Yield of Non-Invasive Phase 1 Presurgical Evaluation in Drug-Resistant Epilepsy Patients

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ABSTRACT: **Background:** Resective epilepsy surgery is an accepted treatment option for patients with drug-resistant epilepsy (DRE). Presurgical evaluation consists of a phase 1 non-invasive evaluation and a phase 2 invasive evaluation, when necessary.

Objectives: To assess the results of phase 1 evaluation in patients with focal DRE.

Methods: This observational retrospective study was performed in all consecutive DRE patients admitted to our clinic from January 2001 to July 2010, and who underwent a presurgical evaluation which included at least magnetic resonance imaging (MRI) scan and long-term video EEG monitoring (LTVEM).

Results: A total of 253 consecutive patients with a diagnosis of DRE (according to the ILAE recommendations) who underwent presurgical evaluation were extracted from our clinic and department registry. In 45 of these patients either imaging or ictal video EEG data were missing; the final analysis therefore involved 208 patients. The combined result of the LTVEM and the MRI scan were as follows: 102 patients (49% of the cohort) had a lesion on the MRI scan, in 77 patients (37% of the cohort) the LTVEM results were localizing and congruent with the MRI findings, and in 25 patients (12% of the cohort) the LTVEM results were either non-localizing or incongruent with the MRI findings. In 106 patients (51% of the cohort) the MRI scan was normal or had a non-specific lesion. The LTVEM was localizing in 66 of these patients (31.7% of the cohort) and non-localizing in 40 (19.2% of the cohort).

Conclusions: Although some of the patients with focal DRE can be safely treated with resective surgery based solely on the findings of phase 1 evaluation, a substantial percent of patients do need to undergo a phase 2 evaluation before a final surgical decision is made.

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KEY WORDS: drug-resistant epilepsy (DRE), presurgical evaluation of epilepsy, epilepsy surgery, intractable epilepsy

Approximately 30% of epilepsy patients suffer from drug-resistant epilepsy (DRE) and continue to experience seizures despite appropriate antiepileptic drug therapy. Possible treatments for these patients are implantation of a vagal nerve stimulator [1] or resective epilepsy surgery, which is the most effective treatment option for patients with focal DRE [2]. The goal of the presurgical evaluation is to define the potential epilotegenic zone [3,4].

All DRE patients who are candidates for surgery should undergo an initial presurgical evaluation. If the initial phase 1, which comprises scalp long-term video EEG monitoring (LTVEM) and brain magnetic resonance imaging (MRI) presurgical evaluation, defines the epileptogenic zone with high probability, no further evaluation is needed before surgery. However, if the initial phase 1 evaluation cannot define the epilpotgenic zone with high precision, or if epileptic surgery jeopardizes eloquent cortical regions, further invasive investigation (phase 2) is needed prior to surgery. The aim of this study was to assess the results of initial non-invasive presurgical evaluation in patients with focal DRE.

PATIENTS AND METHODS

The Rambam Epilepsy Center is located in northern Israel and is equipped with two LTVEM beds. Since it is the only LTVEM unit in the region, many DRE patients in northern Israel are referred to our unit for evaluation.

This was an observational retrospective study that included all consecutive patients with a diagnosis of focal DRE admitted to our clinic or to our LTVEM unit from January 2001 to July 2010. Demographic and clinical data including age, gender, disease duration, seizure frequency (yearly, monthly, weekly, daily), number of current drugs, number of drugs used in the past, MRI results and LTVEM data were gathered retrospectively from the patients' files. All data gathering was approved by our institutional review board.

ELIGIBILITY

DRE patients were defined according to the ILAE (International League Against Epilepsy) definition as patients who have failed an adequate trial of two tolerated and appropriately chosen antiepileptic drugs [3]. The study included patients who had a workup of an MRI scan and LTVEM. All MRI scans were viewed by a neuroradiologist. All LTVEMs were reviewed by a trained epilepsy neurologist.

