patients with CRE pointed out too much heterogeneity among studies due to differences in patient's inclusion criteria, surgical techniques and presurgical evaluations, or use of different classifications of surgical outcomes, and concluded that the clinical usefulness of these studies is seriously limited.[10] Recently, a systemic review comparing surgery with medical treatment in patients with CRE failed to show any significant benefits of surgery.[11] Another long-term outcome study in patients with newly diagnosed CM indicated significantly worse outcome of early surgery compared with conservative management in newly diagnosed patients with CM at the assessment of 5-year follow-up, which casts a doubt about the benefit of early surgery in patients presenting with CRE.[12]

Recent ILAE-report stated that it was not necessary to wait until the rigorous criteria of drug resistant epilepsy (DRE) proposed by ILAE[13] being fulfilled but the

failure to an appropriately conducted first drug trial should be considered sufficient to recommend a presurgical evaluation.[2] This statement seems to reflect current expert's opinions, which requires a caution for adopting it as evidence-based practice guidelines.[14] Decision about the optimal timing of patient's referral to surgery needs to be individualized and should be based on accurate risk-benefit assessment for surgery, which requires reliable longitudinal outcome data of AEDs therapy in patients with new onset of CRE. We conducted the investigation to identify the clinical courses and related prognostic factors in patients with CRE who were newly treated with AEDs therapy at the epilepsy clinic.

MATERIALS AND METHODS

Patients and treatment

We conducted a retrospective analysis of Yonsei Epilepsy Registry, which is a prospective patient registry to the Yonsei Epilepsy Clinic in Seoul, Korea.[15] A total of 73 patients were registered under the diagnosis of untreated CRE during the period between 2000 and 2011. The patient's inclusion criteria were: (1) well-established diagnosis of partial epilepsies as defined by the International Classification of Epilepsies and Epileptic Syndromes[16]; (2) presence of CM by brain magnetic resonance imaging (MRI); (3) Electroencephalography (EEG) evaluation; (4) lack of any clinical (semiology) or EEG evidence suggesting non-CRE, (5) at least one episode of seizure during the previous year before commencing AEDs therapy, (6) at least a two-year follow-up. Reasons for exclusion were: (1) previous

surgery for CM (n = 13); (2) less than two-year follow-up (n = 11); (3) previous AED therapy before their referral (n = 10); (4) Non-CRE (n = 2); (5) no EEG evaluation (n = 2); (6) No seizure event during last one year before treatment (n = 1).

The age at seizure onset, gender, duration of illness, seizure frequencies before and after treatment, EEG and brain MRI findings, prescribed AEDs and surgical information were documented. Epilepsy syndrome and seizure classification[16] were based on thorough clinical assessments (i.e., history taking, neurologic examination, ictal semiology, and so on), and careful clinical correlations with EEG and brain MRI. Patients usually visited the clinic at one to six month intervals and their seizure frequency was assessed at every clinic visit. AEDs therapy consisted of initial monotherapy of the first-line drugs (lamotrigine, carbamazepine, oxcarbazepine, valproate, topiramate, levetiracetam, and phenytoin) for partial-onset seizures. If patients developed seizure recurrences during adequate trial of first drug regimen, second drug was chosen and tried either in substitution monotherapy or combination therapy. If the first drug was discontinued due to emergence of adverse effects at lower doses than its usual target dose, the drug trial was not considered adequate to be counted as the first drug regimen. Caring epileptologists were fully responsible for the treatment regimens during the follow-up period.

Evaluations and assessments

EEG and brain MRI were acquired in all patients. Brain MRI sequences included

T2-weighted axial slices with a regular high-resolution MRI unit (1.5-tesla or 3.0-Tesla Sigma)[17]; range of in-plane resolution 0.449 - 0.898 mm; slice thickness 1 - 5 mm; slice spacing 1 - 2 mm. Gradient recalled echo sequences were not routinely applied but only in a few selected cases.

A neuroradiologist and a neurologist evaluated the MRI data for each patient independently to assess the number, side, localization, and maximal diameter of CM by using a predefined form, which was followed by a joint session for harmonizing the differences in interpretation. The location of CM was classified as temporal, frontal, parietal, occipital and infratentorial lesions. In patients with multiple CMs, the localization of epileptogenic lesion was determined to the lobe harboring the lesion correlating with the patient's seizure descriptions, EEG features, or the largest lesion if their correlations were not clear. The maximal diameter of CM without the hemosiderin rim was measured and divided into $\leq$20 mm and $>$20 mm. Baseline seizure frequency was defined as monthly seizure frequency by counting seizure numbers during the last three months in patients having monthly seizures or during the last 12 months in patients with less frequent seizures before the commencement of AEDs therapy. After AEDs therapy, seizure frequency was calculated at each clinic visits and assessed annually as seizure-free or not seizure-free until the last follow-up visit. 1-year seizure remission (SR) was defined as freedom from seizure for 12 months during each year of follow-up, whereas 1-year terminal seizure remission (TSR) indicated no seizure during the last one year of follow-up. If there was only one seizure during the year, we categorize them as

