Classification of structural lesions in magnetic resonance imaging. Surgical implications in drug-resistant epilepsy patients

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Introduction. The presence of a structural lesion in the preoperative magnetic resonance imaging (MRI) of drug-resistant epilepsy patients has been usually associated with a favourable surgical outcome. We present our experience in our Epilepsy Surgery Unit.

Patients and methods. Clinical records from 265 patients, operated on from 1990-2010 in our institution, were reviewed. Patients were classified, according to MRI findings, into three groups: surgical lesion (SL), tumors or vascular malformations requiring surgery 'per se'; orientative lesion (OL), dysplasia, atrophy or mesial temporal sclerosis; and (NL) group, with normal MRI. Seizure outcomes were analysed in relation to this classification.

Results. Period 1990-2000, 151 patients: 87% of SL, 65% of OL and 57% of NL patients were in Engel class I or II at the two-year follow-up. Among temporal lobe epilepsy cases (TLE), 87% of SL, 67% of OL and 56% of NL patients achieved seizure control. Differences were statistically significative. Period 2001-2010, 114 patients: 100% of SL, 90% of OL, and 81% of NL patients were in Engel's class I or II. Both TLE and extratemporal (ETLE) SL patients obtained a 100% seizure control. Among the OL patients, 95% with TLE and 43% of ETLE achieved seizure control. In the NL group, the percentages were 88% in TLE, and 50% in ETLE.

Conclusions. In our series, SL was a predictor of a favorable outcome. In TLE patients, good results were achieved despite normal MRI. Patients with ETLE and NL did not have a worse outcome than those with OL. A classification in SL, OL and NL seems more helpful for predicting the surgical outcome than the traditional classification lesion versus non-lesion MRI. Radiological findings must be carefully evaluated in the context of a complete epilepsy surgery evaluation.

Key words. Dysplasia. Epileptogenic area. Magnetic resonance imaging. Mesial temporal sclerosis. Refractory epilepsy.

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Introduction

The essential condition for a good surgical outcome in epilepsy surgery is the precise identification and resection of the epileptogenic brain tissue, after which patients would theoretically be seizure free [1-5]. The decision algorithms in the selection of surgical candidates are not uniform among centres, and they are usually modified according to the experience of the different specialized multidisciplinary teams [4,6-13].

Surface electroencephalography (EEG) and magnetic resonance imaging (MRI), among others, are considered fundamental tools in the selection of patients with drug-resistant epilepsy as candidates for resective surgery [14,15]. The presence of any abnormal findings in the MRI has been associated with good clinical response [16,17], mostly because the most frequent anomalies detected by MRI are the mesial temporal sclerosis (MTS) and tumors [2,4,18-20]. Moreover, MRI is routinely utilized to guide the implantation of intracranial monitoring, along with other preoperative tests [18,21-25]. A classification in lesional and non-lesional epilepsy is commonly used in studies on epilepsy surgery [26,27], and there are authors that have even been questioned whether patients with normal MRI should be considered for surgery [7]. Other studies suggest that patients without any MRI abnormalities may have good prognosis, as long as intracranial EEG recordings are performed in the preoperative evaluation [15,28]. We consider that the radiological findings should be carefully evaluated in the context of a complete presurgical evaluation.

The aim of this study is to analyze the association between the presence of a structural lesion in the presurgical MRI and the postoperative outcome of patients with drug-resistant epilepsy that are considered for surgery. With this objective, we have classified the drug-resistant epilepsy patients undergoing resective surgery in our Epilepsy Surgery Unit, between the years 1990-2010, into three groups:

Table I. Clinical features of our drug-resistant epilepsy patients undergoing resective surgery in our epilepsy surgery unit (mean ± standard deviation).

	1990-2000	2001-2010
Age (years)	31.0 ± 11.1	34.2 ± 10.6
Gender (male/female)	84/67	66/58
Epilepsy onset (years)	12.5 ± 10.5	12 ± 10
Follow-up (years)	5.7 ± 3.4	4 ± 2
Epilepsy duration (years)	18.8 ± 10.4	21.6 ± 11

Patients with normal MRI (NL), patients with MRI findings suggesting surgical lesions, including tumors or vascular malformations that require surgery 'per se' (SL), and patients with MRI showing orientative lesions, consisting of brain malformations, dysplasia or MTS (OL). A correlation of this classification with the clinical outcome at the two year follow-up and the pathological findings has been analysed.