RESEARCH PROTOCOL

MRI scan results were classified as one of the following: normal MRI, mesial temporal sclerosis (MTS), space-occupying lesion (SOL), malformation of cortical development (MCD), encephalomalacia, cavernous hemangioma, arteriovenous malformation, and non-specific (widespread atrophy, unidentified bright objects, microangiopathy). LTVEM results were classified according to the interictal recordings and ictal events including ictal semiology and ictal electroencephalogram (EEG) as: unilateral temporal, unilateral extra-temporal, unilateral hemispheric, bilateral temporal, partial undermined or multifocal, and generalized. The LTVEM results were further classified as localizing if there was an obvious ictal source or non-localizing if there was no clear ictal source.

The combined LTVEM and MRI results were then classified as congruent (e.g., LTVEM results of unilateral left temporal and left MTS on MRI), or incongruent (e.g., LTVEM results of unilateral right temporal and left MTS on MRI). If the MRI scan was normal, LTVEM results were classified only as localizing or non-localizing.

STATISTICAL ANALYSIS

Descriptive statistical analysis was done using SPSS software version 13.0 of the SPSS system for windows.

RESULTS

The data of 253 consecutive patients with a diagnosis of focal DRE who underwent an initial presurgical evaluation were extracted from the epilepsy clinic and the neurology department registries. In 45 of these patients the data of either imaging or video EEG results were missing, hence 208 patients were included in the final analysis. All basic patient characteristics are summarized in Table 1.

The MRI results of patients are summarized in Table 2. Slightly less than half the patients had a normal MRI scan, while in more than a third of the patients the MRI scan revealed a potentially resectable lesion. Video EEG results are summarized in Table 3. The video EEG succeeded in localizing the seizure onset in almost 70% of patients. The combined result of the LTVEM and the MRI scan were as follows: 102 patients (49% of the cohort) had a lesion on the MRI scan: in 77 patients (37% of the cohort) the LTVEM results were localizing and congruent with the MRI findings, and in 25 (12% of the cohort) the LTVEM results were either non-localizing or incongruent with the MRI findings. In 106 patients (51% of the cohort) the MRI scan was normal or showed a non-specific lesion. The LTVEM was localizing in 66 of these patients (31.7% of the cohort) and non-localizing in 40 (19.2% of the cohort).

Table 1. Patients' characteristics

Mean age	34.8 ± 15.1 years
Females	55.8% (116 patients)
Mean disease duration	17.9 ± 12.2 years
No of AEDs in use	2.6 ± 1.0 (1–5)
No of AEDs failed	5.1 ± 2.2 (2–13)
Seizure frequency	
Daily	28.8% (60 patients)
Weakly	34.6% (72 patients)
Monthly	25% (52 patients)
Yearly	6.7% (14 patients)
Unknown	4.8% (10 patients)

AED = anti-epileptic drug

DISCUSSION

In presurgical evaluation for epilepsy surgery, six different zones must be identified:

- symptomatogenic zone: the area causing symptoms during seizures
- seizure onset zone: the area where the seizure arises
- irritative zone: the area generating the interictal discharges
- epileptogenic lesion: the lesion probably causing the seizures
- functional deficit zone: the cortical area causing neurological deficit between seizures
- epileptogenic zone: the cortical area to be removed in order to render the patient seizure free.

The first three zones are defined by using LTVEM, the fourth zone is defined by an MRI scan, and the fifth zone is defined by neurological examination and PET-CT (positron emission

Table 2. Imaging results

MRI results	No. of patients
Normal MRI scan	38.9% (81 patients)
Mesial temporal sclerosis	22.6% (47 patients)
Space-occupying lesion	4.3% (9 patients)
Malformation of cortical dysplasia	9.1% (19 patients)
Encephalomalacia	8.2% (17 patients)
Cavernous hemangioma	3.3% (7 patients)
Arteriovenous malformation	1.4% (3 patients)
Non-specific lesion	12% (25 patients)

Table 3. Video EEG results

Video EEG results	No. of patients
Unilateral temporal	52.9% (110 patients)
Unilateral extra-temporal	11.5% (24 patients)
Unilateral hemispheric	7.7% (16 patients)
Bilateral	6.7% (14 patients)
Partial undetermined/multifocal	8.2% (17 patients)
Generalized	13% (27 patients)

EEG = electroencephalography

tomography-computed tomography). In contrast to the other zones, the epileptogenic zone is a hypothetic zone and is defined by integrating the information from the other zones [3].

