Arq Neuropsiquiatr 2006;64(2-B):363-368

SURGICAL OUTCOME IN PATIENTS WITH REFRACTORY EPILEPSY ASSOCIATED TO MRI-DEFINED UNILATERAL MESIAL TEMPORAL SCLEROSIS

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ABSTRACT - *Introduction:* Several pre-operative work-up protocols have been used while selecting epileptic patients for surgery among different centers. The relative value of the different available pre-operative tests is still under discussion. *Objective:* We report on the surgical outcome obtained in patients with refractory temporal lobe epilepsy associated to mesial temporal sclerosis (MTS) and who were evaluated pre-operatively by interictal EEG and MRI alone. *Method:* Forty one patients with refractory unilateral temporal lobe epilepsy were evaluated using interictal EEG and MRI. MRI disclosed unilateral MTS in all patients. All patients had at least 4 interictal EEG recordings. All patients were submitted to cortico-amygdalo-hippocampectomy at the side determined by MRI. *Results:* Interictal EEG showed unilateral epileptiform discharges compatible with MRI findings in 37 patients; in four out of the 41 patients, bilateral discharges were found. Mean follow-up time was 4.3±1.1 years. Thirty-nine patients (95.1%) were classified as Engel's Class I (70.6% Engel I-A). Two patients (4.9%) were rated as Engel's Class II. All patients in whom bilateral discharges were found were in Engel's Class I. Pathological examination showed MTS in all patients. *Conclusion:* It is possible to adequately select good surgical candidates for temporal lobe resection using MRI and interictal EEG alone. In patients with MRI-defined MTS we should expect a postoperative remission rate higher then 90%. The finding of MTS on MRI is the most important good prognostic factor after temporal lobe resection.

KEY WORDS: refractory temporal lobe epilepsy, hippocampal sclerosis, surgery, electroencephalography, magnetic resonance image.

Resultados cirúrgicos em pacientes com epilepsia refratária associada a esclerose mesial temporal unilateral definida por ressonância magnética

RESUMO - *Introdução:* Protocolos diferentes têm sido utilizados para a investigação pré-operatória de pacientes epilépticos nos diferentes centros. No entanto, o valor relativo de cada teste disponível ainda é controverso na literatura. *Objetivo:* Relatamos os resultados cirúrgicos de pacientes com epilepsia refratária do lobo temporal associada a esclerose hipocampal (EH), cuja investigação pré-operatória consistiu exclusivamente de estudo de eletrencefalograma (EEG) inter-crítico e ressonância magnética (RM). *Método:* Foram estudados 41 pacientes com epilepsia refratária do lobo temporal, avaliados pré-operatoriamente somente por meio de EEG interictal e RM encefálica. Foram incluídos somente pacientes em quem a RM mostrava apenas EH unilateral. Todos pacientes possuíam ao menos quatro EEG inter-ictais. Todos os pacientes foram submetidos a córtico-amígdalo-hipocampectomia no lado demonstrado pela RM. *Resultados:* A análise do EEG interictal revelou atividade epileptiforme unilateral, compatível com os achados da RM em 37 pacientes. Nos outros quatro pacientes, o EEG evidenciou comprometimento bilateral. O tempo médio de seguimento pós-operatório dos pacientes foi 4,3±1,1 anos. No período pós-operatório, 95,1% dos pacientes encontravam-se em classe I de Engel (70,6% em Engel I-A) e 4.9% em classe II de Engel. Todos os pacientes com achados bilaterais ao EEG estavam em classe I de Engel. O estudo anátomo-patológico das amostras cirúrgicas revelou EH em todos os pacientes. *Conclusão:* É possível selecionar bons candidatos à ressecção temporal utilizando-se apenas dados de RM e EEG inter-ictal. Nos pacientes com EH unilateral na RM, espera-se um índice de remissão pós-operatória das crises superior a 90%. O achado de EH na RM é, isoladamente, o maior fator indicativo de bom prognóstico após ressecção temporal.

PALAVRAS-CHAVE: epilepsia do lobo temporal refratária, esclerose hipocampal, cirurgia, eletrencefalografia, ressonância magnética.

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Received 4 October 2005, received in final form 16 January 2006. Accepted 15 March 2006.