Patients and methods

The clinical records, preoperative evaluations and pathology results of drug-resistant epilepsy patients undergoing resective surgery in our institution, between 1990 and 2010, were evaluated. All patients had undergone a complete presurgical evaluation consisting of a VEEG, MRI, SPECT or PET, and a neuropsychological and psychiatric evaluation; some selected cases underwent a VEEG with foramen ovale electrodes, deep or subdural electrodes [3,29].

The MRI results were classified into three groups, according to the report validated by the neuroradiologist:

– *Normal MRI (NL):* MRI without any abnormalities, with unspecific changes, anatomical variations or incidental findings unrelated to the current process.
– *Surgical lesion (SL):* findings corresponding to occupying lesions in anatomical relationship with the epileptogenic zone (brain area where the electrical seizure onset is located), vascular malformations or low grade tumors. These lesions require surgical treatment 'per se' since they entail a potential risk of growing or bleeding.
– *Orientative lesion (OL):* MRI suggestive of MTS, dysplasia, atrophy or brain malformations.

Patients' clinical outcomes two years after surgery were classified according to the Engel Scale [30]. Patients in Engel's classes I or II were considered as having a 'good postoperative outcome'. We separately evaluated patients operated on during the first period, 1990-2000, and those operated on in the second period, 2001-2010, according to the use of different resolution MRI (0.5 and 1.5 T, respectively). We classified the pathological findings into three groups, corresponding to the radiological classification: NL, normal parenchyma; SL, tumor, arteriovenous malformation, OL, nonspecific lesions, dysplasia, atrophy, reactive changes, gliosis, and mesial temporal sclerosis.

Temporal lobe resective surgery consisted, in the majority of cases, in a temporal lobectomy and amigdalohipocampectomy according to Spencer's technique [31]. Extratemporal surgery consisted, essentially, in the removal of the epileptogenic zone. Intraoperative electrocorticography was performed in all cases.

Data were analyzed using the statistical program Stata 2009. For significance testing a bilateral contrast was always used, setting the significance level at $p < 0.05$. The analysis of the variables was carried out by comparing their values using non-parametric tests (Pearson Chi-square test). Normality was evaluated using the Kolmogorov-Smirnov test.

Results

Patients demographics

We studied the medical histories of 336 patients with drug-resistant epilepsy, who had undergone resective surgery in our Epilepsy Surgery Unit since 1990. Among these, we selected 265 patients with a complete radiological report and a longer than two-year follow-up, 151 patients operated on in the first period (1990-2000), and 114 patients in the second period (2001-2010). Demographic characteristics are presented in table I. Mean age and epilepsy duration were statistically higher in the second period, whereas the follow-up was significantly longer for patients in the first period ($p < 0.05$).

Out of 151 patients operated on between 1990 and 2000, seven patients had a history of a significant traumatic brain injury related to the onset of the seizures. Ten patients had a prior resection of brain lesion, or were diagnosed with a brain lesion by biopsy, without resection, before they were referred to our institution. In 6 cases, patients had a history of encephalitis or meningitis during infancy, and 7 patients had a history of hypoxia or foetal distress.

In the second period (years 2001-2010), among the 114 patients, there were three cases with a history of a previous surgery for a brain tumor, six cases of perinatal hypoxia, and fifteen cases of febrile convulsions. Eleven patients had had meningitis or encephalitis, and nine had a traumatic brain injury.

In the first period, the frequency of the seizures was daily in 42% of the patients, 44% of patients had weekly seizures, and 14% had monthly seizures. In the second period, the frequency of seizures was daily in 28% of patients, and weekly and monthly in 60 y 12% of them, respectively.

Videoelectroencephalography (VEEG) recordings

Corresponding to the period from 1990 to 2000, we obtained data about the implantation of foramen ovale electrodes in 141 patients. Of the 141 cases, 130 were implanted with foramen ovale electrodes, all with temporal epilepsy. Of the 11 non-implanted patients, 4 subsequently underwent an extratemporal resection. Subdural electrodes were implanted in 6 cases, all of them affected by extratemporal epilepsy.

During the period 2001-2010, foramen ovale electrodes were implanted in 88 patients and were not implanted in 26. Thirteen of the 26 patients had extratemporal epilepsy. Bilateral depth electrodes were implanted in a patient with temporal epilepsy, and in two patients with extratemporal epilepsy. Eight patients with extratemporal epilepsy underwent subdural electrodes implantation.