Presurgical evaluation of DRE patients is subdivided into two phases: phase 1, an initial non-invasive workup phase consisting mainly of an MRI scan and scalp interictal and ictal EEG (LTVEM); and phase 2, invasive LTVEM if necessary. Previous studies have shown that phase 1 evaluation is sufficient to guide epilepsy surgery in patients with well-defined lesions and concordant EEG data [3]. Moreover, previous studies have shown that epilepsy surgery, based on a well-defined unilateral temporal seizure onset on video EEG data, can yield reasonable surgical results and thus can be considered without additional investigations [3,4].

Although the final decision whether or not to proceed to invasive evaluation depends on the experience and facilities of the epileptic center, there are several consensuses regarding situations in which there is a need to consider invasive evaluation. These include: normal MRI, extratemporal epilepsy, discordant non-invasive data, proximity to eloquent cortex, and specific lesions that tend to be diffuse such as cortical dysplasia and tuberous sclerosis [5].

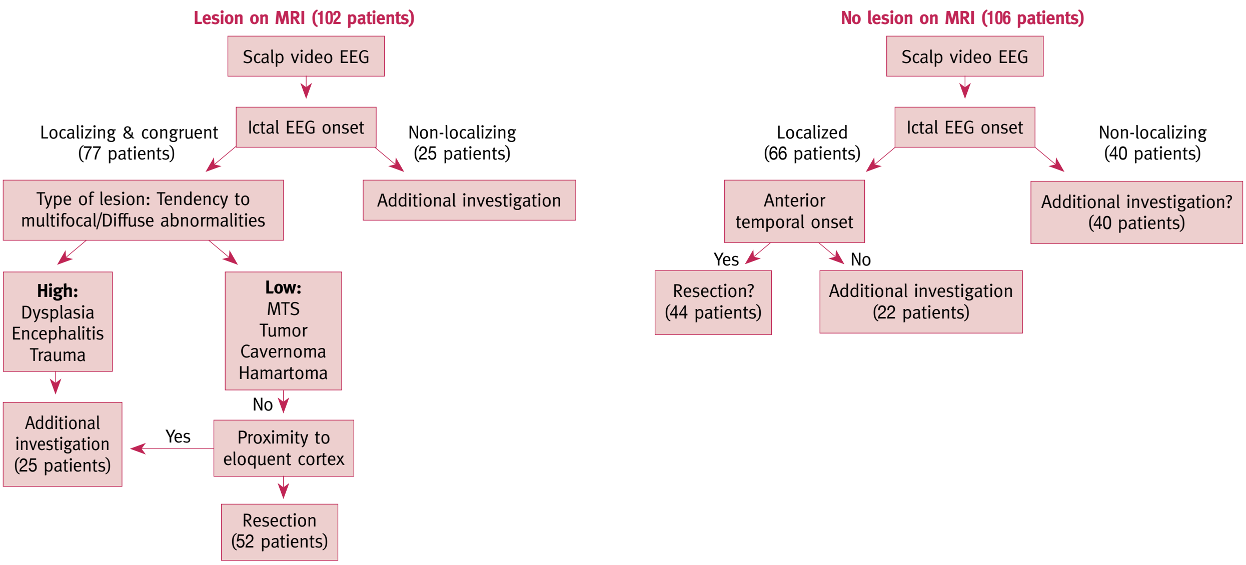
Our study yielded three main findings. First, approximately 50% of the patients undergoing initial presurgical evaluation had an abnormal MRI scan showing the putative abnormality causing epilepsy. Second, in approximately 60% of the patients, surface LTVEM results localized the seizure onset. Third, in approximately 37% of the patients, surface LTVEM results were localizing and congruent with a lesion on the MRI.