epilepsy with rare seizure (ERS). If there were two or more seizure recurrences during one year after adequate trial of second drug regimen, DRE was diagnosed. Patients were divided into two groups according to the achievement of 1-year TSR; patients who have achieved 1-year TSR were assigned to Group-1, whereas Group-2 included patients who had seizure relapses during the last one year of follow up (patients with DRE and ERS).

Statistics

Data processing and analysis were performed with SPSS Version 18.0 for Windows. Data were expressed as mean standard deviation (SD), and median values were calculated. For subgroup analysis, the Chi^2 test (or Fisher's exact test) and independent two-sample t-test were performed. Significance was assumed for all comparisons at the two-sided *p*-value of ≤ 0.05.

RESULTS

Demography and Clinical Characteristics

Among 34 patients, 20 (58.8%) were male. Mean age of patients at their presentation to the epilepsy clinic was 42.2 year-old (SD ± 16.62) and the mean age of seizure onset was 35.2 year-old (SD ± 17.09) with the mean duration of epilepsy being 6.09 years (SD ± 8.64). Mean baseline seizure frequency was 4.93 episodes (SD ± 12.63) per month and median seizure frequency was 0.85 (1.92) episodes per month. Seizure frequency was less than one per month in 18 (52.9%) patients, one

or more seizures per month in 14 (41.2%) patients, and daily seizures in two (5.9%) patients. Mean duration of follow up was 5.88 ± 3.15 years (range 2-12). CMs were located in the frontal lobe in 17 (50.0%) patients, temporal lobe in 15 (44.1%), and parietal lobe in two (5.9%) patients. Six patients (17.6%) showed multiple CMs in MRI and one of them had a positive family history of CM. Among those with multiple CMs, four patients were assigned to the frontal lobe epilepsy and one patient each to the temporal lobe and the parietal lobe epilepsy on the basis of clinical-EEG and MRI correlations (n = 3) or location of the largest lesion (n = 3). The mean size of CM was 1.2 ± 6.29 cm (range 0.4-3.0). Twenty two (64.7%) patients achieved 1-year TSR, thus assigned to Group-1. Among those, 18 (52.9%) patients achieved 1-year TSR by the first drug monotherapy and four patients (11.8%) did so by the second drug regimen. AEDs were withdrawn in two patients after prolonged seizure remission by their strong desire to be free of AEDs, and have been remaining seizure-free for three and five years each. Among 12 (35.3%) patients who were assigned to Group-2, six patients were under duotherapy, two patients under triple drug therapy and one patient was taking five drugs in combination. Remaining three patients had ERS and were kept on the first drug monotherapy after further dose escalations. Lamotrigine was the most frequently used AED for monotherapy, whereas various combinations of AEDs were used for duo- or triple drug therapy.

Outcome of AEDs Therapy

Nineteen patients achieved 1-year SR by the first drug treatment but seizures relapsed in four of them. Among those four patients who did relapse, two patients were ERS and were followed-up with gradual dose-escalations of the first drug, whereas two other patients underwent trials of second drug regimen with achievement of 1-year TSR in one and failure to achieve seizure remission in the other. Among 15 patients who have failed to the first drug, three patients achieved 1-year TSR with a dose escalation of the first drug and another three patients by the trial of the second drug regimen. 1-year TSR and cumulative 1-year SR were 64.7% (22/34) and 73.5% (25/34), respectively. Nine patients (26.5%) continued to have seizure recurrences despite of adequate trials of two AEDs, thus satisfied the criteria of DRE. 1-year TSR was achieved by the first drug regimen in 18 patients (52.9%). The second drug regimen was successful in four of 13 (30.8%) patients who failed to the first drug. None of patient who failed to the adequate trial of second drug regimen achieved 1-year TSR by further drug trials. Remaining three patients who had ERS during the first drug trial were kept on the first drug monotherapy after progressive dose-escalations by the judgment of caring physicians (Figure 1).

