Decision-making in temporal lobe epilepsy surgery

Sabine Uijl

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Sabine G. Uijl

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(met een samenvatting in het Nederlands)

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Co-promotor	Dr. F.S.S. Leijten

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CHAPTER 1

CHAPTER 1

Introduction

Diagnostic research

With the rapidly progressing technical developments in medicine during the last decades, more and more diagnostic tools have become available to clinicians. As a consequence, diagnostic decision-making in clinical practice has become more complex.[1-7]

Research is necessary to determine the role and usefulness of each diagnostic test in clinical practice.[1;2] While in the past diagnostic research used to focus on a single test under study, in clinical practice a diagnosis or decision is rarely based on information provided by a single diagnostic test. Therefore, the clinical value of a diagnostic test should be assessed in the context of the results of other diagnostic tests, which requires a multivariable approach.[3-7] By using a multivariable approach in diagnostic studies, it is possible to determine whether a particular test independently (i.e., beyond other, existing tests) contributes to the diagnostic process and whether the same diagnosis can be made with fewer tests without a decrease in the diagnostic accuracy of process.[3-7]

In diagnostic research, ideally the 'true' presence or absence of the disease under study is established in study patients with the same reference test or 'gold' standard.[2;8;9] However, such a reference test is not available for all diseases or the available reference test is such an invasive test with potential complications that its use in all study patients would be unethical.[6;10] In these research situations, an alternative is to use a consensus diagnosis established by a panel of experts as reference (either or not combined with clinical follow-up).[2;8;9;11]

Temporal lobe epilepsy surgery

The decision to perform resective surgery in patients with drug-resistant temporal lobe epilepsy is based on a complex diagnostic work-up. There is not a single reference test to determine eligibility for surgery that is appropriate for all potential surgical candidates. Surgery, with resection of the part of the brain that causes epilepsy, is a valid treatment option for a subgroup of patients with focal temporal lobe epilepsy refractory to medication.[12;13] Although postsurgical results

are excellent (70% of patients become seizure free, and in 95% a worthwhile reduction of seizures is achieved),[13;14] it is stated that surgery is underutilized worldwide.[15] Generally, the presurgical work-up to decide whether or not a patient is a candidate for surgery involves a series of consecutively performed diagnostic tests resulting in a final diagnosis or a final decision regarding eligibility for temporal lobe epilepsy surgery.[16;17] In the Netherlands, all potential surgical candidates undergo the same consecutive diagnostic work-up in a national program. A multidisciplinary team determines – after each consecutive test result is obtained – whether a final diagnosis or decision regarding eligibility can be made or whether additional tests are still required, using a consensus method. This multidisciplinary team consists of experienced epileptologists, (child) neurologists, clinical neurophysiologists, neurosurgeons, neuropsychologists, and neuroradiologists.[17] Consecutive diagnostic test results and all decisions made during the diagnostic work-up are recorded in a database. Over a period of about 30 years this has resulted in a rich source of information for a large cohort of patients that is available for research purposes.

This thesis describes the analysis of this cohort of patients referred for presurgical evaluation for temporal lobe epilepsy surgery. The main aims were to quantify to what extent certain diagnostic tests or consecutive steps in the presurgical diagnostic work-up truly contribute to the decision to proceed, or not, with temporal lobe epilepsy surgery. This posed two challenges. The first was to quantify each test or step of the diagnostic work-up. To achieve this, a panel of clinical neurophysiologists, experienced in the field of epilepsy, evaluated all potentially performed diagnostic tests (ranging from patient history to highly invasive intracranial EEG monitoring) and developed a long list of test results that could contribute to the decision to perform surgery in patients with temporal lobe epilepsy. The members of the multidisciplinary team, who are responsible for all decisions concerning epilepsy surgery in the Netherlands, provided input for the

development of this list. Then, every predefined test result was checked for uniformity of coding and interpretation, using kappa analysis between scoring researchers.[18;19]

The second challenge was the absence of one single adequate reference test that was performed in all patients to ultimately set the true decision for or against surgery. Intracranial EEG monitoring could be seen as the reference test for this situation. However, because this is such an invasive procedure (electrodes are placed intracranially directly on the brain or even in the brain tissue and only a small percentage of patients (4%) generally undergo this procedure), it would be unethical to perform this test in all patients entering the presurgical work-up. On the other hand, including the data of only those patients that indeed underwent intracranial monitoring would lead to biased results. [1;2;20-22] For these reasons, we used the final consensus diagnosis established by the multidisciplinary team, a diagnosis that was available for all patients in the cohort.

Outline of the thesis

Chapter two provides a systematic review of the literature on the presurgical work-up or diagnostic decision-making process for temporal lobe epilepsy surgery.

In chapters three to five, we assessed the independent contribution of different diagnostic tests used in the presurgical work-up to the diagnosis or decision whether to perform temporal lobe epilepsy surgery. Chapter three describes the contribution of basic non-invasive tests (patient history, routine EEG, MRI, and video EEG monitoring) to the decision regarding eligibility for surgery.

In chapter four, we describe the added value of positron emission tomography (FDG-PET), additional to that of non-invasive tests, to the decision whether to perform temporal lobe epilepsy surgery.

In chapter five, we focus on the intracarotid amobarbital procedure (Wada test), which is performed to assess language lateralization and the risk of

development of postsurgical global amnesia. We assessed the added value of a contralateral injection during the Wada test, compared to an ipsilateral injection only, regarding the decision to perform surgery.

In chapter six, we focus on the prediction of seizure freedom one year after surgery in patients who underwent temporal lobe epilepsy surgery, based on a multivariable model including all known potential predictors for post-surgical seizure freedom.

In chapter seven, we discuss the magnitude of, and reasons for, underutilization of epilepsy surgery in the Netherlands.

Lastly, in chapter 8, we discuss our findings and give recommendations for future research.

CHAPTER 2

CHAPTER 2

What is the current evidence on decision-making after referral for temporal lobe epilepsy surgery? A review of the literature.

SG Uijl

FSS Leijten

J Parra

JBAM Arends

AC van Huffelen

KGM Moons

Seizure 2005; 14(8):534-540.

Abstract

Objectives. Many patients thought to have temporal lobe epilepsy, are evaluated for surgical treatment. Decision-making in epilepsy surgery is a multidisciplinary, phased process involving complex diagnostic tests. This study reviews the literature on the value of different tests to decide on whether to operate.

Methods. Articles were selected when based on the consensus decision whether to perform temporal lobe surgery, or on the consensus localization or lateralization of the epileptic focus. The articles were scrutinized for sources of bias as formulated in methodological guidelines for diagnostic studies (STARD).

Results. Most studies did not fulfill the criteria, largely because they addressed prognostic factors in operated patients only. Ten articles met our inclusion criteria. In most articles a single test was studied; SPECT accounted for five papers. Unbiased comparison of the results was not possible.

Conclusion. Surprisingly little research in epilepsy surgery has focused on the decision-making process as a whole. Future studies of the added value of consecutive tests are needed to avoid redundant testing, enable future cost-efficiency analyses, and provide guidelines for diagnostic strategies after referral for temporal lobe epilepsy surgery.

Introduction

Epilepsy surgery is an established treatment for patients with seizures refractory to medical therapy. Temporal lobe epilepsy surgery in particular has a good outcome, with 70% of patients becoming seizure-free and 95% reaching a worthwhile reduction of seizure frequency of at least 90%.[13;14]

The diagnostic work-up to decide whether or not patients should undergo surgery is a consecutive, stepwise process focusing on the lateralization and localization of the epileptic focus, and risk factors that may compromise the surgical outcome.[23-26] A recent survey among epilepsy surgery centers worldwide showed that centers use the same phased diagnostic approach with more or less comparable techniques.[16]

During the last two decades, the number of tests in the diagnostic work-up has increased. It is recognized that different tests may provide overlapping information and that the risk of false-positive results increases with the number of tests used.[27-29] Although many diagnostic tests have been thoroughly evaluated, they were often studied in isolation. Given the consecutive diagnostic protocol, it is more important to know the relative or independent contribution of each consecutive diagnostic test to the decision-making process.[3;4] Other fields of medicine have shown that whereas a diagnostic test may be accurate, it may not have any added value to other tests and may thus be redundant for the diagnostic or therapeutic decision-making process.[30;31]

We searched for current evidence on the accuracy of different tests to the decision whether to perform temporal lobe epilepsy surgery or not. Thus, we searched for articles that studied the diagnostic, rather than prognostic, accuracy of one or more tests.

Methods

Selection of the current literature

A literature search was conducted using Medline, ScienceDirect and BioMedNet (January 1990 - March 2003) to identify publications on the diagnostic work-up

regarding surgery in suspected temporal lobe epilepsy. We used combinations of the following keywords: epilepsy; temporal; temporal lobe / diagnosis; diagnos*; diagnostic techniques and procedures; prediction; presurg*; process assessment health care. The reference lists of retrieved papers and personal files were scrutinized for additional sources.

We looked for the most important methodological biases in diagnostic studies,[20;21;32-34] as recently stipulated in the STARD guidelines.[2;35] Table 2.1 shows the criteria we used that address outcome, description of assessed tests, and patient recruitment.

Table 2.1. Criteria used to select studies in hierarchical order

Criteria
1 Proper description of outcome: Decision to perform surgery yes / no using a consensus diagnosis *or* Localization of a temporal epileptic focus using a consensus diagnosis *or* Lateralization of a temporal epileptic focus using a consensus diagnosis.
2 Proper description of the diagnostic tests under study
3 Proper description of patient recruitment: Patients should be selected if temporal lobe epilepsy may be present (making them potential candidates for epilepsy surgery). Patients should not be selected on having undergone surgery (to avoid verification bias).

1. Outcome. Articles were included if they studied the diagnosis of an operable unilateral temporal focus or the decision to operate as outcome variable. In epilepsy surgery practice, unlike in other diagnostic areas, there is not a unique 'gold standard' or reference test to assess the final diagnostic outcome. In the absence of a single established reference standard, judgment of an expert panel

is ideally used as reference.[9] Fortunately, in epilepsy surgery the final diagnosis depends on such a consensus among a multidisciplinary team that takes into account all information from diagnostic test results and known prognostic and diagnostic factors. Accordingly, the consensus decision or the consensus diagnosis of the localization or lateralization of a unilateral temporal focus was used as outcome measure. Studies using a single test as outcome (e.g. MRI or invasive EEG monitoring) were excluded from this review.

2. Description of assessed tests. Studies were included only if they provided original data on the test results and described the tests under study. Overviews and review articles were excluded, but their references were checked.
3. Patient recruitment. We selected studies that included all patients suspected of having temporal lobe epilepsy who were analyzed for epilepsy surgery, and excluded studies focusing on only those patients who actually underwent surgery. This was to avoid verification or work-up bias leading to overestimation of the predictive values, sensitivity, and specificity of the diagnostic tests under study.[20;33;34] Essentially, the population should reflect the population of all referred candidates for epilepsy surgery as encountered in practice.

Statistical analysis

The sensitivity, specificity, positive likelihood ratio, and positive and negative predictive value of the diagnostic test studied in relation to the outcome (consensus decision for surgery or consensus localization or lateralization of the epileptic focus) were retrieved or calculated.

Results

Using the mentioned keywords, 654 articles were identified (table 2.2), of which only 102 reported on the diagnostic work-up of epilepsy surgery, with the final consensus decision or diagnosis as outcome. Most (86%) of the other 552 articles were excluded because of a different study outcome. Another 76 articles (14%)

used a single test, such as intracranial or video EEG monitoring, as reference test instead of a consensus diagnosis, and were therefore excluded. Of the 102 selected articles, 77 studied one or more diagnostic tests and provided original test results; 25 were either reviews or overviews. However, only 10 of the 77 articles fulfilled the stringent STARD criterion of adequate patient recruitment to avoid verification bias.[20;33;34]

Table 2.2. Inclusion of studies

Criteria		*Excluded*	*Included*
	Start search		654
1	Outcome	552	102
2	Assessed diagnostic test	25	77
3	Patient recruitment	67	10

These selected 10 papers are presented in table 2.3. Two studies used the decision whether or not to operate as study outcome,[36;37] seven dealt with the localization of the epileptic focus,[38-44] and one dealt with the lateralization of the epileptic focus.[45] Only one study included more than 100 patients.[38] All studies were retrospective, except for the study by Oliviera et al.[41]

Table 2.4 shows the sensitivity, specificity, positive likelihood ratio, and positive and negative predictive values of the assessed diagnostic tests. These estimates were either provided directly or calculated from the data provided. They could not be calculated from the article by Kilpatrick et al.[37] These authors did describe the diagnostic work-up until the decision for surgery, but presented the results for a selected group of operated patients only. Only one of the articles presented parameters of uncertainty (e.g. 95% confidence intervals). [41]

Table 2.3. Selected papers

Author (year)	*Study population*		*Diagnostic tests*										
	N	*Positive outcome*	*Clin. Exam.*	*MRI*	*InterI EEG*	*Video EEG*	*SPECT*	*PET*	*NPT*	*IntraC EEG*	*TPAS*	*Wada test*	*Surgical diagnosis*
Outcome: Decision for surgery													
Dellabadia[36] (2002)	69	33		✦✓		✦✓	✓	✦✓	✓				
Kilpatrick[37] (1997)	75	65		✦✓		✦✓	✦✓	✦✓	✦✓				
Outcome: Localization epileptic focus													
Henkel[38] (2002)	336	223		✓		✦✓	✓	✓					
Brekelmans[39] (1998)	82	60		✓	✓	✓		✓		✦			
O'Brien[40] (1999)	34	24		✓		✓	✦✓						
Oliveira[41] (1999)	48	43	✓	✓		✓	✦✓		✓			✓	
Tatum[42] (1995)	20	17		✓	✓	✓	✦		✓		✓	✓	✓
Velasco[43] (2002)	93	84		✓		✓	✦✓			✓			
Lee[44] (2002)	24	3		✓	✓	✓	✦✓	✓					✓
Outcome: Lateralization epileptic focus													
Ogden-Epker[45] (2001)	56	56							✦[a]				

N= total number of patients; ClinExam. = clinical examination; InterI EEG = interictal EEG; NPT = neuropsychological testing; IntraC EEG = Intracranial EEG; TPAS = thiopental activation study; Positive outcome: number of patients undergoing surgery or number of patients with localized or lateralized (operable) epileptic temporal focus; ✦ Test under study, of which the diagnostic accuracy was estimated; ✓ Tests used to set the outcome and form the consensus diagnosis, i.e. the tests that were included in reference standard; [a] The outcome was the consensus of the diagnostic work-up; which tests were included in this consensus was not specified.

Table 2.4. Accuracy parameters.

Authors	*Assessed diagnostic test*	*N*	*Sensitivity*	*Specificity*	*LR*	*Positive predictive value*	*Negative predictive value*
Standard tests, performed in all patients							
Dellabadia[36]	MRI	69	0.66	0.68	*2.06*	0.68	0.66
	Sleep-deprived EEG		0.66	0.68	*2.06*	0.68	0.66
Henkel[38]	Seizure semiology during video-EEG (Abdominal aura)	336	*0.52*	*0.88*	*4.33*	*0.90*	*0.49*
Ogden-Epker [45]	*Neuropsychological testing*	56	0.66	-	-	-	-
Ancillary tests, performed in a specific selection of patients							
Dellabadia[36]	PET	69	0.86	0.59	*2.10*	0.68	0.80
Brekelmans[39]	*Subdural EEG monitoring*	82	*0.60*	*0.82*	*3.33*	*0.90*	*0.43*
	Depth EEG monitoring		*0.87*	*0.55*	*1.93*	*0.84*	*0.60*
O'Brien[40]	Postictal SPECT	34	*0.83*	*0.10*	*0.92*	*0.69*	*0.20*
Oliveira[41]	Ictal SPECT	48	0.93 (0.79-1.06) [a]	0.93 (0.79-1.06) [a]	*13.08*	0.93 (0.79-1.06) [a]	0.93 (0.79-1.06) [a]
	Interictal SPECT		0.77 (0.64-1.09) [a]	0.65 (0.51-0.79) [a]	*2.20*	0.69 (0.56-0.82) [a]	0.74 (0.60-0.88) [a]
Tatum[42]	Interictal SPECT	20	0.67	0.25	*0.89*	-	-
Velasco[43]	*Interictal SPECT*	93	*0.81*	-	-	-	-
Lee[44]	1st + 2nd ictal SPECT	24	0.54	-	-	-	-

N = Total number of patients; LR = Likelihood ratio of positive test; Italic values: diagnostic parameters that were not given in the article, but retrieved by the authors from the results sections; - = Values could not be retrieved or estimated from the described results; [a] 95% confidence interval

Of the standard tests, only seizure semiology obtained from video EEG appeared to have good diagnostic accuracy, i.e. identified patients suitable for surgery with a relatively high specificity, likelihood ratio, and positive predictive value. Sleep-deprived EEG and neuropsychological testing had a rather poor diagnostic accuracy. Surprisingly, MRI also showed modest positive and negative predictive values. Of the ancillary tests, usually performed when standard tests provide conflicting results, SPECT was investigated in five articles. From the papers that met our methodological stringent criteria, only ictal SPECT showed a relatively high diagnostic accuracy (sensitivity, specificity, positive, and negative predictive values all 0.93, likelihood ratio 13.08). By contrast, interictal and postictal SPECT had a rather poor diagnostic accuracy. Intracranial monitoring with subdural electrodes showed a relatively high specificity, likelihood ratio, and positive predictive value and PET appeared to be useful for excluding candidates from surgery, having a high sensitivity and negative predictive value.