Although the percentage of abnormal MRI in our study was lower than reported in other studies, the distribution of the different pathologies was similar, with MTS being the most frequent pathology, and MCD, SOL, encephalomalacia and vascular malformation less frequent [6]. Berg [7] pointed out that the single most important prognostic factor for good epilepsy surgery outcome is a clear anatomic abnormality seen on MRI and limited to the resection region, with MTS showing the best post-surgical outcome. Low grade glioma and cavernous angiomas had similar post-surgical results as MTS [8,9], with 75% of the patients being seizure free 2 years post-surgery and 50% 10 years after surgery [10]. On the other hand, a study assessing 38 patients with MRI-negative temporal lobe epilepsy found that only 40% of patients were seizure free post-surgery at a mean follow-up of 5.8 years [11].

Figure 1, a flowchart, defines the decision-making process regarding the need for invasive monitoring in a presurgical candidate [12]. When applying this flowchart to our study group, 52 patients (25% of all phase 1 patients) with a lesion on the MRI and localizing congruent LTVEM could be referred to surgery based solely on phase 1 evaluation. In 44 patients (21% of all phase 1 patients) with LTVEM pointing to unilateral temporal lobe onset and no lesion on the MRI, surgery could be considered based on phase 1 evaluation, but since MRI is normal, many centers would prefer invasive procedures before deciding on surgery. In the remaining 112 patients (54% of all phase 1 patients), resection could not be based solely on phase 1 evaluation and invasive procedures should be considered.

We found only one other study that attempted to identify surgical candidates from a cohort of DRE patients treated in an epilepsy center. The decision-making process was based on concordant seizure semiology, interictal epileptiform discharges on standard EEG, and brain MRI changes. Fourteen

Figure 1. Flowchart of decision-making process (adapted from reference 12)



patients (17% of the cohort) had complete concordance of seizure semiology, MRI, and EEG. Of these patients, 11 had mesial temporal sclerosis on MRI and 3 had focal cortical dysplasia [13]. In contrast to our study they did not use LTVEM.

In another study (the multicenter study) conducted in advanced epilepsy centers [14], 70% of all patients who had presurgical evaluation were eventually operated. The main reason for not having surgery was a normal MRI scan. Clear MTS augmented the chance of having surgery. Non-invasive video EEG results had a substantial impact on the decision whether or not to operate the patients. Patients with localized ictal video EEG results had an 80% chance of having surgery compared to only 50% in patients with non-localizing ictal video EEG results. Congruent localizing imaging (MRI) and electrophysiological (ictal video EEG) results further increased the probability of having epilepsy surgery (92%). It is important to emphasize that while phase 1 workup can be performed in basic epilepsy centers, additional investigations require an advanced epilepsy center with full capabilities of invasive procedures [12]. Previous studies reported that 60% of candidates could be operated in basic epilepsy centers, and in only 20% of patients with temporal lobe epilepsy is there a need for invasive investigations. Other studies showed that in 34% of candidates there was a need for invasive monitoring [12,14-17].

In contrast to those studies, we found a much lower rate of patients (25%–46% of all phase 1 patients) who could be operated in a basic epilepsy center. This could be due to several reasons. First, we serve as a primary epileptic center and conduct the primary evaluation of all DRE patients in our area, in contrast to the epilepsy centers in the studies cited above where the subjects were referred after a primary evaluation elsewhere. Secondly, some of the patients who had a normal MRI scan on the 1.5 T machine could have a lesional zone on the MRI had they done the scan on a 3T machine. However, it is important to note that studies comparing a 1.5T machine to a 3T machine have not shown a significant difference in the number of lesions identified [18,19]. The third reason is that we did not take into account other non-invasive presurgical tests including interictal PET and interictal magnetic encephalography (MEG). Although PET hypometabolism may be an indicator for good postoperative outcome in presurgical evaluation of drug-resistant temporal lobe epilepsy, the actual diagnostic added value remains questionable. PET does not appear to add value in patients localized by ictal scalp EEG and MRI [20]. MEG provides additional information mainly in patients with normal interictal EEG [21] and might have helped in better determining epilepsy origin in the 17 patients (8.2%) in our series with undetermined epilepsy origin.

In conclusion, although some of the patients with focal DRE can be safely treated with resective surgery based solely on the findings of phase 1 evaluation, a substantial percent of patients do need to undergo a phase 2 evaluation before the final surgical decision.

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