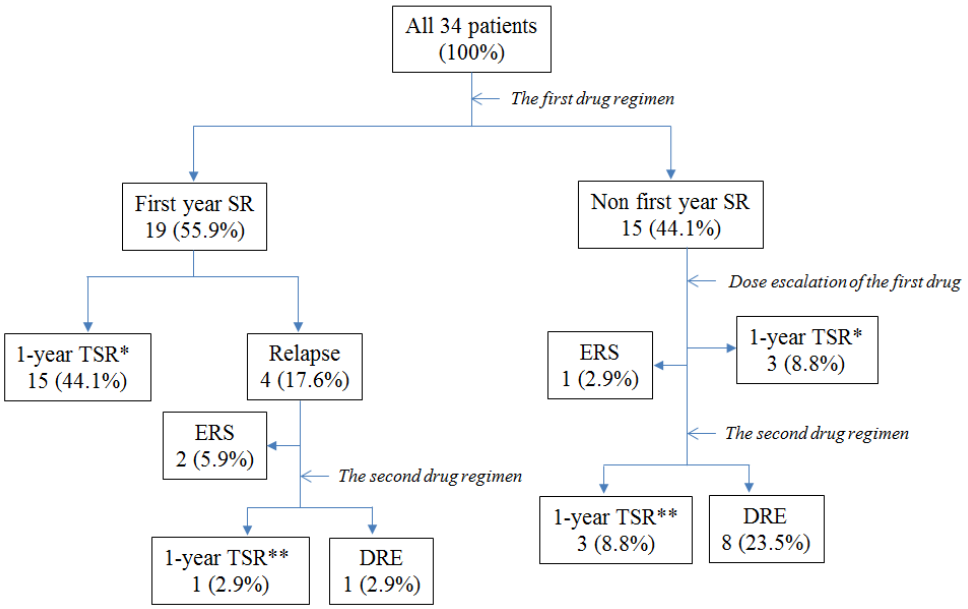

Figure 1 Flowchart of overall seizure outcome.

Abbreviation: First year SR=seizure remission during the first one year; Non first year SR=not seizure free during the first one year; 1-year TSR=seizure free during the last one year of follow-up; ERS=epilepsy with rare seizure (only one episode of seizure relapse during the previous one year of follow-up); DRE=drug resistant epilepsy (two or more seizures during the previous one year of follow-up); *=The patients achieved 1-year TSR by the first drug regimen; **=The patients achieved 1-year TSR by the second drug regimen.

Clinical variables related with the outcome of AEDs therapy

We conducted an univariate analysis of multiple clinical variable to assess their correlations with the long-term outcomes of AEDs therapy, which were age of

seizure onset, seizure frequency before treatment, duration of illness, location, numbers, and size of CM, and EEG features. Among those, location of CM was the only one prognostic factor significantly correlating with the outcome of AEDs therapy (Table 1).

Table 1 Comparison between characteristics of the Group 1 and Group 2

Patients	Group 1 (N = 22)	Group 2 (N = 12)	
	Mean ± SD	Mean ± SD	*p*-value
Age (year-old)	38.27 ± 17.47	29.50 ± 115.47	0.144
Seizure duration (year)	5.32 ± 3.08	6.92 ± 3.15	0.168
Seizure frequency (monthly)	4.33 ± 9.89	6.04 ± 17.02	0.753
	Number	Number	
Sex (M/F)	14/8	6/6	0.487
EEG findings			
Normal/Abnormal	11/11	6/6	1.000
IEDs (+)/(-)	9/13	5/7	1.000
Single/Multiple lesion	16/6	12/0	0.069
Size of lesion ≤2.0cm	19	12	0.537
Temporal/Extratemporal location	6/16	9/3	0.012

Abbreviation: SD=standard deviation; EEG=electroencephalography; M=male; F=female; IED= interictal epileptiform discharges.

* Statistically significant at $p \leq 0.05$.

Temporal lobe CM was more common in patients assigned to Group 2 (9 of 15 patients), whereas extratemporal location of CM were much more common in Group 1 (16 of 19 patients), which were statistically significant (p=0.010) (Table 2). None of other clinical variables showed any significant correlations with the location of CM using the logistic regression. Among 15 patients with temporal CRE, four (26.7%) achieved 1-year TSR by the first drug treatment compared to 14 of 19 (73.7%) patients with extratemporal CRE (p=0.006). Among 8 patients with temporal CRE who underwent the trial of second drug regimen, 2 patients (25%) achieved 1-year TSR, whereas 2 of 5 (40%) patients with extratemporal CRE did achieve 1-year TSR by the second drug regimen.

