Original Article

Microsurgical treatment of patients with refractory epilepsy and mesial temporal cavernous malformations: Clinical experience of a tertiary epilepsy center

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INTRODUCTION

Cerebral cavernous malformations are known to be highly epileptogenic lesions, but the underlying epileptogenic mechanisms are not fully understood. Asymptomatic microhemorrhages into the surrounding brain, with subsequent perifocal hemosiderosis and gliosis, are considered the major cause of seizure activity. Mesiotemporal cavernomas (MTC) can occur in 10–20% of patients with cerebral cavernomas and are frequently associated with refractory epilepsy. Asymptomatic microhemorrhages into the surrounding brain, with subsequent perifocal hemosiderosis and gliosis, are considered the major cause of seizure activity.

Background: Mesiotemporal cavernous malformation can occur in 10–20% of patients with cerebral cavernomas and are frequently associated with refractory epilepsy.

Methods: A retrospective investigation was performed in the epilepsy clinic of a Brazilian tertiary referral epilepsy center, from January 2000 to March 2012.

Results: A total of 21 patients were included in the study. Thirteen patients (62%) evolved to Engel I; 5 (24%) to Engel II, 2 (10%) to Engel III, and 1 (5%) to Engel IV. We observed that 10 (48%) patients with 12 years or less of epilepsy duration evolved to Engel I and 1 (5%) to Engel II; whereas from a total of 10 patients with epilepsy duration of more than 12 years, 3 (30%) evolved to Engel I and 7 (70%) to Engel II, III, or IV (P < 0.001 [bilateral]; P₁ ≠ P₂).

Conclusion: Postsurgical seizure outcome for temporal lobe epilepsy associated with mesiotemporal cavernomas is very satisfactory.

Key Words: Cavernous malformations, mesiotemporal cavernous malformation, temporal lobe epilepsy
are frequently associated with refractory.\textsuperscript{[21,22]} Surgical removal of safely achievable symptomatic lesions has been frequently consistent with good long-term seizure outcomes.\textsuperscript{[8,9,21,22]} The aim of the present study is to analyze retrospective data on consecutive patients with temporal lobe epilepsy associated with MTC (TLE-MTC), surgically treated in a Brazilian tertiary epilepsy referral center, in order to assess the effect of microsurgical resection on seizure activity and general outcome.

METHODS

Study delineation
A retrospective observational investigation was conducted with data collection from all inpatients and outpatients treated in the epilepsy clinic of Faculdade de Medicina de Sao Jose do Rio Preto, a Brazilian tertiary referral epilepsy center, diagnosed with TLE-MTC from January 2000 to March 2012. Clinical data were obtained retrospectively from the patient records and files. For all patients with the diagnosis of MTC on magnetic resonance images (MRIs), the following data were collected: Gender, age at the surgery, handedness, type and number of antiepileptic drugs (AEDs) used, and results of formal neuropsychological evaluations. In addition, noninvasive video-electroencephalography (EEG) data and side of surgery were registered.

Presurgical evaluation
Patients were submitted to video-EEG monitoring using the Neuro Workbench software (Nihon Kohden Corporation) and Nihon Kohden hardware (Nihon Kohden Corporation) to record and later evaluated all the epileptic events. Every patient was analyzed by an experienced epileptologist as an integral part of inpatient assessment. All patients were submitted to a neuropsychological assessment pre- and post-surgically (at 12 months). Verbal memory was assessed by a list of learning design, and figural memory by a design learning test using independent items. Memory deficits were defined as performance one standard deviation (SD) below of the normal performance of age-matched controls.

Brain MRI was obtained accordingly with specific epilepsy protocol using a 1.5 tesla scanner, Philips, at the Department of Neuroradiology in our institution. All MRIs were analyzed by an experienced neuroradiologist that confirmed the visual radiological diagnosis of mesial temporal lobe (parahippocampal gyrus, hippocampus, amigdalum, and uncus) cavernomas. Displaying the sagittal three-dimensional T1-weighted gradient-echo sequences, the next sequences were an axial and coronal fluid-attenuated inversion recovery fast spin-echo (section thickness, 2 mm) and T1-weighted inversion recovery sequences (section thickness, 5 mm) [Figure 1].

Biopsy specimens were obtained from all patients with chronic drug-resistant and radiological evidence of MTC, who underwent surgical treatment. Surgical removal of the hippocampus was clinically indicated in every case, and all the patients were submitted to complete lobectomy. The standardized neuropathological analysis was performed in all the patients under this study. Surgical specimens submitted for neuropathological evaluation were microscopically analyzed by using hematoxylin and eosin staining. The pathologist reported their findings without the clinical or imaging data.

Outcome assessments and follow-up
Follow-up investigations were carried out in operated patients. At the 12 months follow-up, all the patients received a neurological examination including observation of behavior disorders, exploration of seizure outcome, and a cerebral 1.5 tesla MRI. Seizure outcome was classified as completely seizure-free since surgery, that is, Engel I, or not seizure-free (Engel II–IV).