Clinical results by radiological type

The study included 225 patients with temporal lobe epilepsy and 40 patients with extratemporal epilepsy. Among the temporal lobe epilepsy patients, 130 were operated on during the first period and 95 patients, during the second period. Out of the 225 patients, 102 were left and 123 were rights side resections. Twenty-one patients with extratemporal epilepsy were operated on during the first period, with resections that were located in the frontal lobe in 16 patients, in the parietal lobe, in two patients, and in the frontoparietal areas in three patients. Nineteen patients with extratemporal epilepsy were operated on during the second period: Eleven 11 patients had frontal resections, four patients, parietal resections, one patient underwent a frontoparietal resection, and three patients had occipital resections.

Table II. Relationship between the radiological classification and the pathological subgroups in our series of patients, undergoing resective surgery for drug-resistant epilepsy. In italics, the percentage of patients in each radiological group that coincided with the diagnosis of the surgical specimen.

	Periods	Normal tissue	SL pathology	OL pathology
NL MRI: 24%	*1990-2000: 23%*	*0%*	12.5%	87.5%
	2001-2010: 27%	*37.5%*	6.3%	56.3%
SL MRI: 23%	1990-2000: 31%	0%	*70.2%*	29.8%
	2001-2010: 12.2%	8.3%	*58.3%*	33.3%
OL MRI: 52%	1990-2000: 46%	3.3%	8.2%	*88.5%*
	2001-2010: 60.5%	13.2%	13.2%	*73.7%*

MRI: magnetic resonance imaging; NL: no lesion; OL: orientative lesion; SL: surgical lesion.

Most patients (52%) were diagnosed as having an OL in MRI, followed by NL in 24%, and a SL in 23% of the patients. In the second period, there is an increase of patients with OL compared to the first period (60.5% compared to 46%), at the expense of a smaller number of patients with surgical lesions (12% versus 31%). The percentage of patients classified in the NL group was 23% in the first period and 27% in the second period (Table II). In the first period, extratemporal OL consisted in poststroke or posttraumatic gliosis in all but two cases, whereas in the second period, OL were brain malformations and dysplasia.

The percentage of patients in Engel's classes I and II two years after surgery, by radiology groups and periods, is presented in table II. Overall, 78% of the patients were in Engel's classes I and II (70% in the first period and 89% in the second period). The radiological group with the best clinical outcome in both periods was the SL subgroup (considering both periods, 90% of patients were in I and II Engel classes), followed by the OL subgroup (77%). Patients with the postoperative worst prognosis were those with NL, with 68% of patients in Engel classes I and II ($p < 0.05$).

The percentage of patients with temporal lobe epilepsy in Engel classes I and II, two years after surgery, is significantly higher for those with OL (79%) than for patients with NL (69.5%); however, this relationship was not found in patients with extratemporal epilepsy, in which patients without lesions in the MRI have a better prognosis than those with OL (70% in Engel classes I and II at two years in patients with NL, versus 49.8% in patients with OL) (Fig. 1).

Figure 1. Percentage of patients in Engel's classes I and II, two years after resective surgery for epilepsy drug-resistant, by MRI findings, epilepsy type and surgical period.

