

Drug-resistant temporal lobe epilepsy due to cavernous malformations

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Object. Supratentorial cavernous angiomas may be associated with drug-resistant focal epilepsy. Surgical removal of the malformation may result in seizure control in a number of patients, although in most studies a long history and high frequency of attacks have been recognized as indicators of unfavorable seizure outcome. In the literature, there are no clear indications regarding the optimal diagnostic presurgical workup and the surgical strategy for this particular subgroup of patients with symptomatic epilepsy. In this paper the authors focus on the preoperative workup and the surgical management of the disease in eight consecutive patients undergoing surgery for drug-resistant temporal lobe epilepsy (TLE) due to cavernous malformations (CMs), and the relevant literature on this issue is also reviewed.

Methods. Preoperatively, all patients were assessed using a noninvasive protocol aimed at localizing the epileptogenic zone on the basis of anatomical, electrical, and clinical criteria. The presurgical assessment yielded an indication for lesionectomy in two cases, lesionectomy plus anteromesial temporal lobectomy in four cases, and lesionectomy plus extended temporal lobectomy in two cases. At follow-up examinations, seizure, neuropsychological, and psychiatric outcomes were all evaluated. Seven patients were categorized in Engel Class IA (seizure free), and one was categorized in Engel Class IB (occasional auras only). No adverse effects on neuropsychological or psychosocial functioning were observed.

Conclusions. Epilepsy surgery can be performed with excellent results in patients with intractable TLE caused by CMs. Noninvasive presurgical evaluation of these patients may enable a tailored approach, providing complete seizure relief in most cases.

KEY WORDS • cavernous malformation • drug resistance • seizure • temporal lobe epilepsy • epilepsy surgery

EPILEPTIC seizures are the most common presenting symptom of supratentorial CMs, occurring in up to 70% of patients.^{2,10,17,23,29} The clinical profile of these patients varies widely, ranging from sporadic seizures that are well controlled by medical therapy to drug-resistant focal epilepsy. A high frequency and long history of seizures have been recognized as the most important factors favoring the development of drug resistance.^{5,8,18}

The optimal surgical strategy for treating drug-resistant focal epilepsy due to cavernomas is still an open issue.

Abbreviations used in this paper: AED = antiepileptic drug; AMTL = anteromesial temporal lobectomy; CM = cavernous malformation; EEG = electroencephalography; MR = magnetic resonance; TLE = temporal lobe epilepsy.

Both lesionectomy (removing the surrounding hemosiderin and gliotic ring or leaving it in place) and tailored resection after invasive EEG recording have been proposed, with controversial results.^{18,25,31} Caution should be used in comparing different studies, because there are many disparities in definitions of drug resistance, presurgical protocols, resective treatment, and postoperative seizure outcome assessment. Moreover, the patients included in the published case series were often not homogeneous in terms of the kind of focal epileptic syndrome and epilepsy severity.

The studies support the suggestion that the seizure outcome following removal of the cavernoma is much better in patients with less severe epilepsy. Although nearly 95% of patients with a short history of epilepsy and rare attacks were seizure free after lesionectomy alone, 50 to 73% of

patients with drug-resistant epilepsy attained only partial remission or showed no improvement after a similar surgical procedure.^{5,8,14}

Based on the assumption that the lack of seizure control after lesionectomy could be due to the extension of the epileptic focus in the cortex surrounding the lesion,^{19,20} a growing number of authors believe that a tailored surgery is a more appropriate approach.^{3,5,15,21,25,26} Nevertheless, most studies do not provide a clear, detailed description of such tailored treatment. Terms such as “temporal lobectomy,”¹⁸ “extended resection,”⁸ and “anterior temporal lobectomy”²⁵ have all been used to designate resection of noneloquent brain tissue adjacent to the angioma. In most cases, the type of resection was determined based on invasive studies such as preoperative or intraoperative electrocorticography. Recently, magnetoencephalography has been proposed as an alternative, noninvasive method to identify nonlesional epileptogenic areas bordering the CM.²⁷

In this paper we focus on the preoperative workup and the surgical management of TLE caused by CMs. We review the relevant literature and report a series of eight consecutive patients who underwent a standardized, non-invasive diagnostic presurgical protocol, followed by epilepsy surgery.