DellaBadia et al. were the only investigators who evaluated combinations of tests.[36] They assessed eligibility for surgery after one or more positive interictal tests, after two or more positive interictal tests, and after three positive interictal tests. This, however, was regardless of which interictal test was included. They showed that the sensitivity decreased from 0.97 to 0.40 when more interictal tests were positive, while the specificity increased from 0.35 to 0.91.

Discussion

This methodological study searched the available literature on the value of diagnostic tests for the decision whether or not to perform temporal epilepsy surgery. Applying stringent STARD criteria, we conclude that there are surprisingly few unbiased studies in the literature that deal with decision making in epilepsy surgery. Notwithstanding the importance of seminal papers on epilepsy surgery that did not meet our criteria, our review shows that the information currently available in the literature is not sufficient to quantify the relative or independent contribution of each consecutive diagnostic test in the

decision-making for epilepsy surgery. Below, we will discuss some methodological issues and clinical implications of our findings.

Methodological issues

The focus of this review was on the whole decision-making process for temporal lobe epilepsy. We used a limited number of stringent criteria, dealing with the most important sources of bias in diagnostic research in general. We then had to exclude the majority of articles, including some of the seminal articles on epilepsy surgery. Most of these articles were written with a different perspective, focusing only on the outcome after surgery. Other studies compared diagnostic tests for interchangeability.

In total, 84% (552 of 654 articles) of the articles were excluded because the outcome criterion of the study was inappropriate for our purposes. Most of the published articles have limited their focus on the prognostic accuracy of tests to predict the outcome of surgery, such as seizure freedom one or two years after surgery. Although these articles are useful and have influenced diagnostic practice,[46-51] they do not primarily deal with the diagnostic decision-making. Although the prognostic value of a test may be an important factor in the decision-making process, taking into account operated patients only introduces a verification or work-up bias. The decision not to operate on potentially good candidates for surgery may be based on diagnostic factors that are not detected when studying operated patients only. Unfortunately, many of the prognostic studies did not include data on non-operated patients, which would have enabled us to include these papers in our review.

A number of articles assessed interchangeability of tests, and therefore used one test, e.g. chronic intracranial monitoring, as a reference, instead of a consensus from all tests. Such studies contain verification bias as only a sample of patients will undergo the (invasive) reference procedure.[20;33;34]

Clinical implications

Unfortunately, the 10 diagnostic articles that meet our criteria do not reflect current practice of work-up for temporal epilepsy surgery. Most studies deal with SPECT, which is not a routine investigation for candidates for temporal lobe epilepsy surgery, whereas only one article concerned MRI which is performed in every patient. It was not possible to compare the predictive power of the tests described in these studies (table 4) because of the considerable variation in the results, as shown for example by the variability in the sensitivity of ictal SPECT.[41;44] Moreover, ictal SPECT could be performed in only 29% of patients in one study (Oliveira et al.), which highlights the difficulty of performing ictal SPECT in practice.[41]

There is little information on the predictive value of the most basic tests used in surgical decision-making, such as medical history, standard EEG, and MRI. Video-EEG monitoring and dedicated MRI techniques are often used to guide the surgical decision-making process without much being known about the independent contribution of these tests to decision-making. The study by Henkel et al. addressed only one aspect of video-EEG monitoring.[38] MRI has been extensively studied in relation to prognosis of the outcome of epilepsy surgery only. We know that MRI evidence of unilateral hippocampal atrophy is a potent predictor of a good postoperative outcome,[46;49-51] but this is not necessarily a good diagnostic indicator to set a decision for surgery as evidenced by its modest values for sensitivity and specificity reported by Dellabadia et al. (see table 4).[36]

A recent article by the Multicentre Study Group of Epilepsy Surgery described the presurgical decision-making process for epilepsy surgery in general, and the factors influencing the decision to have surgery in a qualitative manner.[52] None of the 10 articles we reviewed addressed the issue of the added diagnostic value of commonly used tests for surgical decision-making. However, such studies do exist regarding the prognosis of epilepsy surgery. For example, Armon et al. performed a multivariate analysis of the predictors of outcome of surgery, assessing the added value of different predictors.[47] Study designs such as these should as well be

applied to the decision-making process to tailor the diagnostic approach in a more cost-effective manner.[3;4]

To answer the question which diagnostic tests truly contribute to decision making in epilepsy surgery and in which order these tests should be performed, the following study design would be desirable.[2-4;20;21;32-35] All epilepsy patients who are potential candidates for temporal lobe epilepsy surgery should be included during a specific period. All these patients should undergo the diagnostic tests in the chronological order commonly applied in clinical practice. The results of each test should be documented for each patient. For each patient, the final decision 'surgery or not' should be made by a multidisciplinary team using the consensus diagnosis method, again in accordance with clinical practice. This decision will be based on all patient information (including known diagnostic and prognostic factors, but probably also, as yet insufficiently studied factors) and can be considered as the reference test result. Hence, for all patients the results of the tests under study as well as the reference outcome is known. This allows a multivariate analysis and modeling of the decision making process, and show which test parameters independently contribute to the final decision 'surgery or not'. Furthermore, such a design makes it possible to characterize specific subgroups of patients requiring a minimum number of tests.

We conclude that few articles have tried to quantify the relevancy of tests for surgical decision-making in temporal lobe epilepsy patients. Knowledge of which test parameters really contribute to determine eligibility as well as ineligibility for surgery is necessary before burdensome, costly, and risky tests can be replaced by more convenient ones. Such knowledge will be essential to future cost-efficiency analyses of epilepsy surgery.[53] It will also allow us to provide tailored clinical guidelines of diagnostic strategies for patients referred for temporal lobe epilepsy surgery.[3;4] And finally, for the future of epilepsy surgery in developing countries where many facilities are lacking,[53;54] such information could be the basis for good risk-benefit assessment without extensive testing.

CHAPTER 3

CHAPTER 3

Decision-making in temporal lobe epilepsy surgery: The contribution of basic non-invasive tests.

SG Uijl

FSS Leijten

JBAM Arends

J Parra

AC van Huffelen

KGM Moons

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Abstract

Purpose. We studied the extent to which widely used diagnostic tests contribute to the decision whether or not to perform temporal lobe epilepsy surgery in the Netherlands.

Methods. This nation-wide, retrospective study included 201 consecutive patients referred for TLE surgery screening. The individual and combined contribution of nine index tests to the consensus decision to perform surgery was investigated. The contribution of each test was quantified using multivariable logistic regression and ROC curves.

Results. Surgery was performed in 119 patients (59%). Patient history and routine EEG findings were hardly contributory to decision-making, whereas a convergence of MRI with long-term interictal and ictal EEG findings correctly identified the candidates considered eligible for surgery (25% of total). Videotaped seizure semiology contributed less to the results. The area under the ROC curve of the combination of basic tests was 0.75. Ineligibility was never accurately predicted with any test combination.

Conclusions. In the Dutch presurgical work-up, when MRI and long-term EEG findings were concordant, a decision for TLE surgery could be reached without further ancillary tests. Videotaped seizure semiology contributed less than expected to the final clinical decision. In our study, basic test findings alone were insufficient to exclude patients from surgery.

Introduction

Temporal lobe epilepsy (TLE) surgery is an established treatment for patients with medically refractory temporal lobe epilepsy.[13;55] Successful epilepsy surgery depends on accurate diagnosis and careful patient selection.[13] The decision-making process or the amount of diagnostic work-up needed to decide whether or not a patient is eligible for TLE surgery, is complex and requires a team of specialists. All epilepsy surgery centers use a phased approach, starting with a similar set of non-invasive, basic tests followed by more invasive and expensive tests.[16] How this leads to a clinical decision whether or not to operate has hardly been studied. For the efficiency of a presurgical work-up it is important, however, to quantify the impact of consecutive tests on decision-making. Recently, guidelines for such diagnostic research have been published (the STARD initiative).[2]

Studies that have been done in TLE surgery usually focused on the value of individual tests, using a univariate approach. However, clearly a clinical decision is not based on a single test.[3;4] Studies that did include combinations of tests usually looked for their prognostic value, i.e. how a good outcome after TLE surgery can be predicted. Therefore, they included only operated patients rather than all patients undergoing the presurgical work-up.[56] Conclusions from prognostic studies are therefore biased and not the best way to study decision-making.

We investigated the extent to which the decision whether or not to perform TLE surgery had been made on the basis of widely used, non-invasive basic tests. We used accumulated data on all Dutch patients in whom epilepsy surgery had been considered.[17] In all patients screened for TLE surgery, we quantified the independent or added value of patient history, routine EEG recordings, MRI, and video-EEG monitoring.

Methods

Patients

This retrospective national study on the decision-making process included all

patients referred for evaluation for TLE surgery between July 2000 and July 2002. Patients were excluded when a definite extratemporal seizure origin could already be inferred at referral for presurgical screening. Thus, patients were excluded if the semiology of the seizure onset, according to the patient's history at referral, included a longstanding or evolving somatosensory aura, generalized hypertonia or atonia, in combination with an MRI without temporal lobe abnormalities.

All patients referred for TLE surgery underwent the same presurgical work-up, using a fixed protocol (figure 3.1), starting with a detailed patient history, routine EEG, MRI, and video-EEG monitoring of seizures.[17] If these tests provided inconclusive results, ancillary tests were often performed (e.g., MEG, PET, SPECT, and intracranial EEG monitoring). A national multidisciplinary taskforce determined the final consensus decision, i.e. whether a patient was eligible or ineligible for surgery.

Diagnostic tests under study

The contribution to the decision-making of the following basic non-invasive tests was evaluated: patient history (four items), routine EEG recordings, MRI, and video-EEG monitoring (three items).

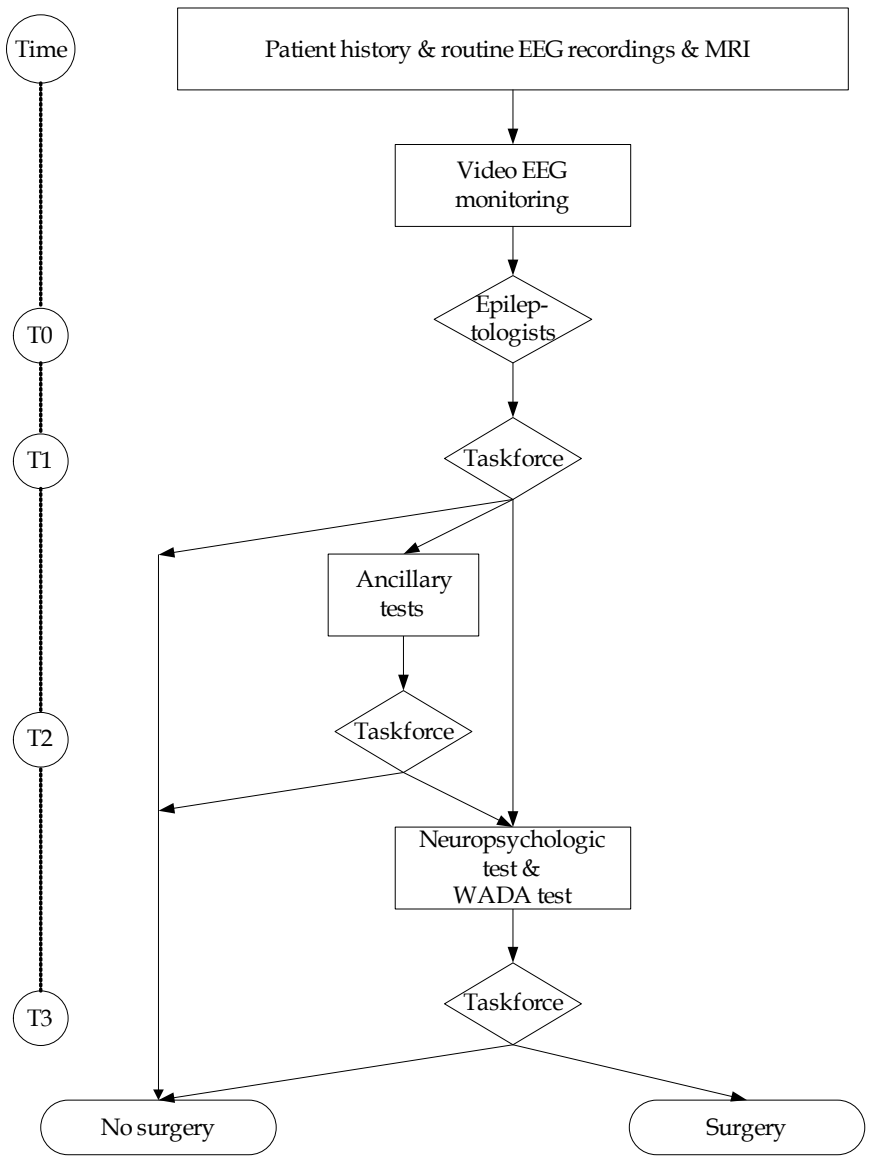
The patient history items we chose were based on literature showing a prognostic value for seizure freedom after surgery. This resulted in the following four items: age at referral, age at onset of non-febrile seizures, previous history of febrile seizures, and temporal (automotor) seizure semiology.[48;57;58] The latter was defined as a seizure duration longer than one minute that included at least four of the following five characteristics: abdominal or experiential aura, impaired consciousness, occurrence of automatisms, unilateral dystonic posturing, or pronounced postictal confusion.[59-61]

The latest representative, routine interictal EEG was evaluated for the presence or absence of unilateral temporal abnormalities, defined as focal epileptiform spikes, sharp waves, or slow waves. When abnormalities were bilateral temporal or both temporal and extratemporal, the test was considered

inconclusive.

MRI 1.5T images including coronal FLAIR were evaluated for the presence of unilateral temporal abnormality or not, according to a standardized epilepsy protocol.[62]

Figure 3.1. Patient flow chart



Three aspects of video-EEG monitoring were evaluated: long-term interictal EEG, seizure semiology, and ictal EEG. The long-term interictal EEG was coded as presence or absence of unilateral temporal abnormalities, defined by presence of focal slow waves, epileptiform spikes or sharp waves at electrodes near the tip of the temporal lobe (F7/F8, F9/F10, Sp1/Sp2, T3/T4, or T5/T6). Abnormalities were defined as unilateral when more than 90% of abnormalities occurred unilaterally. Videotaped seizure semiology was coded as the presence or absence of temporal (automotor) semiology,[59-61] as described above (see patient history). Furthermore, lateralization of semiology was defined by using two characteristics described in literature: dysphasia and dystonic posturing.[60] Ictal EEG findings were coded as the presence or absence of a unilateral regional or (delayed) focal temporal seizure onset.[63]

Study outcome

The dichotomous outcome was the consensus decision whether or not to perform TLE surgery, as determined by a national multidisciplinary taskforce consisting of epileptologists, clinical neurophysiologists, neurosurgeons, neuropsychologists and neuroradiologists. Such a consensus decision is necessarily used in situations as in TLE surgery where there is no single or fixed reference available to make the decision.[2;8;11] The taskforce used all available evidence (e.g. also from ancillary tests, neuropsychology, and Wada testing) for determining the indication for surgery.

Data collection

The results of index tests and the consensus decisions were retrospectively retrieved from the patient files and written reports of the taskforce conferences. All information was coded according to the above-described definitions and entered into a research database. To ensure uniform coding of all tests, kappa analyses between the two scoring researchers (S.U., A.C.) and two independent experts (F.L., J.A.) were regularly performed. After preparatory training, kappa values of

0.70 or higher were obtained.

