Clinical outcome following medical treatment of cavernous malformation related epilepsy

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ABSTRACT

Purpose: The study was conducted to assess the long-term outcome of antiepileptic drug (AED) treatment in drug-naïve patients with cavernous malformation (CM) related epilepsy (CRE).
Method: This is a retrospective, single-center, long-term observational study of 34 patients with previously untreated seizures related to CM. All patients were followed-up for at least two years. 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 seizures (ERSs)".
Results: Terminal 1-year seizure remission (1-YTR) was achieved in 22 (64.7%) patients, nine (26.5%) patients were diagnosed as DRE, and three (8.8%) patients were as ERSs. 1-YTR was achieved in 18 (52.9%) patients by the first drug regimen and in additional four (11.8%) patients by the second drug regimen. None of nine patients who failed to first two drug regimens did achieve 1-YTR. The location of CM in the temporal lobe was the only prognostic factor predicting a poor seizure outcome (p = 0.012).
Conclusion: The outcome of AEDs therapy in patients who were presented with new onset of CRE was quite comparable with that of patients with newly diagnosed epilepsy. Failure to achieve seizure-free after adequate trials of two AEDs seems appropriate as the criteria for their referral to surgical treatment. For patients with temporal lobe CRE, earlier presurgical evaluation may be considered justifiable once they failed to an adequate trial of the first drug.

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1. 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 CM-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 (YR) rate by AED therapy at 5-year follow-up period was 47%, which was lower than the 2-year seizure remission rate (68%) in a community based study [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 magnetic resonance image (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, thus evidence-based guidelines for the management of newly diagnosed patients with CRE are not available yet.

Recent International League Against Epilepsy (ILAE)-report stated that it was not necessary to wait until the rigorous criteria of drug resistant epilepsy (DRE) proposed by ILAE [6] 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 rather than evidence-based practice guidelines [7]. 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 newly diagnosed CRE. The study was conducted to investigate the long-term outcome of AEDs therapy and related prognostic factors in patients with newly diagnosed CRE.

2. Methods

2.1. Patients and treatment

We conducted a retrospective analysis of Yonsei Epilepsy Registry, a prospective patient registry, which was described in detail in a previous study [8]. Among 73 patients who were registered under the diagnosis of untreated CRE during the period between 2000 and 2013, 34 patients satisfied the patient's inclusion criteria, which were: (1) well-established diagnosis of partial epilepsies as defined by the International Classification of Epilepsies and Epileptic Syndromes [9]; (2) presence of CM by brain MRI; (3) performed electroencephalography (EEG) evaluation; (4) history of two or more seizures in the past with at least one episode of seizure during the previous year before the commencement of AEDs therapy, (5) follow-up of at least two years. Thirty-nine patients were excluded from the study due to previous surgery for CM (n = 13), less than two-year follow-up (n = 11), previous AED therapy before their referral (n = 10), epilepsy not related to CM (coincidental MRI finding) because of seizure semiology or focal epileptiform discharges or slowing on EEG inconsistent with CM location (n = 2), no EEG evaluation (n = 2), and no seizure event during the 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 were based on thorough clinical assessment [9], 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 for partial-onset seizures. If patients developed seizure recurrences during adequate trials of the 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 drug regimens during the follow-up period.

We received approval from the Yonsei University Severance Hospital ethical standards committee on human experimentation for experiments using human subjects.

2.2. 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 (22 patients with 1.5-T and 12 patients with 3.0-T) [10]; range of in-plane resolution 0.449–0.898 mm; slice thickness 1–5 mm; slice spacing 1–2 mm. 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 hemosiderin rim was measured and divided by different cutoff values, which were 10 mm and 20 mm respectively. 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-YR was defined as freedom from seizure for 12 months during each year of follow-up, whereas 1-YTR 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 seizures (ERSs). 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-YTR; patients who have achieved 1-year TSR were assigned to good prognosis (GP) group, whereas poor prognosis (PP) group included patients who had seizure relapses during the last one year of follow up (patients with DRE and ERSs).