Clinical Material and Methods

Patient Population

We studied eight consecutive patients (one man and seven women, mean age 39.1 years) with CMs of the temporal lobe (Table 1). These individuals were drawn from a large case series of 174 patients with TLE who underwent surgery at the Epilepsy Surgery Unit of the Neuromed Institute between September 1999 and January 2006. The duration of epilepsy had a bimodal distribution; it was less than 2 years in four patients and more than 10 years in the remaining four. All patients had failed to respond to at least two adequate trials of first-line AEDs and two new add-on drugs.

Preoperative Assessment

All patients underwent a comprehensive presurgical assessment protocol, which has been described in detail elsewhere²² and will only be summarized here. First, a detailed medical history is collected, with particular attention to seizure semiology, followed by a full clinical examination. Second, EEG recordings are obtained with the patient in the awake state and during sleep, and these are evaluated to assess the presence of background abnormalities and interictal slow and epileptiform activity. Also, a 1.5-tesla MR imaging examination, including gradient echo sequences, is performed.

Although patients with seizures dating back more than 2 years are invariably required to undergo long-term video-EEG monitoring and comprehensive neuropsychological and psychiatric assessment, patients with a seizure history of 1 to 2 years follow two different paths, depending on the concordance between anatomical, clinical, and EEG findings. If seizure semiology as determined by both history and interictal EEG is concordant with lesion side and location, TLE is diagnosed and lesionectomy is offered without the need for further investigations. On the contrary, if interictal or clinical data are discordant, the patients undergo long-term video-EEG monitoring and neuropsychological and psychiatric assessment. All patients enrolled in video-EEG monitoring have at least one seizure recorded, and these findings help establish the diagnosis of mesial, lateral, or mesiolateral TLE.

After completion of the assessment protocol, patients are offered three different interventions: lesionectomy for lateral TLE, AMTL for mesial TLE, and extensive temporal lobectomy for mesiolateral TLE.

Surgical Procedure

All operations were performed by the same epilepsy specialist (V.E.). Extensive temporal lobectomy and AMTL both included microsurgery of the amygdala and en bloc excision of the hippocampal formation and para-

TABLE 1
Clinical data in eight patients with drug-resistant TLE*

Case No.	Age (yrs), Sex	Age at Onset (yrs)	Duration of Dis (yrs)	MRI	Preop Findings							Seizure	
					Interictal EEG		Video-EEG			Op	Histopath	FU	
					Slow	Epileptiform	Ictal Onset	Early Symptoms	Ictal Pattern				
1	39, F	18	11	cav, rt T, neoc	T, focal	T, focal	T, focal	RES; aud; OAA; dys	Type 2	les & rt ETL	cav	IA	46
2	56, F	55	1	cav, lt T, neoc	T, reg	T, focal	ND	ND	ND	les	cav	IA	43
3	30, M	28	2	cav, lt T, neoc	T, reg	T, focal	T, focal	SA; OAA	Type 2	les & lt AMTL	cav	IA	38
4	28, F	27	1	cav, rt T, neoc	T, reg	T, focal	T, focal	RES; OAA	Type 1	les & rt AMTL	cav	IA	24
5	50, F	35	15	cav, lt T, neoc	T, reg	T, reg	T, reg	PES; OAA	Type 1	les & lt ETL	cav	IA	15
6	27, F	11	16	cav, rt T, mes	T, focal	T, focal	T, focal	veg; PES; OAA; dys	Type 1	les & rt AMTL	cav	IB	12
7	53, F	10	43	dual path, lt T	T, focal	T, focal	T, focal	olf; OAA	Type 1	les & lt AMTL	cav & MTS	IA	2
8	30, F	29	1	cav, lt T, neoc	T, focal	T, focal	ND	ND	ND	les	cav	IA	2

* Aud = auditory symptoms; cav = cavernous angioma; Dis = disease; dual path = dual pathology; dys = contralateral upper-limb dystonia; ETL = extensive temporal lobectomy; FU = follow up; les = lesionectomy; mes = mesial; MTS = mesial temporal sclerosis; ND = not done; neoc = neocortical; OAA = oroalimentary automatisms; olf = olfactory symptoms; PES = psycho-experiential symptoms; reg = regional; RES = rising epigastric sensation; SA = speech arrest; T = temporal; Type 1 = anterotemporal ictal pattern, 5- to 9-Hz discharge (probable onset in mesial temporal structures); Type 2 = temporal ictal pattern, 2- to 4-Hz discharge (probable onset in lateral neocortical temporal structures); veg = vegetative symptoms.