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Temporal lobe epilepsy (TLE) is the commonest epileptic syndrome and represents up to 40% of the epileptic patients. It is the most frequently refractory epileptic syndrome[1-3]. Mesial temporal epilepsy (MTE) is the most frequent refractory epileptic syndrome in adults and its treatment represents two-thirds of the epilepsy surgery procedures[4]. Very good surgical outcome has been reported in patients with MTE. Engel[5] argued that MTE was the best prototype of a "surgically remediable epileptic syndrome". In this patient population, a 70% to 90% postoperative seizure remission rate might be expected[6-7].

More recently, many centers have reevaluated the relative value of each exam included in the preoperative workup of epileptic patients[8-10]. The need for video-EEG seizure's recording in all patients has been extensively studied[11,12]. Many authors emphasized the value of MRI and interictal EEG findings in patients with TLE who were considered candidates for surgery[13-15]. Better surgical outcome related to seizures was found in patients with concordant MRI and interictal EEG findings, especially when MRI disclosed unilateral mesial temporal sclerosis (MTS)[12,16,17].

We studied the surgical outcome of patients with TLE and MTS selected based on the anatomical findings provided by MRI and that were submitted to cortico-amygdalo-hippocampectomy (CAH) at the side shown by imaging.

METHOD

Forty-one consecutive patients (23 women and 18 men) with refractory TLE and unilateral MTS that were submitted to surgery at the Hospital Brigadeiro Epilepsy Surgery Program from 1997 to 1999 were studied. The study protocol was approved by Hospital Brigadeiro IRB.

Mean age at surgery was 32.7±8.8 years (range: 11-51 years) and all patients had TLE and unilateral MTS as shown by MRI.

All patients had clinical and semiological findings compatible with TLE. All had refractory epilepsy and had been previously unsuccessfully treated by at least two adequate antiepileptic drug (AED) regimens. All patients had unilateral MTS on MRI and at least 4 interictal EEGs performed over the last 2 years showing unilateral or bilateral temporal lobe spiking. All patients were submitted to CAH at the Hospital Brigadeiro Epilepsy Surgery Program.

Patients that had been previously operated , had normal MRI, other extra-hippocampal lesions or pseudo-seizures were excluded from the study.

The clinical diagnosis was based on the International Classification of Seizures[18] and Epileptic Syndromes[19]. The following clinical characteristics were considered as diagnostic for TLE: simple partial seizures of the *déjà vu* or *jamais vu type,* or including epigastric or psychic manifestations (p.e., fear) followed by complex partial seizures characterized by staring and masticatory automatisms, accompanied or not by superior limb automatisms or contralateral superior limb distonia.

The following clinical variables were analyzed: sex, age at onset of seizures, weekly seizure frequency, type of seizure, pre- and post-operative AED regimen and the presence or not of febrile seizures in childhood.

All patients had 32-channels (Medelec, Profile) interictal EEG (10-20 system) recordings including zygomatic electrodes. The presence of temporal lobe interictal spiking and absence of extratemporal discharges were considered findings related to TLE[12,16]. The finding of at least 90% of the discharges at one side was considered a lateralizing sign in patients with bilateral EEG findings.

All patients had high resolution MRI which showed MTS in all of them. MRI examinations included sequences for the adequate study of the hippocampal formation: 3 mm thick (0.3 mm interval) FLAIR, T2 and IR coronal slices; 6 mm thick T1, T2, gradient echo, FLAIR and IR axial slices and T1 sagittal slices. MTS was diagnosed when there was clear-cut volumetric reduction of the hippocampus as seen on T1 coronal slices and increased hippocampal signal in T2 and FLAIR coronal slices as noted by two independent observers.

All patients were submitted to CAH at the side determined by MRI. The procedure was carried out under general anesthesia and without intraoperative electrocorticography.

Surgery consisted of cortical resection that included the superior, middle, and inferior temporal, parahippocampal and fusiform gyri (with its posterior border at the level of the central artery), total hippocampectomy and resection of the intratemporal portion of the amygdala. All patients were operated by the same surgeon (Arthur Cukiert, Hospital Brigadeiro Epilepsy Surgery Program).

All surgical specimens were analyzed and MTS was found in all of them.