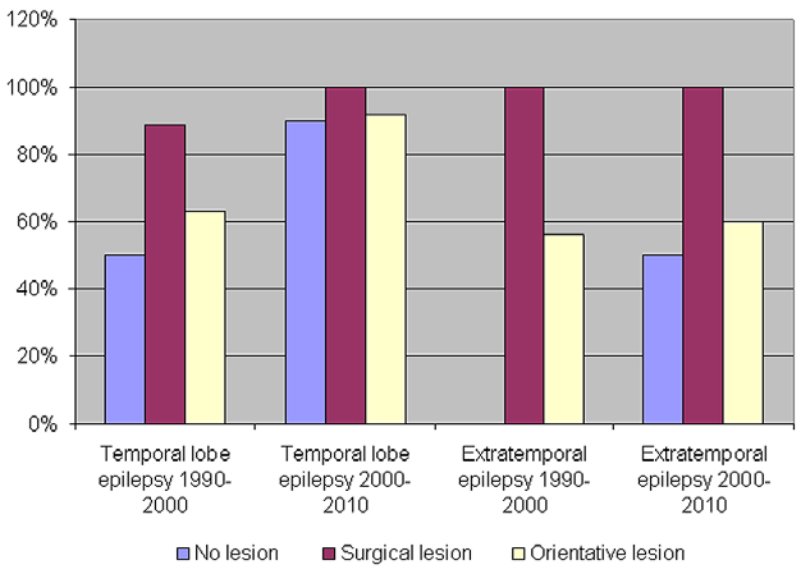
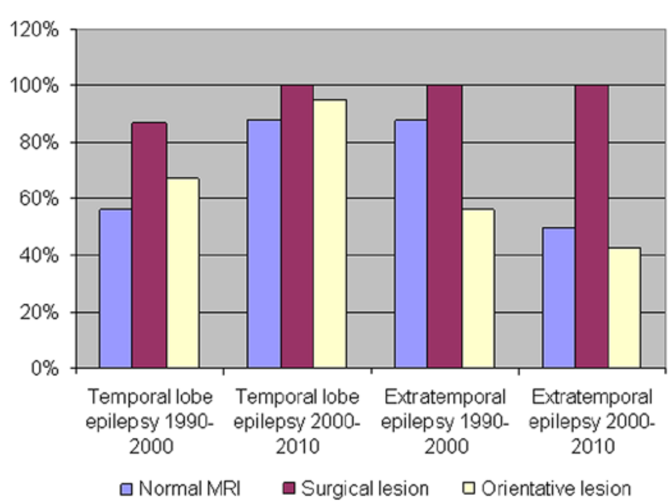


Figure 2. Percentage of patients in Engel's classes I and II, two years after resective surgery for drug-resistant epilepsy, by epilepsy type, anatomopathological findings and surgical period.



Clinical results by pathological type

We could collect the pathological analysis results in 211 patients (140 patients in the first period and 71 in the second period). Most of the patients presented OL (66%), followed by patients with SL in 27% of patients, and patients with normal tissue in 6% of the samples. According to the histopathological classification, patients with SL obtained the best clinical outcome (91% of patients in Engel classes I and II at two years after surgery (88% in the first period and 100% of patients in the second period), followed by patients with OL (79% of patients in Engel's classes I or II, 625 in the first period and 85% in the second period), and finally by those with normal samples (69%, 50% of patients in the first period, and 83% in the second period in Engel's classes I or II). This proportion is consistently maintained in both periods in temporal and extratemporal epilepsy surgery (Fig. 2). The differences were statistically significant ($p < 0.05$).

The overlap between the radiological and pathological classifications is greater for patients with OL (88.5% and 73.7% of patients in the same group in both classifications, respectively), followed by those with SL (70.2% and 58.3% of matches in the first and second period, respectively). Of those patients without radiological lesions in the first period, 100% fell into the same pathology group, while in the second period, the sample was abnormal in 66.6% of patients with normal MRI. Lesions that were unnoticed in the MRI were mainly OL in both periods (Table II). The correlation was statistically significant ($p < 0.001$).

The perioperative complications of resective surgery are shown in table III. There was no postoperative mortality.

Discussion

In the 1950s, Penfield postulated that the presence of a lesion in the pathological sample of patients with intractable epilepsy undergoing resective surgery predicted a favourable prognosis [32]. He argued that the low probability of success in patients with non-lesional epilepsy could be associated with multifocal sources of seizures, failure of the EEG to identify the epileptogenic area, and the presence of subcortical generators of seizures [33-36]. However, in recent series, the differences between patients with a structural lesion in the MRI and those with normal MRI seem less evident [37-39]. A comparison among series is difficult because of differences in the radiological findings and outcome classifications, length of follow-ups and type of patients [26,27,40]. These problems prevent us from obtaining significant evidence of the relative importance of the different radiological findings in the selection of candidates.

In a meta-analysis performed in 2010, in which 40 studies involving more than 2860 patients with lesional epilepsy and 697 with non-lesional epilepsy were included, patients with temporal epilepsy were 2.63 times more likely to be seizure free if they had a structural lesion in the MRI than those with NL, and in those undergoing extratemporal surgery, the probability was 2.5 times higher [26]. However, specific favourable radiological findings or factors associated with topographical differences (temporal epilepsy versus extratemporal) were not identified [26,27,41].