2.3. Statistics

All data were expressed as mean ± standard deviation, and median values were calculated. For subgroup analysis, the Chi-square test or Fisher's exact test were used for categorical variances and independent two-sample t-test was performed for continuous variables. Statistical analyses were performed using commercially available software (SPSS, Ver. 20.0), and a two-tailed P value < 0.05 was considered significant.

3. Results

3.1. Demography and clinical characteristics

Mean baseline seizure frequency was 4.9 ± 12.6 episodes per month and median seizure frequency was 0.9 (interquartile range, 1.9) 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 5.9 ± 3.2 years (range 2–12). CMs responsible for patient's seizure 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). Mean size of CM was 12.1 ± 6.3 mm (range 4.2–31.5 mm). Lamotrigine was the most frequently (23.5%) used AED for monotherapy, whereas various combinations of AEDs were used for duo- or triple drug therapy.
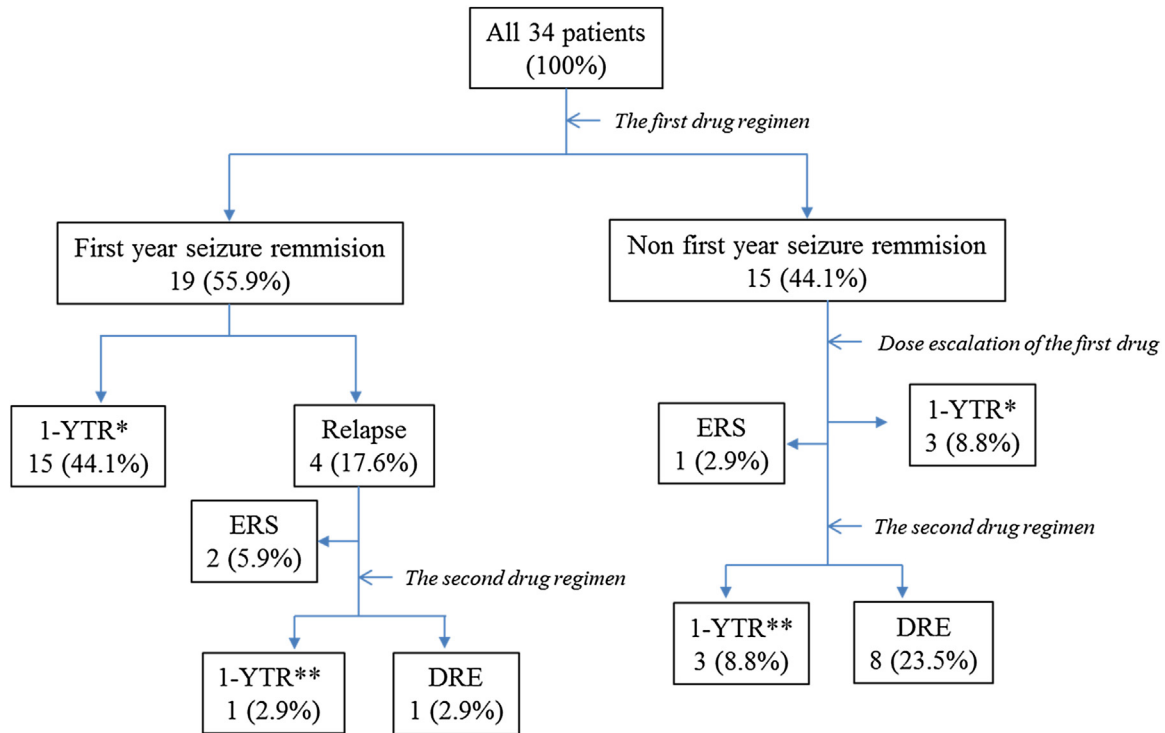
Fig. 1. Flowchart of overall seizure outcome.
1-YTR, seizure-free during the last one year of follow-up; ERS, epilepsy with rare seizure (only one episode of seizure relapse during the previous one year of follow-up); DRE, drug resistant epilepsy (two or more seizures during the previous one year of follow-up); *, the patients achieved 1-YTR by the first drug regimen; **, the patients achieved 1-YTR by the second drug regimen.