Engel's scale was used to rate post-operative outcome, and could be summarized as follows[20]: Class I: No seizures or simple partial seizures (SPS) only; Class II: 90% or more seizure frequency reduction; Class III: Seizure frequency reduction from 50-90%; Classe IV: Seizure frequency reductions lower then 50% or no worthwhile reduction.

RESULTS

Men were significantly younger than women (mean=28.44±9.17 versus 36.04±7.07 years) by the time of surgery (p=0.005). No other gender difference was noted when analyzing age at seizure onset, weekly seizure frequency or seizure type. Mean age at the onset of seizures was 9.60±8.24 years for women and 8.46±8.44 years for men. Mean weekly seizure frequency was 3.02±3.23 for women and 3.47±2.34 for men. There was no significant relationship between age of seizure onset and its weekly frequency.

Single partial seizures (SPS) occurred in 34 patients (82.9%). The most frequent SPS types were vegeta-

Table 1. Distribution of patients according to interictal EEG and MRI findings.

Interictal EEG	MRI findings					
	Right MTS		Left MTS		Total	
	n	%	n	%	n	%
Bilateral	1	4.4	3	16.7	4	9.8
Right temporal	22	95.6	0	0.0	22	53.6
Left temporal	0	0.0	15	83.3	15	36.6
Total	23	100	18	100	41	100
			p < 0,001			

MTS, Mesial temporal sclerosis.

Table 2. Distribution of Engel I patients according to the presence or not of postoperative SPS and preoperative seizure type.

Preoperative seizure type	Postoperative outcome (ENGEL I)					
	No seizure		With SPS		Total	
	n	%	n	%	n	%
CPS	0	0.0	1	10.0	1	2.6
CPS – GTC	6	20.7	0	0.0	6	15.4
SPSp – CPS	4	13.7	0	0.0	4	10.3
SPSp- CPS - GTC	5	17.2	2	20.0	7	17.9
SPSs- CPS - GTC	1	3.4	0	0.0	1	2.6
SPSv – CPS	6	20.7	0	0.0	6	15.4
SPSv- CPS - GTC	7	24.3	6	60.0	13	33.2
SPSvi – CPS	0	0.0	1	10.0	1	2.6
Total	29	100	10	100	39	100
			p=0.034			

Seizuretype, CPS-complex partial seizure; SPSv, vegetative simple partial seizure; GTC, generalized tonic-clonic seizure; SPSvi, visual simple partial seizure; SPSp, psychic simple partial seizure; SPSs, sensitive simple partial seizure.

tive (20 patients; 48.7%) or psychic (12 patients; 29.2%). Complex partial seizures (CPS) occurred in all patients. In 1 patient (2.5%), CPS occurred isolately, while in 6 patients (14.6%) they were associated to generalized tonic-clonic seizures (GTC). No patient presented with isolated GTC. Secondarily generalized seizures occurred in 29 patients (70.7%).

Febrile seizures occurred in 10 patients (24.39%); there was a latency of a mean of 7.61±9.25 years for the appearance of non-febrile seizures. There was no statistically significant relationship between the presence or not of febrile convulsion and age of non-febrile seizure onset.

Bilateral interictal EEG temporal lobe spiking was noted in 4 patients (9.8%, all female). Right interictal EEG findings were noted in 22 patients (53.6%) and in 15 (36.6%) left temporal lobe spiking was noted. There was no significant gender difference.

MRI showed right MTS in 23 (56.1%) and left MTS in 18 (43.9%) patients. There was no significant gender difference.

Among the patients with bilateral interictal EEG findings, 1 (4.4%) had right and 3 (16.7%) had left MTS on MRI. There was a significant relationship between interictal EEG and MRI findings (p<0.001) (Table 1).

Table 3. Pré- and postoperative AED regimens.