Table 2 Comparison between characteristics of the temporal located CM and extratemporal located CM

	Temporal CM (N = 15)	Extratemporal CM (N = 19)	
	Mean ± SD	Mean ± SD	p-value
Age (year-old)	36.27 ± 18.26	34.32 ± 16.57	0.750
Seizure duration (year)	6.40 ± 2.77	5.47 ± 3.45	0.390
Seizure frequency (monthly)	9.03 ± 18.09	1.69 ± 3.60	0.143
Size of lesion (mm)	10.34 ± 5.07	13.51 ± 6.92	0.133
Outcomes	Number	Number	
1-year TSR	6	16	
DRE	6	3	0.010

ERS	3	0	
TSR by the first drug	4	14	0.006
TSR by the second drug	2	2	1.000

Abbreviation: N=number; SD=standard deviation; CM=cavernous malformation; TSR=terminal seizure remission; DRE=drug resistant epilepsy; ERS=epilepsy with rare seizure.

* Statistically significant at $p \leq 0.05$.

Postoperative seizure outcome

Five patients with CRE underwent epilepsy surgery after the failure of second drug regimen. All of them had temporal CRE and complete resection of CM was undertaken. Two patients underwent extensive lesionectomies consisting of resection of the lesion and the surrounding epileptogenic cortex indicated by intraoperative electrocorticography. In remaining three patients, resections of the lesion and surrounding hemosiderin rim were performed without intraoperative electrocorticography. All patients achieved Engel Class-1 outcome and no permanent neurological deficits were encountered after surgery. AEDs were successfully discontinued in two patients without any recurrences of seizure (Table 3).

Table 3 The patients who underwent surgical intervention for CM

Patient No.	Sex/ Age	Seizure frequency*	Size of CM (mm)	Surgery modality	Engle	Current AED
1	F/30	0.7	11.00	Extensive lesionectomy	1A	None
2	M/22	0.7	10.09	Lesionectomy	1D	CBZ
3	M/21	2	17.00	Extensive lesionectomy	1A	LTG
4	F/53	60	14.42	Lesionectomy	1A	CBZ VPA
5	M/23	1	4.19	Lesionectomy	1A	None

Abbreviation: No=number; F=female; M=male; CM=cavernous malformation; AED=Antiepileptic drugs; CBZ=carbamazepine; LTG=lamotrigine; VPA=valproate; *=Seizure frequency per month during last 3 months before treatment

Follow-up brain MRI

Of 34 patients, 20 patients including four patients with multiple CMs underwent follow-up brain MRI. MRI was repeated as a routine follow-up procedure in 15 patients (9 patients were in 1-year TSR at follow-up MRI) and for evaluation of seizure recurrence of seizures in five patients. Mean duration of follow-up was 2.3 years (range 0.5-13.0). Brain MRI showed no significant interval changes in 18 patients (90.0%) including six patients with DREs. Two patients with multiple CMs in initial MRI showed enlargement of CMs in follow-up MRI (risk of 10.0% per person year of exposure) (Table 4). One patient of them repeated brain MRI twice. The first follow-up MRI was repeated to evaluate the seizure relapse

and showed development of hemorrhage and enlargement of the CM in the right frontal lobe. He became seizure-free with a dose escalation of prescribing drug (valproate). After two years, MRI was repeated again because of seizure relapse and development of mild weakness of the left leg. MRI demonstrated further enlargement of the same lesion which had shown hemorrhage and enlargement in previous MRI. He became seizure-free and his left leg weakness was recovered after substitution monotherapy with topiramate. Therefore in our study, two of four patients with multiple CMs showed dynamic changes of CMs in follow-up MRI but none of 15 patients with a single CM.

Table 4 The patients whose lesion changed in repeated brain MRI

Patient No.	Size of CM (mm)*	Location of CM*	Reason**	Interval^{+}	MRI changes	Management
1	9.47	Frontal	Seizure relapse	7 years	Enlargement and hemorrhage of the lesion at the right superior and mesial frontal lobe	Escalation of the AED
			Seizure relapse and left leg weakness	9 years	Enlargement the same lesion to 18.20 mm	Change of the AED
2	12.90	Frontal	Routine f/u	3 years	Enlargement to 17.96 mm	No change of AED

Abbreviation: No=number; CM=cavernous malformation; MRI=magnetic resonance image; *=Cavernous malformations with multiple lesions were classified to the lobe harboring the CM responsible for the patient's seizure, EEG features, or to the largest lesion if their correlations were not clear; **=Reason of repeated brain MRI; $^{+}$= Interval to the first brain MRI

Discussion

Successful seizure outcome was achieved in 18 of 34 (52.9%) patients by the first drug monotherapy and in four of 13 (30.8%) patients who had tried second drug regimen. None of patients who failed to the second drug regimen achieved 1-year TSR by further drug trials. Three patients who had ERS during the first drug monotherapy did not undergo the trial of the second drug regimen by judgment of caring physicians and assigned to Group 2. Josephson et al. reported that 2-year SR rate in patients with newly diagnosed CRE was 47% at 5 year follow-up, while it was 53.8% (seven of 13 patients) at 5-year follow-up in this study.[3] In an univariate analysis of multiple clinical variables, the lobar location of CM was the single important predictive factor associated with the outcome of AEDs therapy with temporal CRE being associated with a poor outcome (no 1-year TSR in 9 of 16 patients) and extratemporal CRE with excellent outcome (1-year TSR in 16 of 19 patients). Casazza et al. reported that the location of CM in the medial temporal lobe was more frequent in patients with refractory CRE[8], however, we were not able to find any meaningful differences in seizure outcomes between the medial and the lateral temporal CREs in our patients (data was not shown).