3.2. Outcome of AEDs therapy

Nineteen patients achieved 1-YR immediately after the first drug treatment but seizures relapsed in four of them. Among those who did relapse, two patients were ERSs and were followed-up with gradual dose-escalations of the first drug, whereas two other patients underwent trials of the second drug regimen with achievement of 1-YTR in one and failure to achieve seizure remission in the other. Among 15 patients who have failed to achieve seizure remission during the first year after the first drug, three patients achieved 1-YTR after dose escalation of the first drug and another three patients by the trial of second drug regimen. Therefore, 1-YTR was achieved in 64.7% (22/34) and cumulative 1-YR was achieved in 73.5% (25/34) during the follow-up, which was quite comparable to the outcome of hospital-based cohort study of newly diagnosed epilepsy [11]. Nine patients (26.5%) continued to have seizure recurrences despite of adequate trials of first two AEDs, thus satisfied the criteria of DRE. In summary, the first drug regimen successfully controlled seizures in 18 patients (52.9%) and the second drug regimen was successful in four of 13 (30.8%) patients who failed to the first drug. 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 failed to the adequate trials of second drug regimen, none achieved 1-YTR by further drug trials (six under duotherapy, two under triple drug combination, and one under five drug combination therapy), thus they were assigned to PP group. Remaining three patients who had ERSs during the first drug trial were kept on the first drug monotherapy with progressive dose-escalations by the judgment of caring physicians and assigned to PP group (Fig. 1).

3.3. Clinical variables related with the outcome of AEDs therapy

Twenty two (64.7%) patients assigned to GP group and 12 (35.3%) were assigned into PP group. Multiple clinical variables including age of seizure onset, seizure frequency before treatment, duration of illness, numbersand size of CM, and EEG features, were compared between GP and PP groups. None of these variables were found significantly different except the location of CM, which was the only one prognostic factor significantly correlating with the outcome of AEDs therapy (Table 1). Among 15 patients with temporal CRE, four (26.7%) achieved 1-YTR by the first drug treatment compared to 14 of 19 (73.7%) patients with extratemporal CRE (p = 0.006). Among

Table 1
Demographic and clinical characteristics of the participants.

	Total	GP (n = 22)	PP (n = 12)	p-value
Age (year-old)	35.2 ± 17.1	38.3 ± 17.5	29.5 ± 11.6	0.144
Sex (M/F)	20/14	14/8	6/6	0.487
Seizure duration (year)	6.1 ± 8.6	5.3 ± 3.1	6.9 ± 3.2	0.168
Seizure frequency (monthly)	4.9 ± 12.6	4.3 ± 9.9	6.0 ± 17.0	0.753
EEG findings				
Normal/abnormal	17/17	11/11	6/6	>0.999
IEDs (+)/(−)	14/20	9/13	5/7	>0.999
Single/multiple lesion	28/6	16/6	12/0	0.069
Size of lesion ≤10 mm		6	6	0.265
Size of lesion ≤20 mm		19	12	0.537
Temporal/extratemporal location	15/19	6/16	9/3	0.012

Numerical values are presented as mean ± standard deviation or number of cases. GP, good prognosis group; PP, poor prognosis group; n, number; M, male; F, female; EEG, electroencephalography; IED, interictalepileptiform discharges.

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

	Temporal CM (n = 15)	Extratemporal CM (n = 19)	p-value
Age (year-old)	36.3 ± 18.3	34.3 ± 16.6	0.750
Seizure duration (year)	6.4 ± 2.8	5.5 ± 3.5	0.390
Seizure frequency (monthly)	9.0 ± 18.1	1.7 ± 3.6	0.143
Size of lesion (mm)	10.3 ± 5.1	13.5 ± 6.9	0.133
Outcomes	Number	Number	
1-year TSR	6	16	
By the first drug	4	14	0.006
By the second drug	2	2	>0.999
DRE	6	3	0.010
ERSs	3	0	

Numerical values are presented as mean ± standard deviation or number of cases.
n, number; CM, cavernous malformation; TSR, terminal seizure remission; DRE, drug resistant epilepsy; ERSs, epilepsy with rare seizures.