Data analysis

Data were analyzed in three steps. First, the univariate association (including sensitivity, specificity, positive and negative predictive value) of each index test was estimated with regard to the consensus decision for or against surgery. Second, multivariable analysis using logistic regression modeling was used to quantify the extent to which the nine index tests independently contributed to the decision. We started with an overall model including all nine variables, which was reduced by step-wise exclusion of the least contributory tests (p-value over 0.20, based on the log likelihood ratio test) and resulted in a reduced model. To assess the discriminative accuracy of the models, the areas under the receiver operating characteristic curve (ROC area) of the overall and reduced model were compared. Thus, we accounted for the dependency between the models as they were estimated on the same subjects.[64] Finally, cross-tabulations were calculated for the combinations of test results from the reduced model with the consensus decision. Tests were considered concordant when both showed unilateral temporal abnormalities on the same side. Tests were considered discordant when they showed unilateral temporal abnormalities on opposite sides.

Some values were missing. Age at onset of seizures was missing in 1% of the patients and occurrence of febrile seizures in 38%. The latter percentage was relatively high but realistic because we coded febrile seizures as unknown when patients themselves or their relatives were not certain whether they had occurred. Reports on routine EEG recordings were missing in 19% of the patients. Since missing values usually do not occur at random, we imputed the missing values of MRI and video-EEG monitoring, using single imputation by linear regression with the addition of a random error term.[65-67]

All statistical analyses were performed with SPSS version 11.5 (Chicago, IL, USA).

Results

During the 2-year inclusion period, 201 patients were referred for presurgical work-up for TLE surgery in the Netherlands. Table 3.1 shows the nine index tests and the consensus decision. Of the 201 analyzed patients, 119 (59%) were considered eligible for TLE surgery. One year after surgery, 72% of these patients were seizure free (Engel score 1A). Of the 201 patients, 82 (41%) were ineligible for TLE surgery. Reasons for ineligibility were multifocal epilepsy in 28 patients, 9 had an unclear focus localization, 9 concomitant diseases, and 3 had an inoperable focus. Furthermore, 8 patients dropped out because they became seizure free during presurgical screening, 13 declined to undergo invasive EEG, one patient died, and 4 dropped out for other reasons. Seven patients were considered eligible for extratemporal and not temporal surgery (in our study, they are classified as not undergoing TLE surgery). Seven other patients were considered eligible for TLE surgery, but renounced surgery on second thoughts.

Besides the basic non-invasive tests, 53 patients underwent a PET; 31 of whom underwent surgery. Ten patients also underwent intracranial EEG monitoring; 9 of whom consecutively underwent surgery. Neuropsychological assessment was performed in 134 patients and a Wada test in 116 patients. Figure 3.2 shows the patient flow from MRI results to ictal EEG results. The results of interictal EEG and seizure semiology are also included.

None of the four patient history items was significantly associated with the decision for or against surgery (all p-values over 0.50). The other basic tests were all significantly associated with the decision, but showed a large variation in sensitivity, specificity, and predictive values (table 3.2). MRI had the highest sensitivity and negative predictive value, whereas long-term ictal EEG showed the highest specificity and positive predictive value, followed by long-term interictal EEG.

Table 3.1. Distribution of investigated diagnostic tests and the decision for or against surgery (N=201)

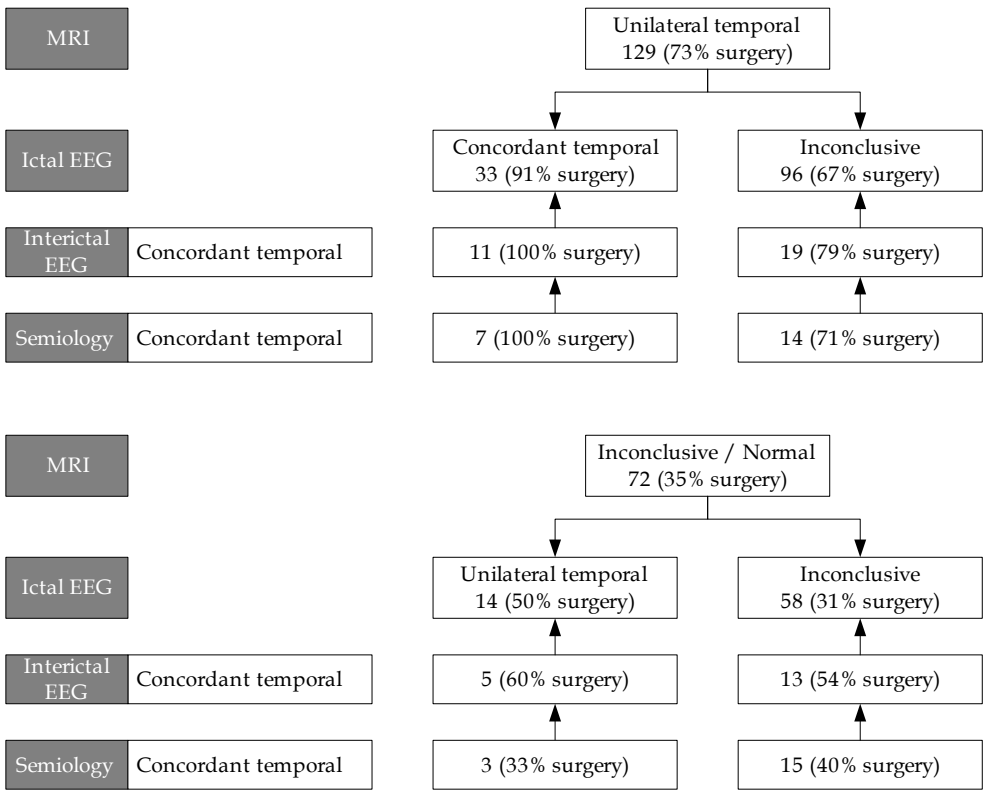
Patient history	
Age at referral for surgery (median (range))	32.5 (1 - 62)
Age at onset epilepsy (median (range))	12.0 (0 - 47)
Febrile seizures	75 (37)
Temporal seizure semiology	131 (65)
Routine EEG recordings	
Unilateral temporal	72 (36)
Normal	5 (2)
Inconclusive[a]	124 (62)
MRI	
Unilateral temporal	129 (64)
Normal	24 (12)
Inconclusive[a]	48 (24)
Video-EEG monitoring	
Long-term interictal EEG	
Unilateral temporal	51 (25)
Inconclusive[a]	150 (75)
Seizure semiology	
Definitely temporal	71 (35)
Not localising	130 (65)
Ictal EEG	
Unilateral temporal	47 (23)
Inconclusive[a]	154 (77)
Study outcome: considered eligible for surgery	119 (59)

Values represent number of patients (percentage) unless mentioned otherwise;
[a] *Inconclusive = not localizing to one temporal lobe*

Table 3.2. Crosstables and association of the tests under study with the decision for or against surgery, estimated by the accuracy parameters with 95% confidence intervals

	Decision for surgery			*Sensitivity*	*Specificity*	*Positive predictive value*	*Negative predictive value*
	Yes (N=119)	*No* (N=82)	*p-value*				
Routine EEG			0.02				
Unilateral temporal	50	22		0.42	0.73	0.69	0.47
Inconclusive / normal	69	60		(0.34-0.51)	(0.63-0.82)	(0.58-0.79)	(0.38-0.55)
MRI			0.00				
Unilateral temporal	94	35		0.79	0.57	0.73	0.65
Inconclusive / normal	25	47		(0.71-0.85)	(0.47-0.67)	(0.65-0.80)	(0.54-0.75)
Long-term interictal EEG			0.02				
Unilateral temporal	37	14		0.31	0.83	0.73	0.45
Inconclusive	82	68		(0.23-0.40)	(0.73-0.90)	(0.59-0.83)	(0.38-0.53)
Videotaped semiology			0.03				
Definitely temporal	49	22		0.41	0.73	0.69	0.46
Not localising	70	60		(0.32-0.50)	(0.63-0.82)	(0.58-0.79)	(0.38-0.55)
Ictal EEG			0.00				
Unilateral temporal	37	10		0.31	0.89	0.79	0.47
Inconclusive	82	72		(0.23-0.40)	(0.79-0.93)	(0.65-0.88)	(0.39-0.55)

Figure 3.2. Patient flow chart and surgery percentages



The overall multivariate model including the nine index tests yielded a ROC area of 0.76 (table 3.3). Excluding variables with a p-value over 0.20 resulted in a model based on routine EEG, MRI, and the three video-EEG monitoring items. The ROC area of this reduced model also was 0.76 (95% confidence interval, 95%CI: 0.69-0.83). In this reduced model, MRI and ictal EEG contributed most to decision-making and routine EEG, seizure semiology, and long-term interictal EEG least. As ictal EEG is always obtained in combination with interictal EEG and seizure semiology during video-EEG monitoring, whereas routine EEG is a separate diagnostic test, we also removed routine EEG findings from the reduced model, resulting in the final reduced model with a ROC area of 0.75 (table 3.3), which was not significantly lower than the overall model (p-value: 0.47).

Table 3.3. Results of the multivariable logistic regression analysis for the overall and reduced model predicting the decision for or against surgery

	Overall model			*Reduced model*		
Determinant	*Odds Ratio*	*95% CI*	*p-value*	*Odds Ratio*	*95% CI*	*p-value*
Age at referral	1.00	0.97-1.03	0.80			
Age at onset epilepsy	1.00	0.96-1.03	0.86			
Febrile seizures	0.81	0.41-1.62	0.55			
Temporal semiology	1.11	0.55-2.24	0.77			
Routine EEG	1.52	0.76-3.06	0.24			
MRI	5.20	2.62-10.34	<0.01	5.14	2.66-9.94	<0.01
Long-term interictal EEG	2.22	0.98-4.99	0.06	2.11	0.67-4.62	0.06
Videotaped semiology	1.38	0.68-2.79	0.38	1.36	0.69-2.68	0.38
Ictal EEG	3.08	1.32-7.20	<0.01	3.06	1.33-7.02	<0.01
ROC area (95% CI)	0.76	0.69-0.83		0.75	0.69-0.82	0.47[a]

95% CI = 95% confidence interval; [a] p-value of the difference in ROC area between the reduced and the overall model

Table 3.4 shows the correlation between combinations of MRI and video-EEG monitoring results and the decision to operate. The first row of each of the combinations can be considered as a positive test result, therefore representing the positive predictive value of the test combination; the last row can be considered as the negative predictive value. In isolation, MRI had a positive predictive value of 0.73 (table 3.2) and in combination with concordant seizure semiology 0.72 (table 3.4). Concordant long-term interictal EEG findings as well as concordant ictal findings improved the positive predictive value of MRI to 0.87 and 0.91, respectively (table 3.4). The negative predictive value of MRI remained the same when MRI was combined with the three video-EEG monitoring items (0.65, table 3.2).

Concordant lateralizing and localizing findings for MRI and ictal EEG (N=33) led to a decision to perform surgery, except in three patients with inconclusive long-term interictal EEG results (table 3.4). Concordant findings on MRI, long-term interictal EEG, and ictal EEG always led to a decision to operate and correctly identified 30 out of 119 (25%) eligible candidates. In this group, 79% had Engel class 1A one year after surgery. Eight of these 30 patients underwent a PET scan, and one also underwent intracranial EEG monitoring.

For patients in whom MRI and long-term EEG were not completely concordant (75% of operated patients), the decision for surgery was usually based on the different combinations of results from MRI, interictal EEG, semiology, and ictal EEG (figure 3.2), or on the results of ancillary tests, when performed. The three video monitoring index tests yielded inconclusive results in a large number of patients. Of all 129 patients with unilateral temporal abnormalities on MRI (table 3.4), 96 had inconclusive interictal EEG findings, 67 (70%) of whom were considered eligible for surgery. Similarly, 74 of 101 (74%) patients with inconclusive seizure semiology and 64 of 96 (67%) patients with inconclusive ictal EEG findings (table 3.4) were eligible for surgery. Truly discordant findings on MRI and video-EEG were found in only 6 patients (table 3.4), of whom 3 were

considered eligible for surgery after ancillary testing. The operated patient with discordant MRI and long-term interictal EEG had an Engel score 2A one year after surgery; the operated patients with discordant MRI and seizure semiology both had Engel score 1A one year after surgery. Thus, no combination of basic tests could reliably identify patients ineligible for surgery.

Table 3.4. MRI in combination with video monitoring in relation to the decision for or against surgery

	Video-EEG monitoring	*Decision for surgery*		*Number of subjects*
MRI	***Interictal EEG***	Yes (fraction)	No (fraction)	
Unilateral temporal	Concordant [a]	26 (0.87) [b]	4 (0.13)	*30*
Unilateral temporal	Inconclusive	67 (0.70)	29 (0.30)	*96*
Unilateral temporal	Discordant	1 (0.33)	2 (0.67)	*3*
Inconclusive / normal	Unilateral temporal	10 (0.56)	8 (0.44)	*18*
Inconclusive / normal	Inconclusive	15 (0.28)	39 (0.72) [c]	*54*
MRI	***Seizure semiology***			
Unilateral temporal	Concordant [a]	18 (0.72) [b]	7 (0.28)	*25*
Unilateral temporal	Inconclusive	74 (0.74)	27 (0.27)	*101*
Unilateral temporal	Discordant	2 (0.67)	1 (0.33)	*3*
Inconclusive / normal	Unilateral temporal	2 (0.67)	1 (0.33)	*3*
Inconclusive / normal	Inconclusive	23 (0.33)	46 (0.67) [c]	*69*
MRI	***Ictal EEG***			
Unilateral temporal	Concordant [a]	30 (0.91) [b]	3 (0.09)	*33*
Unilateral temporal	Inconclusive	64 (0.67)	32 (0.33)	*96*
Inconclusive / normal	Unilateral temporal	7 (0.50)	7 (0.50)	*14*
Inconclusive / normal	Inconclusive	18 (0.31)	40 (0.69) [c]	*58*

[a]Concordant unilateral temporal; [b] Positive predictive value of combination of tests; [c] Negative predictive value of combination of test

Since temporal seizure semiology from video contributed only marginally to the decision, we also assessed whether more refined items from videotaped seizure semiology (table 3.5) did have an impact that we might have missed by reducing the diagnostic test conclusion to temporal seizure semiology, yes or no. Only impaired consciousness and pronounced postictal confusion were significantly associated with the final decision (both p-value 0.01), but all items had positive and negative predictive values that were lower than the positive and negative predictive value of overall temporal seizure semiology as we defined it.

Table 3.5. Coded items for videotaped seizure semiology

Item	*Answer possibilities*
Type of aura	No aura
	Abdominal
	Autonomic
	Sensory
	Somatosensory
	Experiential
Classification of seizure beginning	Restricted to aura
	Autonomic
	Dialeptic / hypomotor
	Tonic
	Tonic-clonic
	Versive
	Hypermotor
	Automotor
	Atonic / astatic
	Aphasic

Table 3.5. Continued

Item	*Answer possibilities*
Classification of seizure course	No change
	Autonomic
	Dialeptic / hypomotor
	Tonic
	Tonic-clonic
	Versive
	Hypermotor
	Automotor
	Atonic / astatic
	Aphasic
Impaired consciousness	No / Yes
Orofacial automatisms	No / Yes
Automatisms of fingers / hands	No / Yes (including side)
Eye blinking	No / Yes
Motor agitation	No / Yes
Version of eyes or head to one side	No / Yes (including side)
Speech	No
	Adequate spontaneous speech
	Unintelligible speech
	Delirious
	Mutism
	Aphasia / dysphasia
	Vocalisations
Arm dystonia	No / Yes (including side)
Clonic contractions	No / Yes (including side)
Problems with naming or understanding	No / Yes
Postictal symptoms	No
	Paresis (including side)
	Agression / psychosis
	Vomiting
	Pronounced confusion

Discussion

Clinical implications

The combination of basic, non-invasive tests we studied had a moderate overall influence on clinical decision-making for patients referred for TLE surgery screening in the Netherlands. This perhaps emphasizes the importance of ancillary tests that were performed but not included in our study. As individual tests, basic tests were slightly more suitable for including rather than excluding patients for epilepsy surgery, since the positive predictive value of routine EEG, MRI and video-EEG was higher than their negative predictive value. This is consistent with our finding that discordant results are not always indicative of ineligibility for TLE surgery.