Ethical statement
The Ethical Committee of our institution analyzed the project of the present study and approved the performance of our investigations. The study complies with the Declaration of Helsinki. Informed consent was taken from all patients and/or genitors.

Statistical analysis
Data collected from all the patients were organized in tables. Averages are expressed as the mean ± SD for parametric data and as median values for nonparametric data. Statistical analysis was performed utilizing the Fisher’s exact test. A $P < 0.01$ was considered statistically significant.

Figure 1: Comparison of surgical outcome between the patients with ≤ 12 years or > 12 years of epilepsy duration (**$P < 0.01$, Fisher’s exact test)
RESULTS

Presurgical demographic and clinical characteristics

At the moment of the study, 533 patients underwent multidisciplinary investigation for epilepsy, and 21 (3.9%) patients fulfilled the inclusion criteria of radiological and pathological diagnosis of MTC. Table 1 summarizes the demographic and clinical data of all patients. The presurgical mean age was of 34.38 ± 8.82 years, with 13 male (61.9%) and 8 female (38.1%). The mean epilepsy duration at surgery was of 11.95 ± 4.25 years. Thirteen patients (61.9%) had complex partial seizures (CPSs) and 8 (38.1%) had generalized tonic-clonic seizures. Nineteen (90.5%) patients were right-handed and 2 (9.5%) left-handed. Nine (42.8%) patients presented a previous history of febrile seizure during infancy. Six patients (28.6%) were taking a single AED, and 15 (71.4%) were taking two or more AEDs. Neuropsychological assessment revealed that 5 (23.8%) presented cognitive impairment before surgery. In addition, 19 patients (90.5%) presented unilateral epileptic discharge on ictal EEG and two bilateral (9.5%); 16 subjects (76.2%) had unilateral and 5 (23.8%) had bilateral epileptic discharges on interictal EEG, respectively. Two patients (9.5%) presented with multiple (2 or more) lesions and 19 (90.5%) with only one lesion on the temporal lobe. The location of the lesion was found as follow: 16 (76.2%) on the lateral temporal neocortex and 5 (23.8%) affecting mesiotemporal structures, that is, two in the head of the hippocampus and three in the parahippocampal gyrus. Radiological investigation also showed some degree of sclerosis of the lateral temporal lobe neocortex and/or the mesial structures in 19 (90.5%).

Seizure control and follow-up

All the patients were followed during a minimum period of 1 year and a maximum of 7 years. The mean follow-up duration was of 3.14 ± 1.68 years. Three patients (14%) were followed during 1 year; 6 (29%) during 2 years; 5 (24%) during 3 years; 2 (10%) during 4 years; 2 (10%) during 5 years; 1 (5%) during 6 years; and 1 (5%) during 7 years. Seven patients (33%) stopped their AED; 6 (29%) reduced, and 8 (38%) maintained the AED use.

Seizure outcome following surgery revealed that 13 patients (62%) became Engel I, 5 (24%) to Engel II, 2 (10%) Engel III, and 1 (5%) Engel IV. We observed that 10 (48%) patients with 12 years or less of epilepsy duration evolved to Engel I and 1 (5%) to Engel II, whereas from a total of 10 patients with epilepsy duration of more than 12 years, 3 (30%) evolved to Engel I and 7 (70%) to Engel II, III, or IV (P < 0.001 [bilateral]; \( P_1 \neq P_2 \)) [Figure 1].

Postoperative neuropsychological assessment showed deterioration in 4 patients with the previous cognitive deficits. One patient recovered to its baseline. No

Table 1: Clinical data of patients with mesiotemporal cavernomas

| Subject number | Gender | Age | Epilepsy duration | Seizure semiology | AED | Cognitive deficit | Affected hemisphere | Surgical technique | Seizure outcome | Follow-up (years) |
|----------------|--------|-----|-------------------|-------------------|-----|------------------|---------------------|-------------------|-----------------|-----------------|
| 1              | Male   | 21  | 10                | CPS               | Stopped | No               | Right               | SAH               | Ia              | 2               |
| 2              | Female | 29  | 11                | GTCS              | Stopped | No               | Right               | ATL               | Ia              | 3               |
| 3              | Male   | 33  | 16                | CPS               | Maintained | Yes            | Left                | ATL               | Ic              | 2               |
| 4              | Female | 28  | 11                | CPS               | Stopped | No               | Right               | ATL               | Ia              | 3               |
| 5              | Male   | 46  | 17                | CPS               | Maintained | Yes            | Left                | ATL               | III             | 5               |
| 6              | Male   | 51  | 19                | GTCS              | Maintained | Yes            | Left                | ATL               | IV              | 7               |
| 7              | Female | 34  | 14                | CPS               | Reduced | No               | Right               | ATL               | II              | 2               |
| 8              | Male   | 27  | 12                | GTCS              | Reduced | No               | Left                | ATL               | Ia              | 4               |
| 9              | Female | 39  | 16                | GTCS              | Maintained | Yes            | Left                | ATL               | II              | 1               |
| 10             | Male   | 37  | 14                | CPS               | Reduced | No               | Right               | SAH               | Ia              | 6               |
| 11             | Male   | 42  | 13                | GTCS              | Maintained | No            | Right               | ATL               | Ic              | 5               |
| 12             | Male   | 24  | 7                 | GTCS              | Stopped | No               | Left                | ATL               | Ia              | 1               |
| 13             | Female | 36  | 9                 | CPS               | Reduced | No               | Right               | ATL               | Ic              | 3               |
| 14             | Female | 22  | 4                 | CPS               | Stopped | No               | Left                | SAH               | Ia              | 2               |
| 15             | Male   | 25  | 6                 | GTCS              | Stopped | No               | Right               | ATL               | Ia              | 3               |
| 16             | Female | 37  | 12                | CPS               | Reduced | No               | Right               | ATL               | II              | 4               |
| 17             | Male   | 41  | 14                | CPS               | Maintained | No            | Right               | ATL               | II              | 2               |
| 18             | Male   | 46  | 18                | CPS               | Maintained | Yes            | Left                | ATL               | III             | 5               |
| 19             | Female | 38  | 13                | GTCS              | Reduced | No               | Right               | ATL               | II              | 1               |
| 20             | Male   | 23  | 4                 | CPS               | Stopped | No               | Right               | ATL               | Ia              | 2               |
| 21             | Male   | 43  | 11                | GTCS              | Maintained | No            | Right               | ATL               | II              | 3               |