8 patients with temporal CRE who underwent the trial of second drug regimen, 2 patients (25%) achieved 1-YTR, whereas 2 of 5 (40%) patients with extratemporal CRE did achieve 1-year TSR by the second drug regimen (Table 2).

3.4. Postoperative seizure outcome

Among six patients with drug-resistant temporal, 5 patients underwent epilepsy surgery. 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). Remaining one patient with temporal CRE, who did not undergo surgery after failure of second drug regimen, continued having seizures under combination therapy of four AEDs during the follow-up of 7 years.

3.5. 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-YTR at the time of 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 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 after a dose escalation of the second drug (valproate). After two years, MRI was repeated again because of another 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.

4. Discussion

This is a retrospective hospital-based, observational study to investigate the long-term outcome of AED therapy in patients with newly diagnosed CRE. The major findings of the present study were as follows: (1) 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-YTR by further drug trials, (2) the location of CM was the only one prognostic factor of AEDs therapy; temporal CRE was associated with worse prognosis than extratemporal CRE, and (3) dynamic changes of CM in patients with CRE werefrequent in patients with multiple CMs but not in patients with single CM.

Table 3
The patients who underwent surgical intervention for cavernous malformation.

Patient	Sex/age	Seizure frequency[a]	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

F, female; M, male; CM, cavernous malformation; AED, antiepileptic drugs; CBZ, carbamazepine; LTG, lamotrigine; VPA, valproate.
[a] Seizure frequency per month during last 3 months before treatment.

Table 4
The patients whose lesion changed in repeated brain magnetic resonance image.

Patient	Size of CM (mm)[a]	Location of CM[a]	Reason of repeated brain MRI	Interval to the first brain MRI	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 follow up	3 years	Enlargement to 17.96 mm	No change of AED

CM, cavernous malformation; MRI, magnetic resonance image; AED, antiepileptic drugs.
[a] 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.

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 [12]. Failure of seizure control by adequate trials of two AEDs defines the diagnosis of DRE [6], in which referral of patients to tertiary epilepsy care centers are strongly recommended for further diagnostic precision and appropriate therapeutic trials including epilepsy surgery. The long-term outcome of further drug trials in patients who fulfilled the ILAE-criteria of DRE is still unclear due to their complex clinical courses characterized by delayed remissions or alternating periods of remission and relapse. Recently, Choi et al. reported that further drug trials in patients who failed to first two AEDs resulted in a prolonged terminal remission in 31% of patients, which was influenced by the type of epilepsy syndromes and duration of follow-up [13].

A prospective study of a pediatric cohort found that 28 of 128 (22%) patients who failed to previous trials of two AEDs achieved 3-YTR at the end of follow-up for 10.1 years [14]. The probability of achieving 3-YTR was strongly related to the etiology of epilepsy; 11% in symptomatic epilepsy and 33% in non-lesional epilepsy (p = 0.003). Another long-term observational study in 79 patients who failed to ≥ two AEDs within two years after diagnosis of epilepsy [15], has shown that 34 (45.3%) patients became seizure-free at the follow-up of 11.7 years. In the study, the neuroimaging features being a single predictive factor for the long-term outcome; SFR was 60% in patients with normal MRI and 9% in patients with abnormal MRI. Therefore, symptomatic etiology or MRI-lesions in patients who failed to adequate trials of two AEDs seems sufficient for consideration of earlier epilepsy surgery if their lesion is surgically accessible, while patients with unknown 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 two AEDs is in good agreement with these studies and we are in a favor of the recommendation for earlier surgical evaluations in patients with CRE 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 ≥8 years of follow up [16]. A recent follow-up study of the SANAD trial reported that 70% of patients who failed to the first drug trial achieved 1-YR at 5 years of follow up and concluded that the predictive accuracy of long-term outcome models after first drug failure was relatively low [17]. On the other hand, failure to the first drug trial was a strong prognostic factor in patients with temporal lobe epilepsy (TLE). Dlugos et al. reported that the failure of first AED trial accurately predicted refractory TLE at 2 years after onset [18]. 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 [19]. In addition, a recent study for the long-term trajectory of patients with DRE has shown that the outcome of TLE was poorer than that of other lobar epilepsies [13]. These studies suggest that the long-term outcome of AEDs therapy in patients with TLE is different from that of other types of focal epilepsies, thus the likelihood of persistent pharmacoresistance after the first drug failure may be higher in patients with TLE, especially in cases with associated MRI-lesions. The assumption seems in good agreement with the results of the present study, which has shown significantly worse outcome in temporal CRE compared to extratemporal CRE. In the present study, two out of 8 patients (25%) with failure of the first AED in patients with temporal CRE and two out of 5 patients (40%) in patients with