AED	Before surgery		After surgery	
	N	Mean daily dose (mg)	N	Mean daily dose (mg)
Carbamazepine	27	1059.3	23	608.7
Phenobarbital	22	113.6	14	96.4
Phenytoin	10	280.0	4	200.0
Oxcarbazepine	8	900.0	0	–
Valproic acid	3	733.3	1	1000.0
Clonazepam	3	2.0	1	4.0
Lamotrigine	2	125.0	0	–
Clobazam	1	20	3	20
Topiramate	1	150	0	–
Gabapentine	1	1200	0	–

At late follow-up (mean: 4.3±1.1 years; range: 9 months - 6 years and 10 months), 29 patients (70.6%) had no seizure during the last follow-up year; 10 (24.5%) presented 1 to 6 SPS; 1 (2.5%) presented 8 partial seizures (5 SPS and 3 CPC) and 1 GTC and 1 patient (2.5%) presented 1 GTC. Thus, 95.1% of the patients were rated as Engel's Class I and the remaining (4.9%) as Class II.

We noted that 5 patients had seizures during their postoperative follow-up that were related to reduction or withdrawal of AED; 4 of these patients had no seizures over the last follow-up year.

We were not able to analyze the data derived from Engel's Class II patients from a statistical point of view since the sample was very small (n=2). Therefore, we analyzed the data from Engel's Class I patients, according to the presence or not of SPS during follow-up.

No statistically significant results were found while analyzing the surgical outcome and any clinical variable such as sex, age of seizure onset, weekly seizure frequency, type of seizure or presence of febrile seizure in childhood (Table 2).

Unilateral EEG findings did not correlate with better surgical outcome; all 4 patients (9.8%) with bilateral EEG findings were seizure-free after surgery.

We noted a relevant reduction on the amount of AED postoperatively. Table 3 summarizes these findings. Before surgery, 14 (34.1%) patients were receiving 1 AED and the remaining 27 (65.9%) were under 2 or more AED. At the last follow-up visit after surgery, 11 patients (26.8%) were receiving no medication, 15 (36.6%) were receiving 1 AED and 15 (36.6%), 2 or more AED.

DISCUSSION

Rigorous presurgical evaluation protocols are essential for adequate focus localization and good surgical outcome in patients with refractorytemporal lobe epilepsy. The introduction of MRI into clinical practice and the better knowledge of the pathophysiology of epilepsy have led many centers to reevaluate the relative role of each exam or technique used in the presurgical evaluation of epileptic patients[4,12,13,17,21].

Jeong et al.[10] studied patients with MTS and showed postoperative seizure remission in 84% of them; these authors considered age at surgery (26.9 ±7.3 years in the seizure-free group versus 35.4±9.4 years in the non-seizure-free group) and duration of epilepsy (14.5±6.8 years in the seizure-free group versus 19.5±8.7 years in the non-seizure-free group) as prognostic indicators of postoperative outcome. On the other hand, McIntosh et al.[22] showed in a meta-analysis study that gender, age of seizure onset and preoperative weekly seizure frequency were not postoperative prognostic factors.

SPS occurred preoperatively in 82.9% of our patients, as was noted by others, who reported that up to 90% of patients with MTS had SPS[4,23]. The most frequently found SPS were vegetative, also in agreement with other findings[7]. CPS occurred in all our patients and secondarily generalized GTC in 70.7% of

them. GTC was not the most usual seizure type in patients with MTS, although 50% of the patients might have one GTC at some point[7]. Our data, which were in agreement with those from Kilpatrick et al.[24], did not suggest that the presence of GTC would be a bad prognostic factor after surgery. On the other hand, Spencer et al.[8] and Henessy et al.[25] suggested that the absence of GTC would be a good prognostic factor after CAH.

French et al.[7] found that febrile seizures were present in 77% of the patients with MTS and that the mean latent period for the appearance of non-febrile seizures was 7.5 years. Although febrile seizures occurred in only 25% of our patients, the latency for the appearance of non-febrile seizures (7.61 years) was the same as found by others. Prolonged febrile seizures had been implicated in the development of MTS. Although some authors considered the presence of febrile seizures in childhood as a poor surgical outcome indicator[26], our data and those from Kilpatrick et al.[24] and Henessy et al.[25] did not support this idea.