† According to the Engel classification.

hippocampal gyrus. These interventions differed in the extent of the neocortical resection. Extensive nondominant temporal lobectomy included excision of 4 to 4.5 cm of the superior and middle temporal gyri, and 5 to 6 cm of the inferior temporal gyrus, whereas extensive dominant temporal lobectomy included excision of 4 to 5 cm of the middle and inferior temporal gyri, and the superior gyrus was resected up to the intersection with a plane passing through the precentral sulcus. On the other hand, in AMTL the extent of the neocortical excision was 3 cm for all of the first three temporal gyri. Lesionectomy consisted of the complete removal of the cavernoma along with the surrounding hemosiderin deposits and gliosis.

Outcome Assessment

All surgically treated patients return 1 and 2 years after surgery to undergo comprehensive follow-up evaluations. At our center, it is common practice to maintain all patients on a steady regimen of AEDs during the first 2 years after surgery.

Seizure outcome was determined by the patient's report to the neurologist during the scheduled follow-up visits, which included 60-minute awake EEG standard recordings,¹¹ and the outcome was classified according to the Engel¹³ scale. Neuropsychological outcome was determined by comparing presurgical and follow-up scores on a comprehensive test battery that included the Wechsler Adult Intelligence Scale and several verbal and visuospatial memory tests. Psychiatric outcome was similarly assessed using several validated measures of personality, depression, anxiety, anger, and quality of life, such as the Minnesota Multiphasic Personality Inventory, the Beck Depression Inventory, the Spielberger State-Trait Anxiety Inventory, the State-Trait Anger Expression Inventory, the 31-item version of the Quality of Life in Epilepsy inventory, and the World Health Organization Quality of Life-100 test.

Results

Lesionectomy was performed in two patients with recent onset of epilepsy and concordance between lesion location and both EEG findings and seizure semiology as determined by their history. Of the six patients in whom the diagnosis of TLE subsyndrome was established after video-EEG recording, four underwent AMTL for mesial TLE and two underwent extensive temporal lobectomy for mesiolateral TLE.

Of seven patients with at least 1 year of follow up, six were in Engel Class IA and one (treated with anteromesial temporal lobectomy) was in Engel Class IB. The latter patient had 3 months of follow up and experienced no seizures during this period (Table 1). Regarding neuropsychological outcome, scores on intelligence and memory tests were available for five and six patients, respectively, and they were quite similar on presurgical and follow-up evaluations. Among five patients who completed psychiatric and psychosocial questionnaires on both occasions, the depression, anxiety, and anger levels were stable or slightly lower, whereas quality of life scores were slightly higher at the follow-up compared with the presurgical assessment.

Discussion

In this report we describe our current approach to TLE caused by CMs. In previous studies the relationship between seizure outcome after surgery and different factors such as sex and age of the patients, location of the malformation, seizure history, and presence of a residual hemosiderin rim on postoperative MR images has been analyzed.^{3,5,7,8,31} The great majority of investigators concluded that the seizure history, in particular the number of attacks and the duration of epilepsy, are the best predictors of the seizure outcome. In reviewing a series of 35 cases, Cappabianca and colleagues⁵ found that all patients with a history less than 12 months and/or one to five preoperative seizures became seizure free, whereas epilepsy in 37.5% of patients with a history greater than 12 months and more than five preoperative seizures remained uncontrolled despite the administration of AEDs.