CPS: Complex partial seizure, GTCS: Generalized tonic-clonic seizure, AED: Antiepileptic drug, ATL: Anterior temporal lobectomy, SAH: Selective amygdalo-hippocampectomy
patients with normal cognition preoperatively evolved memory deficits. No patients reported visual field defect after the surgery.

**Complications**

No operative death (30 days after surgery) was recorded. In the present investigation, 2 (9%) of patients evolved with infection of the surgical wound and were treated exclusively with oral antibiotics. No additional clinical complications where noted.

**DISCUSSION**

Cavernous brain malformations are vascular lesions with an estimated prevalence between 0.4% and 0.9%,\(^2\) appearing mainly as singular supratentorial lesions\(^1\) frequently associated with refractory seizures.\(^{21,22}\) In addition, 35–80% of all patients with supratentorial cavernomas are affected by 1\(^{st}\) time seizures, of which up to 40% are resistant to AED treatment.\(^{2,10,11,14,17}\)

In the present study, we presented our surgical series of 21 patients with refractory TLE-MTC. We found an average incidence of 1.61 case/year, affecting mainly man with age ranging from 30 to 40 years old. It was also noted that CPSs was the most common semiological feature, present in 62% of patients. Kivelev et al.,\(^1\) in 2011, and Sommer et al.,\(^9\) in 2013, although showing different results regarding gender prevalence, presented similar results median age. Elsharkawy et al.\(^10\) and Cohen-Gadol et al.\(^9\) showed that other degenerative lesions, such as mesial temporal sclerosis, presented a better surgical and seizure outcome in comparison with tumors and gliosis. Rydenhag et al.\(^10\) reported the surgical treatment of patients with refractory TLE-MTC, with a good seizure control. In the present investigation, 13 patients (62%) evolved to Engel I and 5 (24%) to Engel II, which is consistent with the previous studies.\(^3,5,18\)

We decide to perform anterior temporal lobectomy associated with amigdalo-hippocampectomy and not only a tailored resection of the lesion for some reasons.\(^3\) Some authors report that hemosiderin may also be epileptogenic\(^11,12\) and, in our cases, sometimes it was difficult to differentiate precisely the tissue and how far should we go to include all the epileptogenic zone;\(^2\) most patients also had some degree of temporal lobe and mesial structures sclerosis, and\(^3\) the preoperative electrophysiological features also suggested an epileptogenic zone usually wider the cavernous malformation size.

The present study also observed that patients suffering from epilepsy for a longer period might present a worse seizure outcome. In our analysis, 10 (48%) patients with 12 years or less of epilepsy duration evolved to Engel I and 1 (5%) to Engel II, whereas from the 8 patients with epilepsy duration of more than 12 years, 1 (5%) evolved to Engel I and 7 (33%) to Engel II, III, or IV (P = 0.0075 [bilateral]; P\(_1\) ≠ P\(_2\)) [Figure 1]. Our results are in agreement with investigators who reported that seizure outcome can be improved if epilepsy surgery is considered earlier in patients with epileptogenic lesions.\(^11,4,7,14,15,18\)

There are several methodological aspects in the present findings, which should be interpreted in the context of a number of limitations. First, this study is a nonrandomized, retrospective investigation performed in a highly selected population of a tertiary epilepsy center. Second, these findings cannot be generalized for all types of TLE since the patients with dual pathology, or single disease other than MTC were excluded. On the other hand, the present study described the surgical outcomes of a relatively large number of patients that underwent surgery due to this uncommon pathology for a relatively extended follow-up duration.

**CONCLUSION**

The present study highlights that seizure outcome after respective epilepsy surgery for epileptogenic lesions, especially MTC, in adults is very satisfactory. However, surgical treatment should be considered early in the course of the disease to improve seizure control and to reduce suffering.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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