In our series, the classification of patients in three radiological groups: SL, OL and NL, gave rise to different results, depending on the type of epilepsy. In temporal and extratemporal epilepsy, the presence of a surgical lesion was an excellent prognostic marker. In patients with temporal epilepsy, post-surgical outcomes were very positive in three radiological groups (100 of patients with SL, 95% of patients with OL and 88% of patients with NL in Engel classes I and II at two years after surgery, in the second period). In these, the presence of an OL was predictive of a more favourable outcome than the absence of lesions. In extratemporal epilepsy, however, this relationship was not found. Normal MRI was not related to a worse clinical response (50% of patients in Engel classes I or II at two years in the second period), than OL (43%). In general, outcomes were less favourable than in temporal epilepsy, except in the subgroup of patients with SL (100% of control in the second period).

These results might suggest that, while patients that have been preoperatively diagnosed with a tumour or vascular malformation are excellent surgical candidates, OL, with the exception of temporal mesial sclerosis, is more difficult to delimitate. The areas of dysplasia identified in imaging studies relate, in many cases, to more extensive areas of dysplasia, which may not be apparent in MRI at the resolution used. This would explain why, in temporal epilepsy, the presence of OL is associated with better prognosis, since it is mainly exhibited by patients with temporal mesial sclerosis. In extratemporal epilepsy, however, an OL would indicate a more complex, extensive and scattered aetiology that darkens the prognosis [29,42]. In a previous study published by our group [43], in which the relative importance of the different preoperative tests –VEEG, EEG, MRI and SPECT– was analyzed, the highest diagnostic value was associated with the VEEG, for which the probability of localizing the epileptigenic zone in patients in Engel's class I two years after surgery was close to 1, while it was 0.7 for the MRI. Therefore, it is important to emphasize that a lack of relevant information in the MRI or a poor correlation between MRI and other preoperative tests should not lead to the discarding of the patient as a candidate for surgery [43]. It is possible that, with the development of more precise and sophisticate imaging methods in the future, the detection of a specific lesion in a preoperative imaging study may accurately predict the postoperative outcome, and thus, determine the selection of certain candidates for surgery. In the meantime, we consider that the classification of structural lesions in SL and OL is more appropriate than the traditional classification in lesion and non-lesion MRI. In any case, MRI findings should be carefully interpreted in the context of the other preoperative evaluations and specially, of the VEEG.

The characteristics of our population were similar to those reported in previous series [4,12,19,21, 30,37,44-49]. Although most of the studies only comprise temporal epilepsy, or extratemporal epilepsy patients, ours is a mixed series [26,27]. It is

Table III. Postoperative complications in our series of patients undergoing resective surgery for resistant epilepsy in our Epilepsy Unit between the years 1990-2010.

	1990-2000	2001-2008
Infections	3 unknown origin fever 2 surgical wound infection 3 meningitis 1 bacteriemia (*E. cloacae*) 1 cerebrospinal fluid fistula	3 meningitis 3 aseptic meningitis 1 unknown origin fever
Hemorrhages	2 subdural hematomas 1 surgical site hemorrhage 2 subarachnoid hemorrhages	1 epidural hematoma 1 surgical site hemorrhage
Neurological	4 dysphasia 2 III craneal nerve palsy 1 symptomatic hemianopsia 1 left hemiparesis 2 dysartria 2 brachial paresia 1 nonspecific decreased level of consciousness 1 status epilepticus	5 hemiparesia 1 disphasia 1 trigeminal neuralgia 1 medial cerebral artery stroke 2 peripheral facial paresia 1 left inferior limb paresia 1 symptomatic hemianopsia 1 IV craneal nerve paresia 1 III craneal nerve paresia 1 right eye ptosis 1 dysmetria
Neuropsychological and others	2 psychosis 1 panic attack 1 memory loss	1 transient agitation 1 memory loss 1 transient edema 1 atrial fibrilation 1 amenorrea 1 gastritis 1 mutism

worth noting the high number of patients evaluated by VEEG with foramen ovale electrodes (130 in the first period and 80 cases in the second period), which is higher than in other published series [50]. In our experience, foramen ovale electrodes improve the selection of patients without significantly added complications to the process [29,42,51,52]. In addition, the overall number of complications is similar in frequency and characteristics to those referred to by other authors [50,53].