Initial monotherapy of the first-line drugs is the rule of AEDs therapy in patients with newly diagnosed epilepsy. If an adequate trial of the first drug fails to control seizures, trials of the second drug regimen either in monotherapy or combination therapy is the next step of treatment. Failure of seizure control by adequate trials of two AEDs defines the diagnosis of DRE[13], in which referral to

tertiary epilepsy care centers are strongly recommended for further diagnostic precision and appropriate therapeutic trials including epilepsy surgery.

Epilepsy surgery is the most effective but often underutilized therapeutic modality for patients suffering from DREs. Randomized controlled trials (RCTs) clearly demonstrated the superior outcome of epilepsy surgery compared to that of continuing AEDs therapy in patients with refractory TLE.[18,19] No RTCs for the outcome of epilepsy surgery in patients with extra-TLE have been conducted yet, however, a meta-analysis have shown that the postsurgical outcome of extra-TLE was significantly worse than that of TLE, especially in patients with normal MRI.[20, 21] Presence of focal, resectable lesions in MRI has been found the most important factor affecting the postsurgical outcome in patients with DREs. In a meta-analysis, SFR after surgery in patients with epilepsy related to focal MRI-lesions (lesional epilepsies) was 70% compared to 46% of non-lesional epilepsies, which was a highly significant difference.[21] These outcome studies made a basis for the recommendation of earlier referral of patients to presurgical evaluation if they failed to adequate therapeutic trials of two AEDs and their epilepsy syndromes are considered surgically remediable. However, the optimal timing of epilepsy surgery in patients with DREs is based on careful risk-benefit assessments in individual patients, which may include perceived benefits and risks related to surgery and presurgical evaluation, severity of epilepsy, and outcomes of further AEDs therapy. In addition, a significant proportion of patients who failed to adequate trial of two AEDs may still have a good chance of prolonged seizure

remission by further drug trials[22], which may raise a significant controversy related to the optimal timing of epilepsy surgery during the course of AEDs therapy.

A prospective study found that 73 of 128 (57%) patients who failed to previous trials of 2 AEDs achieved 1-year SR, however, 50 (68%) of them experienced seizure relapses.[23] At the end of follow-up for 10.1 years, 3-year TSR was achieved in 28 (22%) patients, which was strongly related to the etiology of epilepsy; 11% in symptomatic epilepsy vs. 33% in cryptogenic epilepsy ($p = 0.003$). Another long-term observational study in 79 patients who failed to ≥ 2 AEDs within 2 years after diagnosis of epilepsy[24], has shown that 34 (45.3%) patients became seizure free at the follow-up of 11.7 years with the neuroimaging features being a single predictive factor for the long-term outcome; SFR was 60% in patients with normal MRI vs. 9% in patients with abnormal MRI. Therefore, symptomatic etiology or MRI-lesions in patients who failed to adequate trials of 2 AEDs seems sufficient for consideration of earlier epilepsy surgery if their lesion is surgically accessible, while patients with cryptogenic etiology or normal MRI may be better off with further systematic AEDs therapy for a higher chance of seizure remission as well as less favorable surgical outcomes. The poor outcome of further drug trials in our patients who failed to first 2 AEDs is in good agreement with these studies and we are in a great favor of the recommendation for earlier surgical evaluations in patients who failed to the first two drug regimens.

Prediction of long-term outcomes in patients who failed to the first AED is less clear. A previous study reported that 29 of 72 (42%) patients who failed to the