In our study population, there was a group of patients in whom the decision for surgery could be made without performing further ancillary tests, viz. patients with unilateral temporal MRI abnormalities with concordant findings on both long-term interictal and ictal EEG during monitoring. This represents 25% of patients who were considered eligible for surgery. This is a remarkable finding, because we used a rather crude coding of test results that ignores many nuances that actually led to long discussions in some cases with a request for ancillary tests that in retrospect did not contribute to decision-making. Also, the four patient history items, the routine EEG findings, and videotaped seizure semiology hardly contributed to the decision whether to operate. Again, we have the experience that aspects of patient history or subtle findings in seizure semiology may lead to insecurity about the diagnosis, and thus to further testing. The Dutch taskforce is especially keen on close analysis of videotaped seizure semiology, so its relatively low contribution to the decision-making came as a disappointment. This finding needs confirmation from other centers. In a recent review, So also addressed limitations of the localizing value of videotaped seizure semiology.[68] Serles *et al.* did find a contribution of videotaped seizure semiology,[69] but they did not analyze the value of seizure semiology with regard to other diagnostic tests, such as MRI. Although patient history and routine EEG in our study contributed only

marginally to the decision-making process, it should be noted that these tests were necessary to refer these patients as possible candidates for TLE surgery. Earlier studies show the high specificity with which this can be done with regard to TLE diagnosis.[70] Our retrospective study included only patients after referral.

There are few comparable studies of the decision-making process for epilepsy surgery.[56] Two studies assessed the value of a combination of two diagnostic tests in the presurgical work-up. Berg *et al.* found the highest proportion of patients eligible for surgery with concordant overall MRI and video-EEG results.[52] DellaBadia *et al.* assessed the contribution of the combination of sleep-deprived EEG and MRI.[36] Their results were also consistent with ours, except that we found lower negative predictive values for routine or sleep-deprived EEG, either alone or in combination with MRI. This may be because DellaBadia *et al.* used a stricter protocol for performing sleep-deprived EEG and investigated fewer patients (69 versus 201 patients).

Prognostic studies have shown that concordant MRI, interictal EEG and ictal EEG successfully select candidates for surgery, based on the prognostic value of these tests, i.e. outcome after surgery.[24;71] In our study population, we confirm that the same diagnostic tests can select possible candidates for surgery, with the difference that in our study also patients that were eventually rejected for surgery were included. It is important that these results are complementary because they could form the basis for more worldwide consensus on the use of ancillary tests, e.g. invasive studies. Of course, apart from setting the indication for epilepsy surgery, surgical strategy also plays a role. Some centers will order ancillary tests for performing a specialized kind of resection, e.g. selective amygdalohippocampectomy, which will usually involve some invasive testing for sublobar focus localization. The issue of surgical strategy is not settled and many practices abound. Even given this disparity, we think that our data hold for these different practices when it comes to setting the principle decision whether to perform surgery or not. Our results therefore endorse further thinking about the

use of ancillary tests in some cases, especially when standard or intraoperatively tailored resections are considered. This could make epilepsy surgery programs more cost effective.

Methodological aspects

Some methodological aspects limit extrapolation of our results and need to be discussed. Unfortunately, there is no single reference test to set the decision for surgery. In the absence of a single established reference, we used the consensus judgment of a group of experts to set the decision for TLE surgery, based on all available information. This is considered the best alternative when a reference test is lacking,[2;8;11] but our results should be interpreted with care. A potential disadvantage of this reference method is the possibility of incorporation bias, because the reference is not independent from the index tests under study.[8;9;20] The effect of the incorporation bias, however, can be judged afterwards as it commonly leads to overestimation of the contribution of the index tests. The independent contribution of MRI and video-EEG in our study was so substantial that it is unlikely that this could solely be attributed to incorporation bias.

We believe that the consensus decision of the taskforce was adequate. The overall outcome of surgery in our series was comparable to or higher than values reported in the literature, with 72% of patients being seizure free (Engel score 1A) one year after TLE surgery.[13;14] All patients underwent tailored temporal resections. Long-term follow-up of these patients showed that such surgery did not harm cognitive performance and had only a limited adverse effect on intellectual function.[72;73] Nevertheless, the problem remains that we do not know how many patients were inappropriately rejected for surgery. Patients who have been denied surgery in our program, might have been found eligible at other centers. This objection could have been met by including specialists from other countries in the consensus panel. Even then, there is no definite way to settle this, because the decision for surgery cannot be randomized.

Since our reference test was a final consensus decision including all

diagnostic information, we used a backward statistical approach, starting with inclusion of all index tests. Assessment of the added value of a stepwise decision-making process should mirror clinical practice, starting with the patient history, followed by estimation of the added value of each consecutive test.[3;4] For comparison, we also applied this more commonly used forward approach, which yielded the same results.

The results of the index tests were reduced to a few clinically applicable and widely used essentials. These essentials obviously do not comprise all diagnostic information conveyed by the tests, and some complexities could have been obscured. Considerations of reproducibility and proof of evidence from the literature played a major role in the choice of items to study. Seizure semiology and MRI were used both as a diagnostic test under study and as an exclusion criterion, since we wanted to confine the study to patients screened for temporal lobe surgery, i.e. patients who do not have unequivocal extratemporal epilepsy. Including extratemporal cases would undoubtedly have improved the negative predictive value of the index tests.

Routine EEG was performed in different centers (local hospitals, university hospitals, or epilepsy clinics) and according to different protocols (sleep-deprived or not, duration of 30 to 90 minutes). Because we wanted to reproduce daily clinical practice, we accepted these differences. For this reason, it is not surprising that routine EEG was not included in the final model whereas long-term interictal EEG was.

Neuropsychological test results were not included as a basic test. They are not used for focus localization purposes in The Netherlands, but mainly for assessment and prediction of cognitive change in those in whom a decision for surgery has been reached. Although this standpoint is well supported,[74] other epilepsy surgery centers would use these test results for localization and thus include them in the basic test battery of all referred patients. The prognostic importance of neuropsychological test results is beyond doubt, however, as far as

we know, there are no data on their contribution to the decision-making process in such a setting.[56]

Conclusions

In this retrospective study from the Dutch population, concordance between MRI, long-term interictal and ictal EEG findings was sufficient to identify a group (25%) of patients eligible for TLE surgery. This suggests that a decision for surgery in these cases could have been reached without further tests. After referral for presumed TLE, analysis of videotaped seizure semiology seemed to have less impact than expected on the final clinical decision. In the Dutch program, patients could not be excluded from TLE surgery based on results of basic tests only.

CHAPTER 4

CHAPTER 4

The added value of [18F]fluor-D-deoxyglucose positron emission tomography in screening for temporal lobe epilepsy surgery.

SG Uijl

FSS Leijten

JBAM Arends

J Parra

AC van Huffelen

KGM Moons

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Abstract

Purpose. FDG-PET is an expensive, invasive, and not widely available technique used in the presurgical evaluation of temporal lobe epilepsy. We assessed its added value to the decision-making process in relation to other commonly used tests.

Methods. In a retrospective study of a large series of consecutive patients referred to the national Dutch epilepsy surgery program between 1996 and 2002, the contribution of FDG-PET, MRI, and video-EEG monitoring findings, alone or in combination, to the decision whether to perform surgery was investigated. The impact of FDG-PET was quantified by comparing documented decisions concerning surgery before and after FDG-PET results.

Results. Of 469 included patients, 110 (23%) underwent FDG-PET. In 78 of these patients (71%), FDG-PET findings led clinicians to change the decision they had made based on MRI and video-EEG monitoring findings. In 17% of all referred patients, the decision regarding surgical candidacy was based on FDG-PET findings. FDG-PET was most useful when previous MRI results were normal ($p<0.0001$) or did not show unilateral temporal abnormalities ($p<0.0001$), or when ictal EEG results were not consistent with MRI findings ($p<0.0001$) or videotaped seizure semiology ($p=0.027$). The positive and negative predictive values for MRI and video-EEG monitoring, which ranged from 0.48 to 0.67, were improved to 0.62 to 0.86 in combination with FDG-PET.

Conclusions. In patients referred for TLE surgery, FDG-PET findings can form the basis for deciding whether a patient is eligible for surgery, and especially when MRI or video-EEG monitoring are nonlocalizing.

Introduction

[18F]-Fluoro-D-deoxyglucose Positron Emission Tomography (FDG-PET) is used in the complex presurgical evaluation of patients with medically intractable temporal lobe epilepsy (TLE).[17;75-77] However, because the technique is invasive and expensive, requiring the injection of radioactivity, and not widely available because cyclotron facilities are needed,[54] it is important to know its diagnostic value compared with that of more routinely performed investigations such as MRI and video-EEG seizure recordings.

Recent studies suggest that FDG-PET is indicated in patients with TLE if MRI does not localize the source in one temporal lobe (either because it is negative or shows bilateral abnormalities), or if ictal EEG findings show a unilateral temporal onset that is not consistent with MRI findings.[78-80] Although several studies have investigated the contribution of FDG-PET to identifying the lobe of seizure onset in patients with TLE, in most studies FDG-PET was evaluated in isolation, without reference to existing MRI and video-EEG monitoring results.[56] Medical decisions are usually based on the results of several investigations and are hardly ever based on a single test result.[3] This is also true for the diagnostic work-up of patients regarding their eligibility for TLE surgery, in which FDG-PET is never performed first. The aim of this study was to determine the clinical or added value of FDG-PET on the decision-making process regarding TLE surgery in the setting of a tertiary referral center. We were particularly interested in determining the contribution of FDG-PET relative to that of MRI and video-EEG monitoring.

Methods

Patients and setting

In the Netherlands, all patients referred for epilepsy surgery enter the Dutch Collaborative Epilepsy Surgery Program (DCESP), a tertiary referral program. Patients undergo a standardized presurgical work-up, including patient history, routine EEGs, MRI, and prolonged video-EEG monitoring of seizures.[17] After these tests, a national multidisciplinary taskforce determines the eligibility of the patient

for surgery and whether additional tests, such as FDG-PET, ictal SPECT, fMRI, MEG, or intracranial EEG monitoring, are needed. The results of ancillary tests are discussed in the ensuing monthly taskforce meeting and a new consensus decision is reached regarding eligibility for TLE surgery, or whether further testing, especially intracranial monitoring, is needed. Only surgical candidates undergo a neuropsychological test and a Wada procedure as well.

The present study is a retrospective cohort study including all consecutive patients referred to the national DCESP for evaluation for eligibility for TLE surgery between January 1996 and July 2002. We specifically chose this starting date because this is when a standardized 1.5 Tesla MRI protocol, including coronal FLAIR images, was introduced.[62] The role of FDG-PET in the diagnostic work-up of epilepsy patients has not changed since then.[78-80] Furthermore, we included data from patients referred between 1986 and 1996, when FDG-PET was performed more or less regardless of previously obtained MRI and video-EEG results, in a sensitivity analysis to evaluate selection or work-up bias in our cohort. We focused on patients referred for TLE surgery. Thus patients were excluded if a definite extratemporal seizure origin was established at the start of the presurgical work-up, that is if the semiology of the seizure onset included a longstanding or evolving somatosensory aura, generalized hypertonia or atonia, in combination with an MRI without temporal lobe abnormalities.

Diagnostic tests

Data were collected during the regular diagnostic work-up, in which all individual test results from the presurgical work-up and all taskforce decisions before and after each test were systematically documented in a clinical database. For the present analysis, the results of FDG-PET, MRI, and video-EEG monitoring were recoded into a research database. To ensure uniform coding of all test results, kappa analyses were regularly performed among the scoring researchers (SU, AC) and two independent experts (FL, JA). After preparatory training, kappa values of 0.70 or higher were obtained for coding of all the items.[18;19]

MR imaging was performed on a 1.5 Tesla machine, including coronal T2-weighted spin-echo and coronal fast fluid-attenuated inversion recovery (FLAIR) techniques. Quantitative MRI image studies, e.g. volumetry or measurement of T2 relaxation time, were not performed. MRI results were coded into four categories: no abnormalities, unilateral temporal abnormalities, bilateral temporal abnormalities, or other abnormalities. We evaluated three aspects of video-EEG monitoring, namely, long-term interictal EEG, seizure semiology, and ictal EEG. Interictal EEG was coded dichotomously as showing or not showing unilateral temporal lobe abnormalities, i.e. focal slow waves, epileptiform spikes, or sharp waves at electrodes over the temporal lobe with 90% predominance on one side. Videotaped seizure semiology was coded dichotomously as the presence or absence of typically temporal semiology,[60] defined as a seizure duration longer than 1 minute including at least four of the following five characteristics: abdominal or experiential aura, impaired consciousness, occurrence of automatisms, unilateral arm dystonia, or pronounced postictal confusion.[59-61] Semiology was considered lateralized if there was ictal or postictal dysphasia or early ictal contralateral arm dystonia.[60] Ictal EEG findings were coded dichotomously as the presence or absence of a unilateral regional or (delayed) focal temporal seizure onset.[63]

Interictal FDG-PET was performed using a Siemens ECAT 951/31R camera (Liège, Belgium) or a Siemens ECAT exact HR+ PET scanner (Amsterdam, both Siemens CTI PET Systems, Knoxville, TN, USA). A static PET study was obtained 30 to 60 minutes after intravenous injection of ^{18}FDG. The protocol has been described in earlier publications.[75;76] FDG-PET results were classified into three categories: normal, showing unilateral temporal hypometabolism, or otherwise (mainly, bitemporal or extratemporal hypometabolism). Combinations of unilateral temporal hypometabolism with confined ipsilateral frontobasal, ipsilateral thalamic, or contralateral cerebellar hypometabolism were considered compatible with unilateral temporal abnormalities.[81;82]

Outcome

There is no single or established reference standard for decision-making regarding TLE surgery. In the absence of such a reference standard, a consensus decision based on all available diagnostic information is often used as outcome measure or reference.[2;8;9] In the Dutch national presurgical work-up program, the consensus decision is made by a multidisciplinary taskforce consisting of neurosurgeons, neurologists, neurophysiologists, neuropsychologists, and radiologists, on the basis of available evidence. The taskforce also establishes whether additional tests are required. All these decisions are fully documented, which gave us the opportunity to compare each decision before and after FDG-PET was performed and to study whether the FDG-PET results indeed changed a decision made on the basis of MRI and video-EEG monitoring findings.

Data analysis

We estimated the association between MRI, long-term interictal EEG, videotaped seizure semiology, ictal EEG, and FDG-PET findings and the final decision regarding TLE surgery as outcome measure. We quantified the contribution of each test by calculating the positive and negative decision predictive value, i.e. the predictive values of each test with the decision for surgery (yes or no) as outcome. To quantify the added value of FDG-PET, two by two tables for the results from FDG-PET in combination with MRI and with video-EEG monitoring were calculated. Results were considered concordant when both tests showed unilateral temporal abnormalities on the same side, and discordant when both tests showed unilateral temporal abnormalities on opposite sides. Other combinations were defined as indecisive. All statistical analyses were performed using SPSS 12.0 (Chicago, IL, USA).