The surgical results reported for patients with MTS varied among centers, and seemed to be better when there was agreement among the clinical, EEG and imaging preoperative findings. The presence of MTS on MRI had been related to a better surgical outcome after CAH[27]. Radhakrishnan et al.[9] found excellent outcome in 95% of the patients with MRI-defined MTS submitted to CAH and only 65% of good results in patients without MTS. In this study, they also pointed out that exclusively unilateral interictal EEG discharges were as important as the MR findings as positive prognostic factor; only 60% of the patients without that interictal EEG finding got good surgical outcome. Gilliam et al.[16] reported good surgical outcome in 77% of the patients with concordant MRI and interictal EEG findings, in contrast to 53% of good results in patients with non-concordant or non-localizatory findings. In our sample, patient selection was essentially based on anatomical MRI data, and the majority of them got excellent results (95%). In our series, the patients with bilateral interictal EEG findings did not have a worst postoperative prognosis. This finding suggests that the presence of MTS on MRI would be the most important positive postoperative prognostic factor after CAH[17]. We found that all patients with MTS on MRI had favorable postoperative outcome. We did not analyze the impact of other (non-MTS) temporal lobe MRI findings.

EEG recordings have always been included as part of the presurgical evaluation of epileptic patients. On the other hand, the introduction of new technological tools in the diagnosis of epilepsy led to the need to reevaluate its role in this setting. All patients were submitted to invasive recordings by the time epilepsy surgery was introduced for adequate focus localization, which is clearly not the actual situation. Williamson et al.[28], in a retrospective analysis of 67 patients, showed that 96% of the patients had interictal EEG abnormalities and that 94% of them were localized over the anterior temporal region. In their study, independent bilateral EEG discharges were found in 42% of the patients; in 50% of them the discharges prevailed over the ictal-onset side. In our study, anterior temporal lobe spikes were present in all patients and bilateral interictal findings were rarely seen. Cascino et al.[29] evaluated the relative role of routine interictal EEG, vídeo-EEG and MRI findings in the postoperative prognosis of patients with TLE. They found that interictal EEG abnormalities were recorded in 81.1% of the patients and were unilateral in 77.3% of them. Bilateral findings with unilateral predominance occurred in 5.6% of the patients and bilateral EEG findings with no lateralization occurred in 6.9% of them, which is in agreement with our data. There was a statistically significant relationship between the MRI and interictal EEG findings.

Pataraia et al.[30] studied 118 seizures from 24 patients with clinical history compatible with TLE, unilateral MTS on MRI and unilateral interictal EEG findings. They concluded that these findings are highly sensitive for focus localization and that ictal recordings did not bring additional useful information in this patient population.

Cendes et al.[12] evaluated MRI and ictal and interictal EEG findings in 184 consecutive patients with MTS. They concluded that all patients with unilateral MTS had congruent ictal and interictal EEG findings and in only 3% of them interictal and ictal EEG were not concordant. They suggested that, in this patient population, serial routine interictal EEG would be sufficient for focus localization. Our findings are in agreement with the latter and, additionally, suggest that MRI findings might be isolately efficacious for focus localization and good postoperative outcome forecast.

We noted that 5 of our patients had GTC after surgery that was related to reduction or withdrawal of AED. Williamson et al.[28] also reported that GTC comprised the majority of the postoperative ictal

events, that they usually occurred during the first 2 years of follow-up and were related to inadequate management of AED.

In this study, we reported a significant reduction on the amount of AED during the postoperative period. It is our policy to initiate clobazam postoperatively in Class II patients; thus, clobazan was the only AED which was added postoperatively. The main objective after epilepsy surgery would be to have a seizure-free patient under no AED[29]. On the other hand, improvement in quality of life could be easily documented in those patients who were not AED-free but were seizure-free under a more modest AED regimen. These patients showed less side effects and lower AED-related costs.

We found persistent SPS (auras) in 10 patients, as reported by others. SPS are often thought as "benign" by most authors. On the other hand, this is not true in some patient's perception, although the majority of them feel comfortable about them in the long term follow-up.

Our study included only patients with unilateral MTS who presumably had the best surgical outcome prognosis. The number of patients who were not rendered seizure-free was very low. This fact made it impossible to further analyze predictive factors in Class II patients. Radhakrishnan et al.[9] found that unilateral MTS on MRI was a strong positive predictive factor for good surgical outcome after CAH, and suggested that other clinical findings did not influence surgical outcome. The finding of unilateral MTS on MRI is the single most important positive predictive factor for good surgical outcome after CAH[10,11].

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