first drug became seizure-free at $\geq$ 8 years of follow up.[25] A recent follow-up study of the SANAD trial[26] reported that 70% of patients who failed to the first drug trial achieved 1-year SR at 5 years of follow up and concluded that the predictive accuracy of long-term outcome models after first drug failure was relatively low. On the other hand, failure to the first drug trial was a strong prognostic factor in patients with TLE. Dlugos et al. reported that the failure to the first drug in patients with TLE was associated with very high positive (0.89; 95% confidence interval 0.76 to 0.96) and negative (0.95; 95% confidence interval 0.87 to 0.99) predictive values for subsequent drug refractoriness.[27] Spooner et al. followed 64 children with TLE for median 13.7 years and found that a long-term seizure-free outcome was achieved in none of 28 children with MRI-lesions compared to 19 of 36 patients with normal MRI.[28] These studies strongly suggest that the long-term outcome of AEDs therapy in patients with TLE is different from that of general epilepsy populations, thus their failure to the first drug is an important predictive factor for persistent pharmacoresistance, especially in cases with associated MRI-lesions in the temporal lobe. The assumption seems in good agreement with the results of this study, which has shown significantly worse outcome in temporal CRE compared to extratemporal CRE (p = 0.006). The responses to the second drug regimen seemed also lower in patients with temporal CRE than patients with extratemporal CRE (25% vs. 40%, respectively). The difference was not statistically significant due to a small number of patients, which should be further investigated in future studies.

Risk-benefit assessment of epilepsy surgery in patients with drug resistant

CRE requires reliable data on postsurgical outcomes. A review of previous surgical series[2] showed Engel class-1 outcome in 70% to 84% of patients, which seemed better or at least not worse than that of surgery of TLE. In a direct comparison of epilepsy surgery of mesial temporal lobe epilepsy (MTLE) due to hippocampal sclerosis (HS) with MTLE due to CM, the latter was associated with a significantly better postoperative outcome (SFR in 42% and 82%, respectively; p=0.029), however, DREs were more common in patients with MTLE due to HS (88%) than MTLE due to CM (36%), which made it as an unfair comparison.[29] In our study, the outcome of lesionectomies in 5 patients who were confirmed to have refractory temporal CRE was excellent to achieve Engel class-1 outcome in all patients without any permanent new neurological deficits, which was strongly in favor of surgery than continuing AEDs therapy in patients suffering from refractory temporal CRE. However, it should be stressed that excision of CM is not without risks, because comparative studies of the early surgery and the conservative management in newly diagnosed patients with CM showed significantly worse outcome in patients underwent early surgical excision.[12] In addition, another comparative studies of early surgery and medical treatment in patients with CRE did not show any significant differences in seizure outcomes between the two groups.[11] Therefore, any recommendations proposing a surgical excision of CM shortly after its diagnosis cannot be justified by currently available evidence.

Considering the result of AEDs therapy and surgical outcomes of refractory TLE in our patients and outcome data from previous studies, different

management strategies based on the location of CM seems more appropriate; failure to control seizures by adequate trial of first AED in patients with temporal CRE may be considered sufficient for their referral to earlier surgery, while second drug trial is preferred in patients with extratemproal CRE due to a reasonable chance of seizure remission by the second drug trial and possibly higher risks associated with extratemporal lobe surgery.

Routine follow-up MRI in patients with CRE has been recommended because CM is considered a dynamic vascular abnormality.[2] Dynamic changes of CM may be related to serial micro- or macro-hemorrhages followed by organization, fibrosis, and calcification. We obtained repeat MRIs in 19 patients and found enlargement of CMs in two patients with combined lesional hemorrhage in one patient, all of whom were harboring multiple CMs. This was in a strong contrast to the result of follow-up MRIs in 15 patients with a single lesion, who did not show any appreciable changes in the size of CM. The behavior of CM in patients with a single CRE may be different and less dynamic than patients carrying multiple CMs or patients presenting with hemorrhages and/or focal neurological symptoms. The future guidelines of repeating MRI in patients presenting with CRE may require further systemic investigations.

The limitation of current study includes that the number of enrolled patient was small and the study was a retrospective observational study, which may be associated with significant bias. However, differences in outcomes of AEDs therapy between the temporal and the extratemporal CREs were quite striking, supporting

different strategies for the planning of optimal management in these two groups of newly diagnosed CRE. It is surprising to find that, despite extensive clinical studies published in the literature, there have been severe shortages of reliable information related to the therapeutic outcomes of CRE. There is urgent need for RCTs for both medical and surgical treatments in patients with newly diagnosed CRE.

V. CONCLUSION

The outcome of AEDs therapy in patients presented with new onset of CRE was quite comparable with that of general populations of newly diagnosed epilepsy. Location of CM in the temporal lobe was a single important factor predicting poor outcome of AEDs therapy. We propose that a failure to an adequate first drug trial in patients with temporal CRE may be sufficient for their referral to epilepsy surgery, while patients with extratemporal CRE require at least adequate trials of two AEDs before their referral to surgery. The probability of finding clinically meaningful dynamic changes of CMs in patients with CRE due to a single lesion was quite low, which requires future investigations for the cost-benefit assessment of routine follow-up MRIs.

References

1. Raychaudhuri R, Batjer HH, Awad IA. Intracranial cavernous angioma: a practical review of clinical and biological aspects. Surgical neurology 2005;63(4):319-28; discussion 328.