Sensitivity analysis

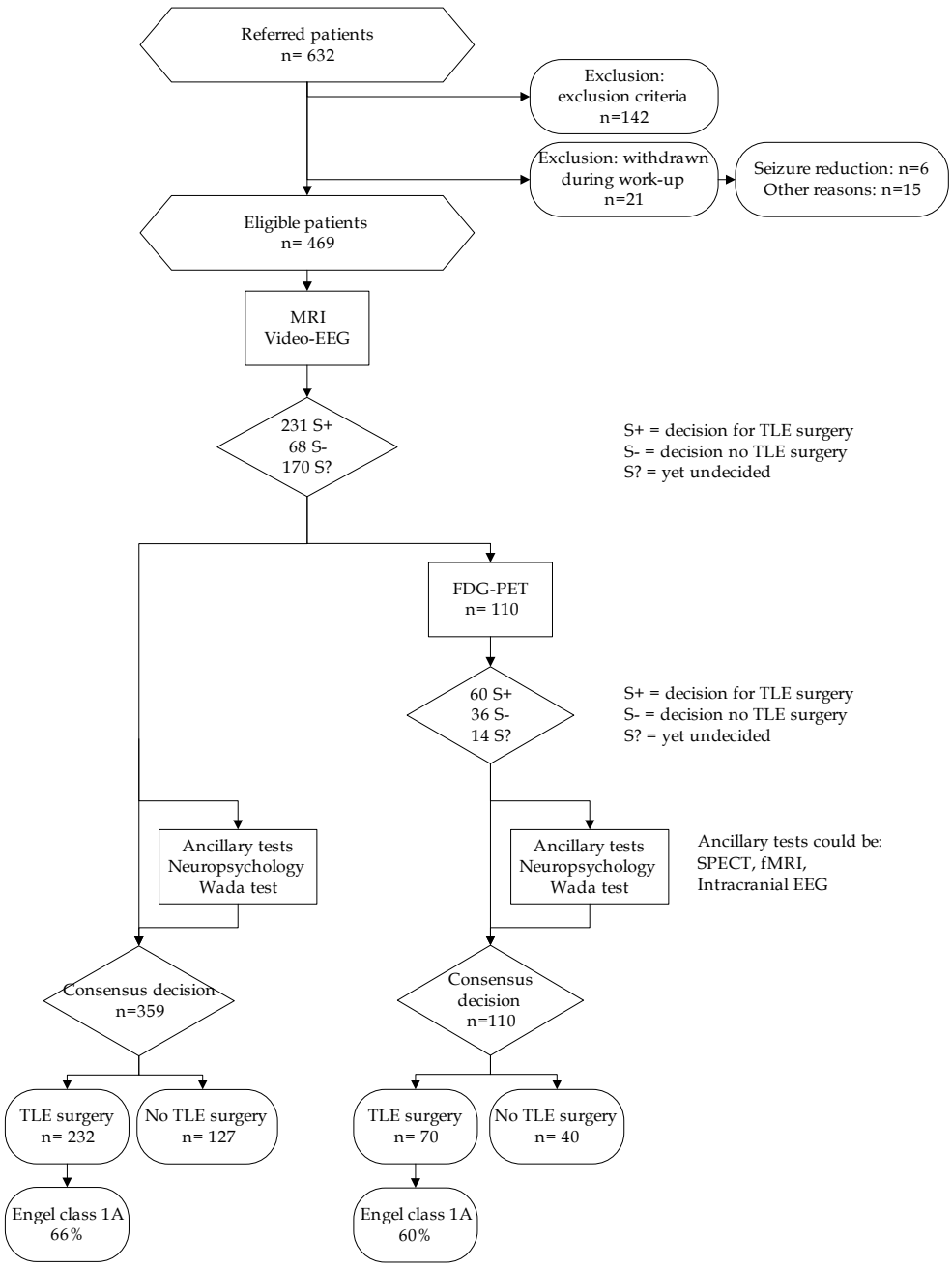
FDG-PET was not performed in all patients, which may have introduced work-up bias due to selective referral for FDG-PET on the basis of previous test results.[2;8;9]

The best way to control for this bias is to impute the "missing" values.[66;83] In the Netherlands in the early years of PET before 1996, when MRI did not yet include coronal FLAIR images, FDG-PET was performed more or less regardless of previously obtained MRI and video-EEG results. This gave us the opportunity to perform a sensitivity analysis to evaluate the potential work-up bias in our data. To this end, we used the data of all patients referred for evaluation of TLE surgery between 1986 and 2002 (803 patients in total) to build a prediction model, using binary logistic regression, in which the intermediate consensus decision after FDG-PET (surgery versus no surgery) was the dependent variable and all other available test results and patient information were the independent variables or predictors. This prediction model was then applied to the data of the patients evaluated from 1996 to 2002, to impute a (virtual) intermediate consensus decision after FDG-PET for the patients who did not undergo FDG-PET. The impact of FDG-PET on the decision to operate was estimated in the imputated cohort and compared with the observed percentage based on the patients who actually underwent FDG-PET in that same cohort.

Results

Between January 1996 and July 2002, 632 patients were referred to the national DCESP for evaluation for epilepsy surgery (figure 4.1). Of these, 142 were excluded because the epileptogenic focus was considered to be extratemporal. Twenty-one patients withdrew from the diagnostic work-up. Therefore, 469 patients were included in the present analysis, of whom 302 (232+70; 60%) underwent surgery. FDG-PET was performed in 110 patients (23%), 70 of whom (64%) were considered eligible for surgery as compared with 232 of 359 patients (65%) who did not undergo FDG-PET. One year after surgery, 64% of all operated patients were completely seizure-free without auras (Engel class 1A); this was the case for 60% of the patients who had undergone FDG-PET. This difference was not statistically significant. The mean follow-up after surgery was 4.2 years, which ranged from 1 to 10 years. Of all operated patients, 51% reached complete seizure freedom at last

Figure 4.1. Patient flow chart, including the diagnostic tests and decisions



follow-up; this was the case in 48% of patients who had undergone FDG-PET. Again, this difference was not statistically significant.

On the basis of MRI and video-EEG findings, 231 patients were considered eligible for TLE surgery (figure 4.2); the taskforce nevertheless decided to perform FDG-PET in 16 of these patients (7%), in most cases because the MRI was not localizing or simply to confirm MRI findings. On the basis of FDG-PET findings, the decision to operate was changed, or intracranial monitoring was requested, in 4 of these patients (25%). Of the 68 patients considered ineligible for surgery on the basis of MRI and video-EEG findings, the taskforce reconsidered and decided to perform FDG-PET in 10 patients (15%). One patient was subsequently considered eligible for surgery; however, this patient did not become seizure-free after surgery. Most patients who underwent FDG-PET had inconclusive results after MRI and video-EEG monitoring. Of the 84 of 170 patients with inconclusive results who underwent FDG-PET, FDG-PET led to a final decision in 72 patients (figure 4.2: 47+25; 86%). Compared with the rest of the cohort, these 72 patients more often had normal MRI findings ($p<0.0001$), less often unilateral temporal abnormalities on MRI ($p<0.0001$), MRI and ictal EEG were less often concordant ($p<0.0001$), and videotaped semiology and ictal EEG were less often concordant ($p=0.027$) (table 4.1). The outcome after surgery of the operated patients with inconclusive results after MRI and video-EEG monitoring who underwent FDG-PET (63% seizure free) was comparable to that of all operated patients (64% seizure free). In total, FDG-PET findings were conclusive regarding surgical candidacy in 78 (figure 2: 4+2+72) of 469 patients (17%) referred for TLE surgery or in 78 of 110 patients (71%) investigated with FDG-PET. With the exception of interictal video-EEG, all included tests (MRI, video-EEG monitoring and FDG-PET findings) were associated with the final consensus decision regarding surgical candidacy (table 4.2). However, in isolation, none of the tests showed good prediction or discrimination for this decision.

Figure 4.2. Decision-making process per step of the presurgical work-up

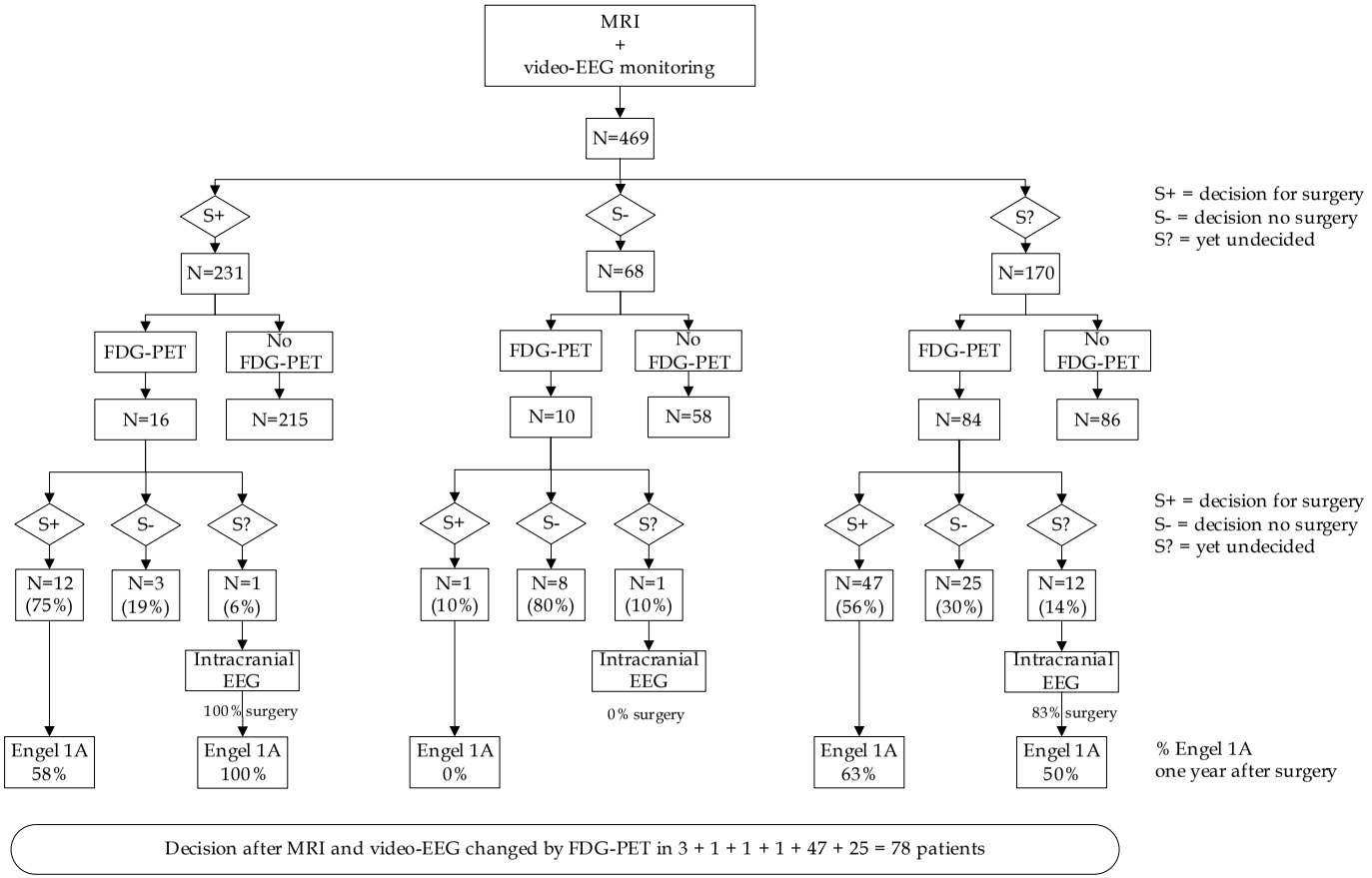


Table 4.1. Characteristics of the patient group with indecisive results after MRI and video EEG in whom FDG-PET results forced a decision compared to the rest of the cohort

	Decision forced by FDG-PET	
	Yes (N=72)	*No (N=397)*
Age (mean ± standard deviation)	33 ± 12	31 ± 13
Male sex	35 (0.49)	195 (0.49)
MRI normal	28 (0.39)	17 (0.04) **
MRI unilateral temporal	34 (0.47)	276 (0.70) **
MRI bilateral temporal	3 (0.04)	21 (0.05)
Interictal video-EEG unilateral temporal	21 (0.29)	129 (0.33)
Videotaped semiology temporal	30 (0.42)	206 (0.52)
Ictal video-EEG unilateral temporal	40 (0.56)	255 (0.64)
Concordance MRI – interictal video-EEG	23 (0.32)	142 (0.36)
Concordance MRI – videotaped semiology	13 (0.18)	106 (0.27)
Concordance interictal video-EEG – videotaped semiology	17 (0.24)	109 (0.28)
Concordance MRI – ictal video-EEG	14 (0.19)	179 (0.45) **
Concordance interictal video-EEG – ictal video-EEG	9 (0.13)	69 (0.17)
Concordance videotaped semiology – ictal video-EEG	11 (0.15)	105 (0.26) *

*Values represent number of patients (fraction), except for age; * Significant at 0.05-level; ** Significant at 0.01-level; Group differences were tested with Mann-Whitney U test (age) or chi-square*

Table 4.3 shows the contribution of FDG-PET combined with MRI and ictal EEG to the decision whether to perform surgery. The first row of each combination can be seen as 'the combined positive test result' and therefore reflects the positive decision predictive value (PDPV) of that test combination. The last row

Table 4.2. Two by two tables and decision predictive values (95% confidence intervals) of FDG-PET, MRI and video-EEG monitoring with the decision for or against surgery after the FDG-PET scan

	Decision after FDG-PET:				*Positive decision predictive value*[d]	*Negative decision predictive value*[e]
	Surgery N=60	*No surgery*[b] N=50	*Total* N=110	*P-value*[c]		
FDG-PET				0.009		
Unilateral temporal	41	22	63		0.65	0.60
Inconclusive[a] / normal	19	28	47		(0.53-0.77)	(0.45-0.72)
MRI				0.009		
Unilateral temporal	35	17	52		0.67	0.57
Inconclusive[a] / normal	25	33	58		(0.54-0.78)	(0.44-0.69)
Video-EEG interictal				NS		
Unilateral temporal	22	15	37		0.59	0.48
Inconclusive[a]	38	35	73		(0.43-0.74)	(0.37-0.59)
Video-EEG semiology				0.033		
Definitely temporal	32	17	49		0.65	0.54
Not localizing	28	33	61		(0.51-0.77)	(0.42-0.66)
Video-EEG ictal				0.035		
Unilateral temporal	39	23	62		0.63	0.56
Inconclusive[a]	21	27	48		(0.50-0.74)	(0.42-0.69)

[a] Inconclusive = not localizing to one temporal lobe; [b] For this analysis, the patient was ineligible for surgery when no consensus decision was reached after the FDG-PET; [c] Based on Chi square test; NS = not significant at 0.05-level; [d] Positive decision predictive value is the proportion of patients accurately predicted to be eligible for surgery; [e] Negative decision predictive value is the proportion of patients accurately predicted not to be eligible for surgery

can be seen as 'the combined negative test result', and therefore as the negative decision predictive value (NDPV) of that test combination. These values can be compared to the PDPV and NDPV of each test in isolation (table 2). Addition of FDG-PET improved the PDPV and NDPV of MRI from 0.67 and 0.57 to 0.77 and 0.68, respectively, and the PDPV and NDPV of ictal EEG from 0.63 and 0.56 to 0.80 and 0.67, respectively. The PDPV and NDPV of long-term interictal EEG increased from 0.59 and 0.48 to 0.71 and 0.62, and the PDPV and NDPV of seizure semiology increased from 0.65 and 0.54 to 0.86 and 0.70, respectively (data not shown).

Table 4.3. FDG-PET in combination with MRI and ictal EEG in relation to the decision for or against TLE surgery.

MRI	***FDG-PET***	***Decision after PET***		
		Surgery	***No surgery*** [b]	***Total***
Unilateral temporal	Unilateral temporal	26 (0.77[c])	8 (0.23)	*34*
Unilateral temporal	Inconclusive[a] / normal	9 (0.56)	7 (0.44)	*16*
Unilateral temporal	Discordant	0	2	*2*
Inconclusive[a] / normal	Unilateral temporal	15 (0.56)	12 (0.44)	*27*
Inconclusive[a] / normal	Inconclusive[a] / normal	10 (0.32)	21 (0.68[d])	*31*
Ictal EEG	***FDG-PET***			
Unilateral temporal	Unilateral temporal	28 (0.80[c])	7 (0.20)	*35*
Unilateral temporal	Inconclusive[a] / normal	11 (0.48)	12 (0.52)	*23*
Unilateral temporal	Discordant	0	4	*4*
Inconclusive[a]	Unilateral temporal	13 (0.54)	11 (0.46)	*24*
Inconclusive[a]	Inconclusive[a] / normal	8 (0.33)	16 (0.67[d])	*24*

Values represent number of patients (fraction of row total); [a] Inconclusive = not localizing to one temporal lobe; [b] For this analysis, a patient was considered ineligible for surgery when no consensus decision was reached after the FDG-PET; [c] Equivalent to the positive decision predictive value of combination of test results; [d] Equivalent to the negative decision predictive value of combination of test results

FDG-PET findings were discordant with MRI or video-EEG findings in nine patients, one of whom was still considered eligible for surgery. This patient did not become seizure-free.