In the first ten years of our series (1990-2000), 70% of the patients were in Engel classes I or II two years after surgery, while in the second period (2001-2010), the overall percentage of patients in Engel class I or II was 89%. Despite differences in the outcome classifications, our patients have achieved similar percentages of seizure control than in other series reported by centers with extensive experience in epilepsy surgery [37,41,54]. The outcome of patients undergoing surgery during the second period was superior to those operated on in the first period, which is consistent with previous experiences described in the literature [3,26,35,55-57]. The greater experience in the assessment and surgical treatment of candidates, as well as the modernization of diagnostic tools, surgical and neuroanaesthesic techniques, increase the successful identification and resection of the epileptogenic focus and, therefore, the patients' outcome. In particular, the MRI resolution was 0.5 T in the first period, and 1.5 T in the second period, which seems to significantly modify the management of certain patients [58]. However, this improvement was not noticed in patients with NL or OL undergoing extratemporal resections. Although given the small number of patients it is not possible to draw any definitive conclusions, none of the ETLE NL patients was finally classified as having a normal pathological sample, which could be related to the lower MRI resolution during the first period. It is also important that, unlike in the first period, the OL group is mainly formed by patients with brain malformations and dysplasia, which might be responsible for the differences in the OL outcome between the two periods [19,59].

With respect to the histopathological classification, in both periods patients with SL achieved the best outcome (88% and 100% of Engel I and II, respectively, in the first and second periods), followed by patients with OL (62% and 85%, respectively); patients who had a less favourable prognosis were those with normal brain tissue (50% and 83%), both in temporal and extratemporal epilepsy. Those patients diagnosed as having a NL MRI may have astrogliosis or other microscopic alterations not visible in imaging tests, but detectable histologically and achieve a good outcome, specially in the first time period, where MRI resolution was 0.5 T. However, microscopic examinations of the samples that correspond to normal parenchyma, could include a percentage of misdiagnoses, as it is expected some histological demonstration is the cause of the focal epilepsy in the majority of cases.

In conclusion, the presence of a structural lesion in the preoperative MRI of patients with drug-resistant epilepsy has been considered a positive predictor of clinical response after resective surgery; in our series, the presence of surgical lesions (brain tumours or vascular malformations that require surgery 'per se') was predictive of a favourable prognosis. However, in patients with temporal epilepsy, very satisfactory results (80-90% in Engel I and II classes), were obtained despite a normal MRI. Patients with extratemporal epilepsy and an OL did not have a better outcome than those with normal MRI so patients with normal MRI should not be excluded from the epilepsy surgery selection process. The presence of a lesion in the MRI associates different outcomes depending on the epilepsy and lesion type, and should be carefully evaluated in the context of a complete presurgical evaluation and especially of the VEEG.

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Clasificación de las lesiones estructurales en resonancia magnética. Implicaciones quirúrgicas en pacientes con epilepsia farmacorresistente

Introducción. En la selección quirúrgica del paciente con epilepsia farmacorresistente, el papel de la resonancia magnética (RM) no se ha cuantificado hasta el momento. Presentamos la experiencia en nuestra Unidad de Cirugía de la Epilepsia.

Pacientes y métodos. Se estudiaron retrospectivamente los pacientes intervenidos por epilepsia farmacorresistente. Distinguimos dos períodos: 1990-2000 (RM de 0,5 T) y 2001-2008 (RM de 1,5 T). La RM preoperatoria se clasificó en tres grupos: RM con lesión quirúrgica (LQ), RM orientativa (LO) y RM normal (NL). También se efectuó una clasificación anatomopatológica similar. Se correlacionaron las distintas clasificaciones y los resultados quirúrgicos.

Resultados. Período 1990-2000: 151 pacientes. El 70% quedó en las clases de Engel I o II. Según la RM, los resultados fueron: LQ, 87%; LO, 65%; y NL, 57%. Las diferencias fueron estadísticamente significativas. Período 2001-2008: 114 pacientes. El 89% quedó en las clases de Engel I o II. Según la RM: LQ, 100%; LO, 90%; y NL, 81%. Las diferencias fueron estadísticamente significativas. Los pacientes con epilepsia del lóbulo temporal y extratemporal con LQ tuvieron un 100% de control; con LO, el 95% con epilepsia del lóbulo temporal y el 43% con estado epiléptico; en aquellos pacientes sin lesión (NL), el 88% con epilepsia del lóbulo temporal se controló frente al 50% con estado epiléptico.

Conclusiones. La RM es una herramienta eficaz en la selección de candidatos quirúrgicos en la epilepsia. La LQ asocia muy buen pronóstico. En la epilepsia del lóbulo temporal se pueden obtener muy buenos resultados (80-90% de control) a pesar de una RM normal. En el estado epiléptico, las LO pueden tener peor resultado que la NL en la RM.

Palabras clave. Área epileptógena. Displasia. Esclerosis temporal mesial. Epilepsia farmacorresistente. Resonancia magnética.