In his surgical series of 51 patients, Cohen, et al.,⁸ reported that complete seizure remission was observed after lesionectomy in 100% of patients with only one preoperative seizure or a seizure history lasting less than 2 months; that complete remission was achieved in 75 to 80% of all patients with two to five seizures or a seizure history lasting 2 to 12 months; and that only 50 to 55% of those with more than five seizures or with preoperative seizure histories lasting more than 1 year attained complete remission. Similar findings were reported by other authors.^{6,7,9,18,27}

Our series included only patients with unfavorable prognostic factors. Seven of eight patients were affected by drug-resistant epilepsy and no patient had a seizure history of less than 1 year, yet an excellent seizure outcome was observed in all cases. Although our findings need to be confirmed by further studies with a larger sample and longer follow-up duration, they corroborate the notion that in patients with seizures resulting from CMs a tailored approach to the epilepsy provides better results than simple, indiscriminate lesion removal.^{21,25,27}

The management option in each of our patients was decided on the basis of a comprehensive presurgical workup aimed at identifying, by means of noninvasive techniques, one of three different TLE subsyndromes (mesial, lateral, and mesiolateral syndromes) encompassing the whole spectrum of symptomatic TLEs.²² Our target was to remove the cortical structures involved in the generation and the primary organization of the epileptic discharge in each patient. In the literature, with the exception of Stefan and colleagues²⁸ who reported the use of magnetoencephalography as a noninvasive tool of investigation, resection of nonlesional cortex has usually been planned on the basis of presurgical invasive EEG recording.^{1,8,18,21,24,25} In some of these series, the indication for a tailored resection was not inferred preoperatively but derived from failure to control seizures with lesionectomy alone, particularly in patients with multiple cavernomas or dual pathology, that is, concurrent finding of CM and hippocampal sclerosis.^{18,24,25} Our experience, which has demonstrated the effectiveness of a noninvasive approach to localize the seizure activity, could contribute to make the management of the disease in these patients simpler and safer.

Two of the eight patients who were entered in our presurgical protocol were scheduled for lesionectomy alone and were both seizure free after surgery. Both patients pre-

sented with a relatively short history (< 2 years) of epilepsy, confirming the prognostic importance of the criterion of disease duration in terms of seizure outcome. Indeed, as suggested by others,^{6,21} this criterion alone would not be sufficient to localize the epileptogenic zone with certainty, a major role being played by the concordance between electroclinical data and anatomical location of the lesion.

In six cases the anatomical, electrical, and clinical data dictated the need for extended extralobular resections. The uncus, amygdala, hippocampus, and parahippocampus were removed in two patients with lesions confined to these structures and in four patients harboring cavernomas of the temporal neocortex. According to some evidence, the rationale for removing apparently normal brain tissue that is distant from a lesion site can be related to the concept of "secondary epileptogenesis," that is, the development of epileptic activity remote from the original lesional focus.^{19,20} Experimental studies support the hypothesis that reiteration of ictal activity may promote the formation of new recurrent excitatory circuits through phenomena of axonal sprouting and synaptic reorganization.^{12,16,30} Our findings strengthen these hypotheses.

The fact that two of six temporal lobectomies were performed in patients with less than a 2-year history of epilepsy suggests, however, that temporomesial structures may be part of the primary epileptogenic process. This hypothesis is consistent with the known propensity of mesial temporal areas to participate in ictal activity. As suggested by previous experience with TLE surgery, it is conceivable that such structures involved in the epileptic activity are no longer functioning.²² Quite the contrary, epileptic rhythms may disturb the physiological rhythms underlying normal cognitive processes.⁴ Based on these hypotheses, resection of structures normally involved in complex cognitive and emotional processes may be attempted safely. Accordingly, all six patients undergoing extended temporal lobectomies experienced complete seizure relief with no adverse effect on neuropsychological or psychosocial functioning.

Conclusions

The seizure outcome of patients with drug-resistant TLE caused by CMs can be significantly improved if these cases are managed in the context of an epilepsy surgery team. This approach allowed us to perform a tailored resection resting on the precise localization of the epileptogenic zone. On the basis of anatomical, electrical, and clinical criteria, the resection can be safely extended from the cavernoma site to the temporal mesial structures, obtaining complete seizure control in most cases.

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Manuscript received April 21, 2006.

Accepted in final form May 30, 2006.

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