Table 4.4. Sensitivity analysis: observed decisions for or against surgery and estimated decisions after imputation of FDG-PET results

Decision before FDG-PET	*Decision after FDG-PET*	*Observed (see figure 4.2)*				*After imputation*			
		N	*Cases*	*Fraction*	*95%CI*	*N*	*Cases*	*Fraction*	*95%CI*
Surgery	Surgery	16	12	0.75	0.51-0.90	232	197	0.85	0.80-0.89
	No surgery		3	0.19	0.07-0.43		32	0.14	0.11-0.23
No surgery	Surgery	10	1	0.10	0.02-0.40	NP			
	No surgery		8	0.80	0.49-0.94				
Indecisive	Surgery	84	47	0.56	0.45-0.66	169	110	0.65	0.58-0.72
	No surgery		25	0.30	0.21-0.40		44	0.26	0.20-0.33

95%CI = 95% confidence interval; NP= analysis not performed

Sensitivity analysis

Table 4.4 shows the results after imputation of the decisions expected to have been made if the patients who had not undergone FDG-PET had undergone FDG-PET. The proportion of decisions regarding surgical candidacy hardly changed after imputation in the patients who were considered eligible for surgery on the basis of MRI or video-EEG findings and in the patients with inconclusive results before FDG-PET. This indicates that the observed results (figure 4.2) for these patient groups were unlikely to have been biased. Unfortunately, imputation was methodologically impossible for the patients considered ineligible for surgery on the basis of MRI and video-EEG findings (the second arm in figure 4.2) as there were only ten cases in this group, of whom only one was considered eligible for surgery after FDG-PET.

Discussion

In 71% of the TLE patients who underwent FDG-PET, the FDG-PET results influenced the decision whether or not temporal lobe surgery could be performed, and in 17% of all referrals for TLE surgery, FDG-PET findings were conclusive regarding surgical candidacy. One year after surgery, 64% of operated patients were seizure free (Engel class 1A). These findings indicate that FDG-PET has important added value for the decision-making process regarding TLE surgery in a tertiary referral setting. This is supported by the increased positive and negative decision predictive values of MRI and video-EEG monitoring in combination with FDG-PET. FDG-PET seemed especially valuable when MRI findings were normal, or when ictal EEG and MRI findings were not concordant - which is in line with indications for FDG-PET in the literature. [78-80] Nevertheless, only 84 of 170 patients (49%) with indecisive results after MRI and video-EEG underwent FDG-PET. One can only guess why FDG-PET was not performed in the other patients. In the Netherlands, PET has always been available for epilepsy surgery purposes (although at first carried out in Liège, Belgium) and because most people have full medical insurance, financial considerations were unlikely to have had a role.

Although the role of FDG-PET in TLE surgery has been studied before, most studies have assessed FDG-PET as a single diagnostic test only or in relation to seizure outcome in operated patients only (the prognostic value of FDG-PET).[56] DellaBadia et al. did address the contribution of a combination of sleep-deprived EEG, MRI, and FDG-PET to the decision-making process.[36] They found that FDG-PET was the most sensitive test when used in isolation. The positive predictive value of the combination of any two tests (with or without FDG-PET) was higher than that of FDG-PET in isolation. However, DellaBadia et al. investigated fewer patients (69 versus 110 in our study). Ollenberger et al. also showed that FDG-PET had an impact on the clinical management of children referred for epilepsy surgery,[84] based on clinicians' personal point of view. They recommended that all children with epilepsy should undergo FDG-PET. However, most of the children in Ollenberger et al's study had extratemporal epileptic foci.

Some methodological limitations of our study need to be addressed. First, our study outcome was the final consensus decision on operability reached by our national taskforce. Although this is the best alternative in the absence of a formal reference standard[2;3;8;9] and the outcome one year after surgery (64% seizure free) was comparable to that reported in the literature,[13;14] there is no way to know whether patients were inappropriately rejected for surgery. Formally, only a randomized design (to operate or not) in patients referred for TLE surgery could settle this issue – which would in our view be unethical.

Second, the consensus decision of the multidisciplinary taskforce was based on all available information, including the results of FDG-PET under investigation. This might have introduced incorporation bias, which could have led to overestimation of the accuracy measures in tables 4.2 and 4.3.[8;9;20] However, as we had systematically documented all intermediate consensus decisions before and after FDG-PET, we could study the change in decision-making due to the FDG-PET results, bypassing this incorporation bias.

Third, in 75% of FDG-PET investigations a flumazenil PET (FMZ-PET)

was performed along with FDG-PET as part of scientific research.[75] In these patients, the consensus decision after FDG-PET might have been influenced by the results of the FMZ-PET investigation. However, FMZ-PET results were similar or less informative than the FDG-PET results in most patients (90%), which is in agreement with earlier studies showing that FMZ-PET is not superior to FDG-PET in detecting the ictal onset zone.[75;85]

Lastly, since the results of MRI, video-EEG, and PET studies were reduced to a few variables, some diagnostic information may have been missed or simplified. The choice of test result categories, however, was based on the literature, clinical practice, and considerations of objectivity and reproducibility.

We conclude that FDG-PET has added value to clinical decision-making in patients referred for TLE surgery. FDG-PET seems especially valuable when MRI and video-EEG monitoring are unable to localize the epileptic focus. FDG-PET findings influenced clinical decision-making in 71% of the patients investigated with FDG-PET and were conclusive regarding surgical eligibility in 17% of patients referred for TLE surgery.

CHAPTER 5

CHAPTER 5

The intracarotid amobarbital or Wada test: unilateral or bilateral?

SG Uijl

FSS Leijten

JBAM Arends

J Parra

AC van Huffelen

PC van Rijen

KGM Moons

Submitted 2007.

Abstract

Purpose. In the Netherlands, presurgical screening for temporal lobe epilepsy (TLE) includes the intracarotid amobarbital procedure (IAP), consisting of two consecutive injections of amobarbital, ipsilateral and contralateral to the epileptic focus. We studied whether a bilateral IAP has added value to a unilateral, ipsilateral IAP.

Methods. This population-based study included 183 consecutive patients referred between 1997 and 2002 for screening for TLE surgery who underwent bilateral IAP. Using multivariable modeling, we assessed the added value of bilateral IAP on the decision for surgery, resection size, amygdalohippocampectomy, postoperative seizure freedom, memory performance, and IQ change.

Results. Given the results from the unilateral IAP, the bilateral IAP had added prognostic value for postoperative change in verbal memory ($p<0.01$) and verbal IQ ($p<0.01$), especially if patients had a left-sided focus. In contrast, information provided by the contralateral IAP was not associated with decision-making or surgical strategy.

Conclusions. We conclude that a bilateral IAP has added value in predicting postoperative verbal memory and IQ. A bilateral IAP is currently not used to guide surgical strategy, but may be used for this purpose when verbal capacity is of particular concern in patients with a left-sided focus. In all other cases, IAP should be performed unilaterally.

Introduction

The intracarotid amobarbital procedure (IAP, Wada test) is part of the presurgical screening for temporal lobe epilepsy (TLE) surgery to assess language lateralization and the risk of developing post-surgical global amnesia. Often, two injections are applied: the first ipsilateral and the second contralateral to the presumed focus side. IAP is an invasive test with a complication rate of up to 1%.[86-88] The true value of the IAP, however, is increasingly under discussion.[89-91] Recently, the added value of the bilateral IAP in predicting memory decline after TLE surgery was debated.[92;93] This prompted us to systematically quantify the added value of the bilateral IAP beyond the unilateral IAP.

In the Netherlands, all patients referred for epilepsy surgery enter the same Dutch Collaborative Epilepsy Surgery Program (DCESP), a nation-wide tertiary referral program in which all patients undergo the same presurgical work-up.[17] After each single test, a multidisciplinary taskforce decides whether the patient will be eligible or ineligible for surgery, if additional tests are needed to make this decision, and what surgical strategy is needed. When a patient is considered eligible for surgery, a bilateral IAP is standardly performed. A minimum residual memory score after ipsilateral injection is an eligibility criterion for TLE surgery.[17;94]

The Dutch setting provided the ideal opportunity to quantify in a large series of patients the true value of the contralateral IAP in the surgical decision-making and in the prediction of postsurgical outcome. In the Dutch program, a minimum residual memory score after ipsilateral injection is an eligibility criterion for TLE surgery.[17;94] Therefore, our study concentrates on the role of the second, contralateral injection. As a bilateral IAP seems to predict memory decline after surgery,[89;91] we hypothesized it results would also be used in the surgical decision-making. Specifically, if the bilateral IAP indicates a high risk of memory decline, we expect a smaller surgical resection size in these patients.

Methods

Patients

This retrospective study included all consecutive patients who were referred to the Dutch Collaborative Epilepsy Surgery Program between July 1997 and July 2002 for diagnostic work-up to determine eligibility for TLE surgery. The present analysis focused on the 183 patients who were considered eligible for surgery (based on previous tests) and subsequently underwent a bilateral IAP. To address the aim to assess the added contribution of the second IAP injection to set the decision for or against surgery, all 183 patients were included. To address the other aims - assessing the added value of the second IAP to decide on the extent of surgery and the added prognostic or predictive value of postoperative outcomes - only the 178 patients who were actually operated were included.

Intracarotid amobarbital procedure

Both IAP injections were performed in the awake patient after transfemoral catheterization of the internal carotid artery, using the Seldinger technique. First, on the side of the expected seizure focus a small amount of radio-opaque contrast was given and a carotid angiogram was performed. The actual test then started and was monitored with EEG and videotaped. In adults, on average 125 mg amobarbital was injected; in children usually 100 mg, depending on weight and age. After 30 minutes, the same procedure was performed on the side contralateral to the expected focus. In case of insufficient amobarbital effect during the first injection, a repeated injection with a higher dose was given after 30 minutes.

After injection resulting in contralateral paresis of the arm, the neuropsychologist assessed language function during 2 to 3 minutes, testing object naming, comprehension of spoken and written tasks, picture description, spontaneous speech, and the Token Test.[95] Language dysfunction was defined by the occurrence of dysnomia, paraphasia or incongruous mistakes on comprehension tasks after injection.[94] Two-and-a-half minutes after the injection five items were presented to the patient to remember. Fifteen minutes after

injection, the patient was asked to recall each of these items by choosing one out of four visually presented alternatives. The delayed memory score consisted of the number of recalled items, each accounting for 20% of the sum score. If a wrong item was recalled, but the category was correctly named spontaneously (e.g. 'it was a card with a stamp'), this was scored as half correct (10%).[94] To undergo ipsilateral TLE surgery, a residual delayed memory score of at least 50% during the ipsilateral injection was required. More details of our IAP protocol can be found elsewhere [94].

Neuropsychological tests

A standard battery of neuropsychological tests was performed within 6 months before surgery, and repeated 6-9 months after surgery.[96] We specifically looked at results from tests of verbal and nonverbal memory. Verbal memory tests included (1) the Fifteen Word Test, a verbal learning test, which is a Dutch adaptation of Rey's Auditory Verbal Learning Test, which scores immediate and delayed recall; (2) the Visual Naming Task, a 15 item test of black-and-white drawings, which scores both number of errors and time to complete; (3) Digit Span Forward as a test of auditory alertness and audioverbal recall. The nonverbal memory test included the Rey-Osterreith Complex Figure Task with scoring of immediate and delayed reproduction. Initial preoperative test performance was expressed qualitatively as normal for verbal and nonverbal memory, or in the lower (lowest quartile of the distribution of the general population) or upper (highest quartile) range. Change in scores postoperatively was also expressed qualitatively as improved, unchanged or deteriorated. Furthermore, we assessed change in verbal IQ and performance IQ assessed with the Dutch version of the Wechsler Adult Intelligence Scale from 1970 (WAIS III),[97] within 6 months before and 2 years after surgery.

Surgery

In the Netherlands, eligible TLE patients usually undergo a tailored temporal lobe resection with amygdalohippocampectomy. In mesiotemporal lobe epilepsy with mesiotemporal sclerosis only, a standard resection with

amygdalohippocampectomy is performed and when appropriate surgery consists of a lesionectomy without amygdalohippocampectomy. Tailoring is done using intraoperative electrocorticography.[96] Selective amygdalohippocampectomy is not performed.

Study outcomes

To assess the contribution of the second IAP injection to the decision-making, the consensus decision by the Dutch multidisciplinary taskforce was taken as outcome. To study the influence of results from the second IAP injection on the extent of surgical resection, outcomes were the size of the lateral temporal resection in centimeters and whether or not the resection included an amygdalohippocampectomy.

The prognostic outcomes after surgery included postoperative seizure freedom, change in memory performance and IQ change. Postoperative seizure freedom was defined as the total absence of seizures (including auras, Engel classification IA) one year after surgery.[98] For memory performance, equal or improved postoperative verbal and nonverbal memory was defined as a positive outcome. Changes in verbal and performance IQ (post- minus preoperative values) were taken as continuous outcome variables.

Data analysis

We quantified in how many patients the positive decision for surgery before the IAP was altered into a decision not to perform surgery and we related this to the memory scores of the ipsilateral and contalateral IAP injection.

To assess the contribution of the contralateral IAP injection to the dichotomous decision for amygdalohippocampectomy we fitted two consecutive logistic regression models, one with only the results of the first ipsilateral IAP injection and one after adding the results of the second IAP injection. Models were fitted both for IAP memory score results and for IAP language lateralization results. The difference between the two models - to determine whether the second

injection had indeed added predictive value - was assessed with the likelihood ratio test. Similarly, for predicting the continuous outcome (surgical resection size), two consecutive linear regression models were fitted. The same analytical approach was used for quantifying the added prognostic value of the second IAP test to determine seizure freedom after surgery and change in memory performance (dichotomous outcome: logistic regression) and to determine change in IQ (continuous outcome: linear regression).

Results

The epileptic focus was left-sided in 104 (57%) out of 183 patients. Table 5.1 shows the patient characteristics. Five patients (3%) did not undergo surgery and 178 (97%) were operated on.

Table 5.1. Patient characteristics (mean ± standard deviation)

Preoperative characteristics		N=183
Sex (% male)		48
Age at onset epilepsy (years)		13 ± 9
Age at surgery (years)		35 ± 11
Focus side (% left)		57
MTS on MRI (%)		47
Other lesion on MRI (%)		27
Verbal memory performance	In lower quartile (%)	38
	Normal (%)	56
	In upper quartile (%)	6
Nonverbal memory performance	In lower quartile (%)	42
	Normal (%)	54
	In upper quartile (%)	4

Table 5.1. Continued

Preoperative characteristics		N=183
Verbal IQ		102 ± 15
Performance IQ		107 ± 15
Memory score during ipsilateral IAP		90 ± 16
Memory score during contralateral IAP		65 ± 31
Language lateralization	Left (%)	87
	Right (%)	6
	Bilateral (%)	7
	Ipsilateral to focus side (%)	49
	Contralateral to focus side (%)	44
Surgical and postoperative characteristics		N=178
Side of surgery (% left)		56
Intraoperative electrocorticography (%)		67
Intraoperative speech mapping (%)		13
Amygdalohippocampectomy performed (%)		94
Resection size (cm)		4.0 ± 1.3
Seizure freedom (% Engel 1A)		65
Seizure freedom (% Engel 1 or 2)		89
Verbal memory performance	Improved (%)	17
	Unchanged (%)	55
	Deteriorated (%)	28
Nonverbal memory performance	Improved (%)	22
	Unchanged (%)	66
	Deteriorated (%)	22
Postoperative verbal IQ		105 ± 15
Postoperative performance IQ		112 ± 14

Value of contralateral injection on surgical decision-making

The memory score on the ipsilateral IAP indicated that five patients (3%) were at risk of global amnesia. Nevertheless, one of these (left-sided focus) was considered eligible for a modified resection, i.e. lesionectomy of an oligodendroglioma without amygdalohippocampectomy. This decision was based on the results of the first IAP only in combination with findings from MRI and video-EEG monitoring. Of the 178 patients with an adequate memory score on the ipsilateral IAP, one patient experienced a spontaneous reduction in seizure frequency and severity and did not want to proceed with surgery. The results of the second IAP again played no role.

Surgery consisted of tailored anterior temporal resection. Given information from the first IAP, information from the second contralateral IAP had no added value on either amygdalohippocampectomy or resection size (table 5.2). This applies to the IAP memory results as well as to IAP language lateralization results.

Prognostic value of contralateral injection

Of the 178 operated patients, 115 (65%) were completely seizure free one year after surgery. Information from the second contralateral IAP had no added value to that from the first injection, in the prediction of seizure freedom one year after surgery (table 5.3). Language ipsilateral to the resection side (information from first injection) was predictive of worse seizure outcome, while bilateral language (information from both injections) seems more predictive of good seizure outcome. The latter, however, was not statistically significant. Furthermore, the predictive value of ipsilateral language function on a worse seizure outcome was fully explained by focus side: left-sided focus was associated with worse seizure outcome: OR=0.41 (95% CI: 0.21-0.79, data not shown).

A combination of a high memory score on ipsilateral and a low score on contralateral injection was associated with better verbal memory outcome after surgery (table 5.4). For language lateralization there was no added predictive value

of the contralateral IAP.

Table 5.2. Predictive value of memory function and language of the two IAP injections on the extent of surgery.