extratemporal CRE showed the good response to the second drug regimen, although the difference was not statistically significant due to a small number of patients.

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 [20,21]. No RCTs 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 with the presence of focal, resectable lesions in MRI being the most important factor affecting the postsurgical outcome in patients with DREs [22,23]. In the 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 [23]. 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.

Referral of patients with DRE to surgery is based on careful risk-benefit assessments in individual patients, which requires reliable data on the postsurgical outcome. A review of previous surgical series in patients with CRE showed Engel class-1 outcome in 70–85% of patients, which seemed better or at least not worse than that of surgery of TLE [2]. In a direct comparison of epilepsy surgery of mesial TLE (MTLE) due to hippocampal sclerosis (HS) with MTLE due to CM, the latter was associated with a significantly better postoperative outcome, 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 [24]. 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. However, a comparative study of the early surgery and the conservative management in newly diagnosed patients with CM showed significantly worse outcome in patients who underwent early surgical excision [25]. In addition, another comparative study of early surgery and medical treatment in patients with CRE did not show any significant differences in seizure outcomes between the two groups [26]. 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 appropriate; failure to control seizures by adequate trial of first AED in patients with temporal CRE may be considered justifiable for their referral to earlier surgery, while the second drug trial is preferred in patients with extratemproal CRE due to a reasonable chance of seizure remission and possibly higher risks associated with extratemporal lobe surgery. However, future controlled trials are in urgent need to provide evidence-based guidelines.

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 recurrent micro- or macro-hemorrhages followed by organization, fibrosis, and calcification. We obtained repeat MRIs in 20 patients and found enlargement of CMs in two patients who were harboring multiple CMs. This was in a strong contrast to the result of follow-up MRIs in 16 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 from 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 hospital-based observational study, which may be associated with significant bias. However, all patients satisfied the strict inclusion criteria, serial AEDs therapy was performed according to the current practice guidelines, and seizure outcomes were assessed appropriately during prolonged period of follow-up. 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 long-term outcome of AEDs therapy in patients with newly diagnosed CRE. There is urgent need of controlled trials for both medical and surgical treatments in patients with newly diagnosed CRE.

In conclusion, the outcome of AEDs therapy in patients presented with newly diagnosed CRE was quite comparable with that of a hospital-based cohort of newly diagnosed epilepsy. Location of CM in the temporal lobe was a single important factor predicting poor outcome of AEDs therapy, which should be addressed in a discussion with patient about the probabilities of refractoriness and its consequences and the possibility of surgery in short term. The probability of finding clinically meaningful dynamic changes of CMs in patients with CRE was high in patients with multiple CMs but quite low in cases with a single lesion.

Authors' contribution

Yoonju Lee: research conception, organization, data collection, statistical analysis execution, writing. Kyoo Ho Cho: statistical analysis execution, writing. Hye Ihn Kim: research organization, data collection. Seung-Koo Lee: review and critique of image analysis. Yang-Je Cho: research organization, data re-check, statistical design. Kyoung Heo: review of research conception and manuscript. Byung In Lee: conception and organization of research project, review of statistical analysis and manuscript.

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Conflict of interest statement

None.

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