2. Rosenow F, Alonso-Vanegas MA, Baumgartner C, Blumcke I, Carreno M, Gizewski ER, et al. Cavernoma-related epilepsy: review and recommendations for management--report of the Surgical Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2013;54(12):2025-35.

3. Josephson CB, Leach JP, Duncan R, Roberts RC, Counsell CE, Al-Shahi Salman R. Seizure risk from cavernous or arteriovenous malformations: prospective population-based study. Neurology 2011;76(18):1548-54.

4. Cockerell OC, Johnson AL, Sander JW, Hart YM, Shorvon SD. Remission of epilepsy: results from the National General Practice Study of Epilepsy. Lancet 1995;346(8968):140-4.

5. Semah F, Picot MC, Adam C, Broglin D, Arzimanoglou A, Bazin B, et al. Is the underlying cause of epilepsy a major prognostic factor for recurrence? Neurology 1998;51(5):1256-62.

6. Baumann CR, Acciarri N, Bertalanffy H, Devinsky O, Elger CE, Lo Russo G, et al. Seizure outcome after resection of supratentorial cavernous malformations: a study of 168 patients. Epilepsia 2007;48(3):559-63.

7. Stavrou I, Baumgartner C, Frischer JM, Trattnig S, Knosp E. Long-term seizure control after resection of supratentorial cavernomas: a retrospective single-center study in 53 patients. Neurosurgery 2008;63(5):888-96; discussion 897.

8. Casazza M, Broggi G, Franzini A, Avanzini G, Spreafico R, Bracchi M, et al.

Supratentorial cavernous angiomas and epileptic seizures: preoperative course and postoperative outcome. Neurosurgery 1996;39(1):26-32; discussion 32-4.

9. Noto S, Fujii M, Akimura T, Imoto H, Nomura S, Kajiwara K, et al. Management of patients with cavernous angiomas presenting epileptic seizures. Surgical neurology 2005;64(6):495-8, discussion 498-9.

10. von der Brelie C, Schramm J. Cerebral cavernous malformations and intractable epilepsy: the limited usefulness of current literature. Acta neurochirurgica 2011;153(2):249-59.

11. Poorthuis M, Samarasekera N, Kontoh K, Stuart I, Cope B, Kitchen N, et al. Comparative studies of the diagnosis and treatment of cerebral cavernous malformations in adults: systematic review. Acta neurochirurgica 2013;155(4):643-9.

12. Moultrie F, Horne MA, Josephson CB, Hall JM, Counsell CE, Bhattacharya JJ, et al. Outcome after surgical or conservative management of cerebral cavernous malformations. Neurology 2014;83(7):582-9.

13. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010;51(6):1069-77.

14. Chalouhi N, Dumont AS, Randazzo C, Tjoumakaris S, Gonzalez LF, Rosenwasser R, et al. Management of incidentally discovered intracranial vascular abnormalities. Neurosurgical focus 2011;31(6):E1.

15. Lee BI, Heo K, Kim JS, Kim OJ, Park SA, Lim SR, et al. Syndromic diagnosis at the epilepsy clinic: role of MRI in lobar epilepsies. Epilepsia 2002;43(5):496-504.

16. Epilepsy CoCaTotILA. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1989;30(4):389-99.

17. Von Oertzen J, Urbach H, Jungbluth S, Kurthen M, Reuber M, Fernandez G, et al. Standard magnetic resonance imaging is inadequate for patients with refractory focal epilepsy. Journal of neurology, neurosurgery, and psychiatry 2002;73(6):643-7.

18. Engel J, Jr., McDermott MP, Wiebe S, Langfitt JT, Stern JM, Dewar S, et al. Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. JAMA 2012;307(9):922-30.

19. Wiebe S, Blume WT, Girvin JP, Eliasziw M. A randomized, controlled trial of surgery for temporal-lobe epilepsy. The New England journal of medicine 2001;345(5):311-8.

20. Tellez-Zenteno JF, Dhar R, Wiebe S. Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. Brain : a journal of neurology 2005;128(Pt 5):1188-98.

21. Tellez-Zenteno JF, Hernandez Ronquillo L, Moien-Afshari F, Wiebe S. Surgical outcomes in lesional and non-lesional epilepsy: a systematic review and meta-analysis. Epilepsy research 2010;89(2-3):310-8.

22. Luciano AL, Shorvon SD. Results of treatment changes in patients with apparently drug-resistant chronic epilepsy. Annals of neurology 2007;62(4):375-81.

23. Berg AT, Levy SR, Testa FM, D'Souza R. Remission of epilepsy after two drug failures in children: a prospective study. Annals of neurology 2009;65(5):510-9.