Prediction of extent of surgery	*First injection*		*First and second injection*	
	OR	***95% CI***	***OR***	***95% CI***
Amygdalohippocampectomy (yes/no)				
IAP memory score (per 10%)				
Ipsilateral injection	1.08 [a]	1.04-1.13 **	1.08	1.04-1.13 **
Contralateral injection			0.99	0.97-1.01
IAP language (yes /no)				
Language ipsilateral to focus	0.28	0.06-1.33	0.28	0.06-1.38
Language bilateral			0.83	0.09-7.41
Resection size (cm)	***RC***	***95% CI***	***RC***	***95% CI***
IAP memory score (per 10%)				
Ipsilateral injection	0.003 [b]	-0.01 – 0.02	0.003	-0.01 – 0.02
Contralateral injection			0.002	0.00 – 0.01
IAP language (yes /no)				
Language ipsilateral to focus	-0.549	-0.92 – -0.18 **	-0.564	-0.94 – -0.19 **
Language bilateral			0.164	-0.62 – 0.95

*OR = odds ratio; RC = regression coefficient; 95% CI = 95% confidence interval; ** p-value < 0,01*

[a] this OR means that the odds (probability) of amygdalohippocampectomy is 1.08 times higher for every 10% increase in the memory score on ipsilateral IAP.

[b] this RC represents the slope of the plot between the resection size in cm and memory score on ipsilateral IAP per 10%, i.e. with a RC of 0.003 the regression line is almost horizontal, indicating no clinically relevant association between resection size and memory score.

Table 5.3. Predictive value of memory function and language of the two IAP injections on seizure freedom.

Prediction of seizure freedom (yes / no)	*First injection*		*First and second injection*	
	OR	***95% CI***	***OR***	***95% CI***
IAP memory score (per 10%)				
Ipsilateral injection	1.02	1.00-1.04	1.02	1.00-1.04
Contralateral injection			0.99	0.98-1.01
IAP language (yes / no)				
Language ipsilateral to focus	0.49	0.26-0.93 *	0.45	0.23-0.85 *
Language bilateral			3.54	0.72-17.33 [a]

*OR = odds ratio; 95% CI = 95% confidence interval; * p-value < 0.05*

[a] *the wide 95% CI is because only 13 patients had bilateral language lateralization.*

In general, verbal and performance IQ increased after surgery (table 5.1, p-value<0.01 for both). A bilateral IAP showing language contralateral to the focus side or bilateral language was predictive of a postoperative increase in verbal IQ, although information from the first IAP injection only conferred no prognostic information for IQ change (table 5.5).

Table 5.4 Predictive value of memory function and language of the two IAP injections on the post-operative verbal and nonverbal memory change.

Prediction of memory change	*First injection*		*First and second injection*	
	OR	*95% CI*	*OR*	*95% CI*
Verbal memory				
IAP memory score (per 10%)				
Ipsilateral injection	1.02	1.00-1.05 *	1.02	1.00-1.05 *
Contralateral injection			0.98	0.97-0.99 **
IAP language (yes / no)				
Language ipsilateral to focus	0.14	0.06-0.30 **	0.12	0.06-0.27 **
Language bilateral			4.69	0.95-23.22
Nonverbal memory				
IAP memory score (per 10%)				
Ipsilateral injection	1.04	1.02-1.07 **	1.04	1.02-1.07 **
Contralateral injection			0.99	0.98-1.00
IAP language				
Language ipsilateral to focus	0.34	0.14-0.82 *	0.35	0.15-0.85 *
Language bilateral			0.76	0.18-3.12

*OR = odds ratio; 95% CI = 95% confidence interval; * p-value < 0.05; ** p-value < 0.01*

Table 5.5. Predictive value of memory function and language of the two IAP injections on the post-operative change in verbal and performance IQ.

Prediction of IQ change	*First injection*		*First and second injection*	
	RC	*95% CI*	*RC*	*95% CI*
Verbal IQ				
IAP memory score (per 10%)				
Ipsilateral injection	0.064	-0.02 – 0.15	0.062	-0.02 – 0.15
Contralateral injection			-0.037	-0.08 – 0.00
IAP language (yes / no)				
Language ipsilateral to focus	-1.884	-4.31 – 0.54	-2.611	-5.02 – -0.20 *
Language bilateral			7.908	2.92 – 12.90 *
Performance IQ				
IAP memory score (per 10%)				
Ipsilateral injection	0.057	-0.05 – 0.16	0.058	-0.05 – 0.16
Contralateral injection			0.018	-0.03 – 0.07
IAP language (yes / no)				
Language ipsilateral to focus	1.559	-1.34 – 4.56	1.367	-1.59 – 4.32
Language bilateral			2.091	-4.03 – 8.21

*RC = regression coefficient; 95% CI = 95% confidence interval; * p-value < 0.05*

Subgroup analyses

To assess whether the above findings were different across specific patient characteristics, the analyses were repeated for four subgroups: mesiotemporal sclerosis on the MRI (N=85); a lesion on the MRI (N=48); a left-sided and a right-sided epileptic focus (N=100 and N=78, respectively). No different results were found. The presence of a left-sided epileptic focus fully explained the added value of the memory score of the contralateral IAP on change in verbal memory: OR=0.98

(95% CI: 0.97-0.99), while no added value was found in the subgroup with a right-sided focus.

Discussion

Clinical findings

This study assessed the true or added value of the bilateral IAP in the presurgical evaluation of TLE, as compared to the unilateral IAP. More specific, we looked whether the prognostic value of the bilateral IAP for memory performance after surgery, was actually reflected in the extent of the surgical resection. The contralateral IAP showed added prognostic value for both postoperative verbal memory (using information from memory scores) and verbal IQ (from language representation), especially in left-sided cases. However, we did not find any influence or added value of the contralateral IAP on the decision to operate, nor on the extent of the surgical resection. This indicates that in the Netherlands, contralateral IAP information is currently not used in clinical decision-making.

An explanation for the lack of incorporation of contralateral IAP results in surgery strategy may be that the neurosurgeons in the Netherlands rely on electrocorticographical tailoring of the resection, regardless of IAP results. Also, the clinical relevance of a decline in postoperative memory on neuropsychological tests is not clear, as it may not reflect the patient's experience. Thus, a patient with a significant decline in verbal memory after surgery, may nevertheless report an overall improvement in quality of life.[99]

The use and value of IAP in TLE surgery, is increasingly under debate.[89-91] Two recent studies showed that IAP, either unilateral or bilateral, is not essential to predict memory decline after surgery when the results of other, noninvasive diagnostic tests are taken into account.[92;93] We were not able to test the clinical value of the ipsilateral injection - which is commonly used to assess the safety of a planned hippocampal resection (memory) and tailored neocortical resection (language).[16;100;101] We rather focused on the added value of a bilateral compared to a unilateral IAP. Two other studies also evaluated the independent prognostic

value of the contralateral IAP injection on postoperative verbal memory performance after TLE surgery. Sabsevitz et al. assessed both the ipsilateral and contralateral IAP and Stroup et al assessed the contralateral IAP.[102;103] Our results are in line with both studies, i.e. results from the contralateral IAP were predictive of postoperative verbal memory decline. Most IAP studies used memory asymmetry scores to predict seizure freedom and memory outcome after surgery.[94;104-106] The prognostic value of asymmetry scores (ipsilateral minus contralateral memory score) was confirmed by our data for change in verbal and nonverbal memory performance (both OR 1.02; 95% CI 1.01-1.03) and for change in performance IQ (RC 4.79; 95% CI 3.00-6.58). Interestingly, and, as far as we know no-one explored this earlier, a consequent influence on surgical strategy was not confirmed by our data. This shows that the true value of a test may not be valued by the very clinicians who use it.

In patients who fail the IAP, Lacruz et al. showed that in case of a low memory score after ipsilateral injection, selective amygdalohippocampectomy has a more favorable outcome than standard temporal lobectomy.[107] In the Dutch program, selective amygdalohippocampectomy is not performed. We did find that patients with a higher residual memory score on ipsilateral injection were more likely to undergo (additional) amygdalohippocampectomy. As expected, in patients with language ipsilateral to the focus side, resections ended up smaller (mean resection size of 3.8 cm compared to 4.3 cm; p-value <0.01). Nevertheless, no added value of the contralateral IAP was found.

Methodological issues

Some methodological issues merit consideration. IAP protocols notoriously differ between centers, especially with regard to timing of presentation, modes and number of memory items. Such a lack of standardization somewhat limits the extensibility of our results and may explain discrepancies with other studies. Interpretation of IAP results may also differ. Our IAP protocol used the memory score after ipsilateral injection as eligibility criterion for TLE surgery.[94] In the Dutch

program, the IAP is considered a test of functional memory reserve of the hemisphere contralateral to the side of injection.[101;108;109] In other centers it is asymmetry in memory scores after ipsilateral and contralateral injections that is used as pass/fail criterion.[94;107]

Second, in our protocol the two IAP injections were performed 30 minutes apart. Other centers use longer periods in between the two injections, or even perform them on different days.[110] Performing a second injection on the same day implicates a risk of misclassification of the memory score after the second injection.[110;111] Performing the second injection on another day, however, is inconvenient to the patient and probably increases the risk of morbidity.[112] An increasing number of international centers now perform IAP unilaterally.[113]

Third, the decision whether or not to perform surgery was a consensus decision by the national Dutch taskforce. Since a formal reference standard to determine (in)eligibility for TLE surgery is lacking, such a consensus decision is generally considered the best alternative.[2;3;8;9] Nevertheless, we do not know how many patients were actually inappropriately operated or rejected for surgery. We believe the decision for surgery of the Dutch taskforce was adequate, since the seizure outcome in our operated patients is comparable to that reported in the literature, 65% of all patients being seizure free without auras (Engel class 1A) one year after TLE surgery.[13;14]

Finally, the neuropsychologists involved in postoperative tests were not blinded to the results of the IAP, which might have introduced bias in interpreting the results.[8] Also, a learning curve between preoperative and postoperative tests could have influenced the results. The influence of learning curve effects on the results is minimized by e.g. the use of different sets of word lists in the repeat test. Also, the event of surgery between the tests will mitigate the learning curve effect.

Conclusion

We confirm that in the prediction of postoperative verbal memory decline and verbal IQ change, the contralateral IAP injection has added value, especially in left-

sided TLE surgery. Nevertheless, we found no evidence that information from the contralateral IAP is currently used in surgical decision-making. We propose that a bilateral IAP should be reserved for patients with a left-sided focus for whom verbal memory and IQ are especially critical, e.g. to professional performance. In other cases, our data do not support the routine use of a bilateral IAP. Refraining from a contralateral injection in these cases would improve the safety and cost-effectiveness of TLE surgery.

CHAPTER 6

CHAPTER 6

Prognosis after temporal lobe epilepsy surgery: The value of combining predictors.

SG Uijl

FSS Leijten

JBAM Arends

J Parra

AC van Huffelen

KGM Moons

Submitted 2007.

Abstract

Although many independent predictors of seizure freedom after temporal lobe epilepsy surgery have been identified, their combined predictive value is largely unknown. Using a large database of operated patients, we assessed the combined predictive value of a multivariable model including previously reported independent predictors.

The database comprised a cohort of 484 Dutch patients who underwent temporal lobe surgery for drug resistant temporal lobe epilepsy. Good outcome was defined as Engel class 1, one year after surgery. All predictors previously reported in the literature were assessed; independent predictors had to have a multivariable p-value of <0.20 to be included.

The final multivariable model included independent predictors obtained from the patient's history (absence of tonic-clonic seizures, absence of status epilepticus), and MRI (ipsilateral MTS, space occupying lesion), video EEG (absence of ictal dystonic posturing, concordance between MRI and ictal EEG), and FDG-PET (unilateral temporal abnormalities) findings. The model had an expected ROC area of 0.63 (95%CI 0.57 to 0.68) for new patient populations. Intracranial monitoring and surgery-related parameters (including histology) were not independent predictors of seizure freedom after surgery. Of the patients with a high probability of seizure freedom, 85% were seizure free one year after surgery; however, of the patients with a high risk of not becoming seizure free, 40% were seizure free one year after surgery.

In conclusion, preoperative and intraoperative findings were only moderate predictors of postoperative seizure freedom after temporal lobe epilepsy surgery, in spite of many predictors that are associated with outcome. It is particularly difficult to predict who will not become seizure free after surgery.

Introduction

Epilepsy surgery is an effective treatment for medically intractable epilepsy, especially in patients with temporal lobe epilepsy (TLE). After TLE surgery, 60% to 70% of patients become seizure free and 90% of patients achieve a worthwhile reduction in seizure severity.[13;14] The presurgical work-up for epilepsy surgery is stepwise and complex, and contradictory findings from standard tests (history, seizure semiology, EEG, and MRI) with regard to lateralization or localization of the seizure focus necessitate additional tests of increasing invasiveness and cost (e.g. ictal SPECT, PET, intracranial EEG recordings). To be able to inform candidates for TLE surgery about their chances of postoperative seizure freedom, it is important to define which characteristics are true or independent predictors of seizure freedom after surgery. This requires a multivariable study approach.[67] The ultimate goal would be to develop a simple clinical prediction model or rule to predict the chance of seizure freedom after surgery for individual patients undergoing TLE surgery.

Previous studies of predictors of postoperative seizure freedom using multivariable analysis differ in their methodology and results.[47;114-129] Although potential independent predictors have been identified, the predictive value of combinations of these independent predictors (i.e., the value of these predictors combined in a single prediction model) has been investigated in only one study, which included patients with all types of epilepsy and not only TLE.[47] The aim of the present study was therefore to use a large homogeneous database of patients who underwent TLE surgery to quantify the predictive accuracy of the combination of previously reported predictors of seizure freedom. Thus, in contrast to the previous chapters of this thesis, this chapter focuses solely on patients who underwent epilepsy surgery.

Patients and methods

Patients

In the Netherlands, all patients referred for epilepsy surgery enter the Dutch

Collaborative Epilepsy Surgery Program, a nationwide tertiary referral program, in which each referred patient undergoes the same step-wise presurgical work-up. Decisions are taken by a multidisciplinary team. The present retrospective prognostic cohort study included a consecutive cohort of 484 patients (in 16 years) who underwent temporal lobe resection.

Surgery consisted of temporal lobe resection, tailored by acute electrocorticography including amygdalohippocampectomy (79%),[73] a standard resection (first two to three centimeters from the temporal pole) with amygdalohippocampectomy (15%), or a tailored lesionectomy without amygdalohippocampectomy (6%).

Prognostic predictors

We selected previously reported pre- and intraoperative predictors of seizure freedom after TLE surgery (see table 6.1).[47;114-129] We also included four potential predictors suggested by the members of the Dutch Collaborative Epilepsy Surgery Program, namely, absence of atypical features for TLE in videotaped seizures, defined as a somatosensible aura or a tonic, hypermotoric or atonic seizure; posterior temporal ictal onset during EEG monitoring; (ipsilateral) delayed anterior temporal theta onset in ictal EEG as described by Risinger et al.[63]; and the side of surgery (left versus right). These potential predictors have not been investigated before.

Prognostic outcome

Outcome was classified according to the Engel classification, one year after surgery. The outcome was dichotomized as Engel class 1 (including all subcategories), i.e. absence of disabling seizures, versus Engel class 2 or higher.[98]

Data collection

Predictors and outcome were retrieved for all 484 patients. Because each step of the presurgical work-up and the postsurgical follow-up is registered, we were able to

Table 6.1. Potential predictors of postoperative seizure freedom, investigated in our study.