24. Wirrell EC, Wong-Kisiel LC, Nickels KC. Seizure outcome after AED failure in pediatric focal epilepsy: impact of underlying etiology. Epilepsy & behavior : E&B 2014;34:20-4.

25. Camfield PR, Camfield CS, Gordon K, Dooley JM. If a first antiepileptic drug fails to control a child's epilepsy, what are the chances of success with the next drug? The

Journal of pediatrics 1997;131(6):821-4.

26. Bonnett LJ, Tudur Smith C, Donegan S, Marson AG. Treatment outcome after failure of a first antiepileptic drug. Neurology 2014;83(6):552-60.

27. Dlugos DJ, Sammel MD, Strom BL, Farrar JT. Response to first drug trial predicts outcome in childhood temporal lobe epilepsy. Neurology 2001;57(12):2259-64.

28. Spooner CG, Berkovic SF, Mitchell LA, Wrennall JA, Harvey AS. New-onset temporal lobe epilepsy in children: lesion on MRI predicts poor seizure outcome. Neurology 2006;67(12):2147-53.

29. Menzler K, Thiel P, Hermsen A, Chen X, Benes L, Miller D, et al. The role of underlying structural cause for epilepsy classification: clinical features and prognosis in mesial temporal lobe epilepsy caused by hippocampal sclerosis versus cavernoma. Epilepsia 2011;52(4):707-11.

Abstract (In Korean)

해면혈관기형 관련 뇌전증 환자를 대상으로 한 약물적 치료의 장기적 예후

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목적: 본 연구에서는 새로 진단된 해면혈관기형 관련 뇌전증 환자를 대상으로 항뇌전증약물을 투여하였을 때 장기적 예후를 분석하고, 적절한 수술 시기를 제안하고자 한다.

방법: 본 연구는 2000년부터 2011년까지 신촌 세브란스병원 뇌전증센터에 방문한 새로이 진단된 해면혈관기형 관련 뇌전증 환자들을 대상으로 하였다. 모든 환자들은 2년 이상 추적관찰을 하였고, 이전에 다른 병원에서 수술적 또는 약물적 치료를 하거나 뇌파 또는 뇌 자기공명영상 검사를 시행하지 않았던 환자, 그리고 발작이 1번 이하로 있었던 경우는 배제하였다. 환자들은 추적관찰을 한 마지막 1년 동안 발작이 없었던 경우를 그룹 1, SF군 (seizure free group)으로, 발작이 있었던 경우를 그룹 2, non SF군 (non-seizure free group)으로 분류하여 그룹간의 차이를 비교 분석하였다. 약물 저항성 뇌전증은 2번의 적절한 약물로 치료했음에도 불구하고 1년에 2번 이상의 발작이 있는 경우로 정의하였다. 환자

가 일 년에 오직 한 번의 발작만 있었던 경우를 “드문 발작”이라고 분류하였다.

결과: 총 34명 (남자 20명)의 새로이 진단된 해면혈관기형 관련 뇌전증 환자를 대상으로 하였다. 평균 추적관찰기간은 5.88 ± 3.15년이었고, 치료 전 마지막 3개월동안의 발작 빈도는 한 달에 4.93 ± 12.63회였다. 추적관찰을 한 마지막 1년 동안 발작이 없었던 환자는 22명으로 64.7%였으며 9명 (26.5%)은 약물 저항성 뇌전증으로, 3명 (8.82%)은 드문 발작으로 분류하였다. 첫 번째 약물에 발작이 없었던 환자는 34명 중 18명 (52.9%)이었고 추가적으로 4명 (11.8%)은 두 번째 약물을 투여하고 발작이 없어졌다. 두 번째 약물은 총 16명 중 13명에게 시도하였으며 드문 발작을 보였던 3명에게는 시도하지 않았다. 두 번째 약물에 실패한 9명과 드문 발작을 한 3명은 추적관찰을 한 마지막 1년 동안에도 발작이 있어 그룹 2로 분류되었다. 예후를 예측하는 다양한 변수를 단일변량 분석을 하였을 때 측두엽에 병변이 있는 경우에만 유일하게 예후가 나빴다. (p=0.012)

결론: 해면혈관기형 관련 뇌전증 환자를 대상으로 장기간 추적관찰을 한 결과 64.7%에서 추적기간 마지막 1년동안 발작이 없이 유지되었다. 두 번의 적절한 약물 투여에도 발작이 지속되었던 환자들에게는 수술적 치료를 하는 것을 강력히 권유하는 것이 바람직하다. 하지만 측두엽에 병변이 있는 환자에서는 첫 번째 약물에 실패한 경우에도 수술을 위한 검사

를 진행하는 것을 고려해야 한다.