History	*MRI*	*Video EEG*	*Additional tests*	*Surgery*
Female sex[128]	Abnormal MRI[46;116;122;126;129]	No ictal dystonic posturing[118]	Unilateral temporal abnormalities on FDG_PET[116]	Larger resection size (in cm)[129]
Febrile seizures[129]	MTS ipsilateral to resection side[119;120;125-129]	No bilateral interictal spikes[46;114;115]	Intracranial monitoring performed[46;114;129]	Postoperative discharges during acute eectrocorticography[129]
Shorter epilepsy duration (in years)[118;124]	Space occupying lesion ipsilateral to resection side[117;122;129]	No extratemp interictal spikes[123]		MTS on histology[128]
Higher age at start epilepsy (in years)[121]	Concordance of MRI & EEG results (both unilateral temporal)[129]	Concordance of interictal & ictal EEG results (both unilateral temporal)[127]		No cortical dysgenesis on histology[115]
No tonic clonic seizures[118;120;123;126] [a]				
No status epilepticus[122]				
Higher total IQ score[121;124] [b]				
Younger age at surgery (in years)[119;125;128]				

[a] *Including secondary generalized tonic clonic seizures;* [b] *Total IQ used as indicator for mental retardation[121] or need for special schooling[124]*

build a research database in which all information on predictors and outcome was coded as described above. During encoding, kappa analyses were performed between the two scoring researchers (SU and AC) and two independent experts (FL, JA), to ensure uniformity. As previously described, only variables with kappa values of 0.70 or higher were included.[18;19;130]

Data analysis

After univariable analysis, the predictors of postoperative seizure freedom were included in an overall multivariable logistic regression model. We assessed whether continuous predictors needed to be transformed, using restricted cubic splines.[67] This model included all predictors from basic preoperative work-up (i.e., from patient history, MRI, and video EEG monitoring). Predictors were excluded from this overall model if the sign of the multivariable regression coefficient was not considered plausible compared to the performance of the predictor in earlier studies, according to the sign OK method.[67;131] Furthermore, the model was reduced by step-wise exclusion of the least contributory predictors (defined as a p-value higher than 0.20, based on the log likelihood ratio test), to determine which predictors independently contributed to the prediction of seizure freedom (model 1). We then assessed the value of additional presurgical tests. In model 2, we added unilateral temporal abnormalities on FDG-PET to model 1, to assess its incremental predictive value, and in model 3 we additionally included intracranial monitoring. In model 4, we also included operative predictors identified from the literature.

The ability of each model to discriminate between postoperative seizure freedom or not was quantified using the area under the receiver operating characteristic curve (ROC area). Agreement (calibration) between the predicted and observed rates of seizure freedom was assessed with the Hosmer-Lemeshow statistic (high p-values indicating good calibration) and a calibration plot.

To prevent optimistic predictions in new patient populations, the internal validity of the prognostic models was studied with bootstrapping

techniques (100 samples).[67] The average difference in performance between the bootstrap samples and the original data gives an impression of the optimism of the model in new patients. Based on these bootstrap results, the ROC area and regression coefficients (odds ratios) of the predictors were corrected for optimism.

As some values were missing and missing values usually do not occur at random, we imputed the missing values to prevent bias, using single imputation by linear regression with the addition of a random error term.[66;83] FDG-PET was not performed in all patients, but was usually performed in patients with inconclusive results after MRI and video EEG monitoring. Imputation of FDG-PET results in patients in whom FDG-PET was actually not performed enabled us to assess the independent value of FDG-PET, as described previously.[66;83;130]

Statistical analyses were performed with S-plus version 6.2 (Insightful Corporation, Seattle, Washington, USA).

Results

Of the 484 patients, 356 patients (incidence 74%, 95% confidence interval (CI): 0.69-0.77) were seizure free (Engel class 1) one year after surgery.

The univariable associations between predictors and outcome are presented in figure 6.1. In the multivariable model, the two continuous predictors 'age at time of surgery' and 'duration of epilepsy' were each included as square root. Reduction of the original model based on history, MRI, and video EEG monitoring findings yielded six independent predictors of seizure freedom (model 1, table 6.2): age at time of surgery, absence of tonic-clonic seizures or status epilepticus in the patient's history, presence of ipsilateral MTS or a space occupying lesion on the MRI, and absence of ictal dystonic posturing. None of the extra predictors proposed by the members of the Dutch Collaborative Epilepsy Surgery Program were of added predictive value to this reduced model.

FDG-PET abnormalities was an independent predictor of seizure freedom (OR = 1.47; 95% CI 0.95 to 2.29; p-value: 0.09) (model 2), whereas intracranial monitoring (OR = 1.14; 95% CI 0.62 to 2.07; p-value 0.68) and operative

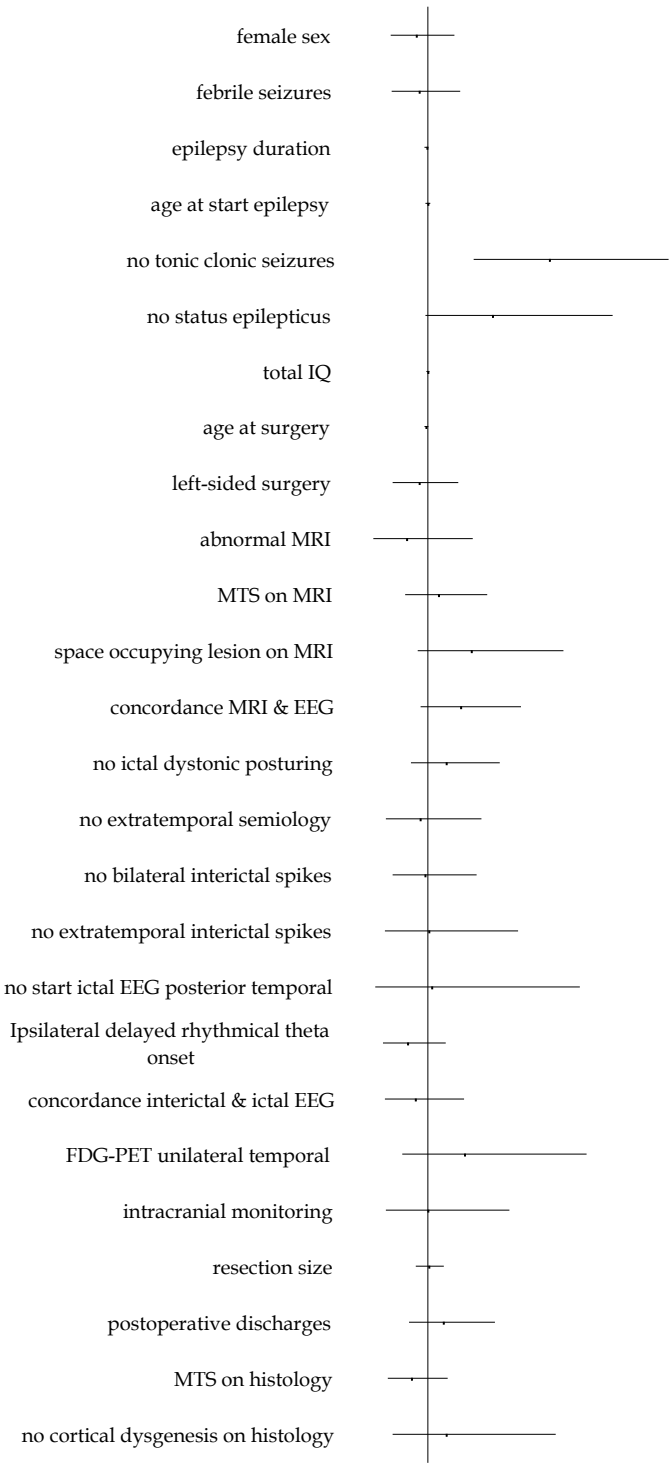


Figure 6.1. Univariable associations of each potential predictor with Engel class 1 (yes / no) as outcome. Lines represent odds ratio's with 95% confidence intervals, reference line at 1

Table 6.2. Models including only the independently contributing predictors for postoperative seizure freedom. Model 1 includes predictors from history, MRI and video EEG; model 2: model1+ FDG-PET result; model 3: model 2 + intracranial monitoring; model 4: model 3 + surgical predictors.

	Model 1		*Model 2*		*Model 3*		*Model 4*	
	Odds Ratio (95% CI)	*P-value*	*Odds Ratio (95% CI)*	*P-value*	*Odds Ratio (95% CI)*	*P-value*	*Odds Ratio (95% CI)*	*P-value*
no tonic clonic seizures	2.24 (1.40-3.58)	0.001	2.31 (1.44-3.70)	0.001	2.32 (1.45-3.73)	<0.01	2.32 (1.45-3.73)	<0.01
no status epilepticus	1.62 (0.88-2.98)	0.12	1.54 (0.83-2.84)	0.17	1.52 (0.82-2.82)	0.18	1.45 (0.78-2.71)	0.24
age at surgery [a]	0.84 (0.68-1.04)	0.10	0.83 (0.67-1.03)	0.09	0.83 (0.67-1.03)	0.09	0.84 (0.68-1.05)	0.12
MTS	1.63 (1.03-2.58)	0.04	1.61 (1.02-2.57)	0.04	1.59 (0.99-2.55)	0.06	1.80 (1.05-3.08)	0.03
space occupying lesion on MRI	1.67 (0.92-3.02)	0.09	1.68 (0.93-3.03)	0.09	1.63 (0.89-2.99)	0.11	1.57 (0.85-2.90)	0.15
no ictal dystonic posturing	1.34 (0.87-2.05)	0.19	1.36 (0.89-2.10)	0.16	1.35 (0.88-2.08)	0.18	1.36 (0.87-2.12)	0.17
FDG-PET unilateral temporal	na [b]		1.47 (0.95-2.29)	0.09	1.47 (0.95-2.29)	0.09	1.50 (0.96-2.35)	0.07
intracranial monitoring performed	na		na		1.14 (0.62-2.07)	0.68	1.14 (0.62-2.13)	0.67
resection size	na		na		na		1.02 (0.86-1.20)	0.86
postoperative discharges	na		na		na		1.15 (0.76-1.77)	0.51
MTS on histology	na		na		na		0.78 (0.46-1.34)	0.37
no cortical dysgenesis on histology	na		na		na		1.17 (0.55-2.49)	0.68

[a] *included as square root, see text;* [b] *na = not applicable*

predictors (model 4) were not.

The Hosmer-Leweshow test indicated good calibration, with a p-value of 0.79 for model 1, 0.35 for model 2, 0.47 for model 3, and 0.57 for model 4. This was confirmed by the calibration plots (not shown).

Model 2, based on predictors from the patient's history, and MRI, video EEG, and FDG-PET findings, was the best prediction model, with an ROC area of 0.66 (0.60-0.70). After correction for optimism, based on bootstrapping, this ROC area was reduced to a ROC area of 0.63 (95% CI 0.57 to 0.68), a value that can be expected if this model is used with other similar patient populations.

Table 6.3 shows the number of patients with and without seizure freedom after one year, across the probability categories predicted by model 2. The observed incidence of seizure freedom increased from 40% in the lowest probability group to 85% in the highest probability group. The risk of not becoming seizure free ranged from 15% in the group with the highest probability of seizure freedom to 60% in the lowest. This means that 40% of patients with the highest risk of not achieving seizure freedom were nevertheless seizure free one year after surgery.

Table 6.3. Number (%) of patients with or without seizure freedom after one year over the probability categories estimated by model 2 (see table 2). N=484.

Estimated probability based on model 2 in table 2	*Seizure freedom* N=356	*No seizure freedom* N=128
<0.45 (N=5; 1% of 484)	2 (40%)	3 (60%)
0.45-0.60 (N=52; 11%)	31 (59%)	21 (41%)
0.60-0.70 (N=112; 23%)	74 (66%)	38 (33%)
0.70-0.80 (N=161; 33%)	118 (73%)	43 (26%)
> 0.80 (N=154; 32%)	131 (85%)	23 (15%)

Discussion

We assessed all 22 predictors found in earlier multivariable studies on seizure freedom after TLE surgery[47;114-129] and identified seven independent predictors of postoperative seizure freedom, i.e., younger age at time of surgery, a history without tonic-clonic seizures, a history without status epilepticus, MRI with ipsilateral MTS, MRI with space occupying lesion, no dystonic posturing during the seizure, and unilateral temporal abnormalities on FDG-PET. The other predictors from the basic diagnostic work-up, additional diagnostic tests, and opertive data did not independently contribute to the prediction of postoperative seizure freedom. Our final model included all predictors reported by Janszky et al., Jeong et al. and Spencer et al..[117;119;120]

Our study presents an overall predictive value, i.e., a measure of how the use of such a model would discriminate between postoperative seizure freedom or not. This overall predictive value of the combination of predictors was moderate, with a ROC area 0.63. This means that we were unable to formulate a simple and stable prediction rule to predict seizure freedom that could be used to inform patients. The model can be used to indicate 'risk' categories for postoperative seizure freedom, however, it performs insufficiently to be used for individual patients to discriminate between becoming and not becoming seizure free.

Of earlier studies, only the one by Armon et al. included a measure of the performance of their model in predicting postoperative seizure freedom.[47;118] Armon et al. found a Somers' D of 0.47, or a ROC area of 0.74 without correction for optimism, on the basis of five preoperative predictors: ipsilateral imaging abnormality, ipsilateral EEG localization (ictal and interictal), intracranial EEG recordings, temporal lobe resection, and age.[47] Since their study involved patients who had undergone temporal or extratemporal resections, their model is not directly comparable to ours. However, the predictors 'ipsilateral imaging abnormality' and 'age' were also included in our model.

Unfortunately, other studies predicting postoperative seizure freedom did not present the overall accuracy of their model (nor could this be reconstructed

with the data provided). The wide variation of preoperative predictors reported in the literature and the moderate overall predictive value of our own model indicate that it is difficult to predict of postoperative seizure freedom one year after TLE surgery. In prognostic medical research, as in all areas of life, prediction becomes more difficult the further ahead we want to predict.[132] This means that the presence or absence of an independent predictor in an individual patient cannot directly be associated with an increased or decreased chance of becoming seizure free after surgery.

To appreciate our results, some methodological aspects need to be discussed. First, the study outcome measure was Engel class 1, one year after surgery. We reanalyzed the data with the outcome absolute seizure freedom (Engel class 1A) one year after surgery, which led to the same results, i.e., the same independent predictors were identified. Secondly, we wanted to include ancillary tests, such as FDG-PET, which were not performed in all patients. FDG-PET was performed in 188 of 484 patients, mostly when MRI and video EEG monitoring results were inconclusive. Imputation of FDG-PET results in patients in whom FDG-PET was not performed, as described earlier, enabled us to assess the independent value of FDG-PET in the complete patient population.[130] We reached the same conclusion when we restricted our analysis to the subgroup of 188 patients in whom FDG-PET was performed. Thirdly, the predictors were necessarily reduced to essentials for categorization. Since the number of predictors that can be included a prognostic model is limited, we only included previously reported predictors of seizure freedom. This obviously does not fully reflect the subtle nuances of interpretation that often arise in clinical practice, and thus the model does not comprise all possible information; these complexities necessarily have been obscured.

In conclusion, whereas the results of many preoperative tests in TLE surgery have a statistically significant association with postoperative seizure freedom, in combination they are only moderate predictors of postoperative

seizure freedom. It is particularly difficult to predict the absence of postoperative seizure freedom. Unfortunately, currently available data do not yet allow the development of a robust prediction rule for postoperative seizure freedom. More refined (software) analysis of existing tests, new diagnostic tests such as EEG-fMRI, and even genetic analysis, may provide future opportunities to improve the prediction of postoperative seizure freedom.

CHAPTER 7

CHAPTER 7

Is epilepsy surgery utilized to its full extent?

SG Uijl
KGM Moons
FSS Leijten
PH Veltman
A Budde
CA van Donselaar

Submitted 2007.

Abstract

It has been stated that epilepsy surgery as a treatment is underutilized. In two random samples of epilepsy patients, one from a secondary and one from a tertiary epilepsy facility, we established how many patients should have been and were actually referred to the Dutch national taskforce for presurgical evaluation.

Using national guidelines for referral, of 578 evaluated patients with epilepsy, 95 patients (16%) should have been referred for presurgical evaluation but only 22 (4%) were actually referred. An expert panel, which reviewed clinical data from the 73 cases that were not referred, thought that 4 of these patients (5%) were potential candidates for presurgical evaluation and that diagnostic testing was insufficient in another 12 (16%). Our results show that, in the Netherlands, 1.3 to 2.4 times as many patients treated in secondary care should be referred for presurgical evaluation as were actually referred and 1.1 to 1.4 times as many patients treated in tertiary care.

We confirm that epilepsy surgery is underutilized in the Netherlands. Neurologists should be more aware of current guidelines, make better use of available non-invasive diagnostic tests, and discuss surgery as treatment option with their patients with drug-resistant epilepsy.

Introduction

In 2001, Jerome Engel jr. stated that epilepsy surgery in patients with drug-resistant focal epilepsy is one of the most neglected successful treatments worldwide.[15] The interval between onset of seizures and epilepsy surgery is 18.8 years on average,[133] whereas guidelines already advise screening for epilepsy surgery when patients have persistent seizures after two consecutive years of medical treatment and when two or three first-line antiepileptic drugs have failed.[13;134;135] On the basis of this information, we investigated whether epilepsy surgery is underutilized in the Netherlands and, if so, sought , to quantify the magnitude of the problem and identify reasons for underutilization.

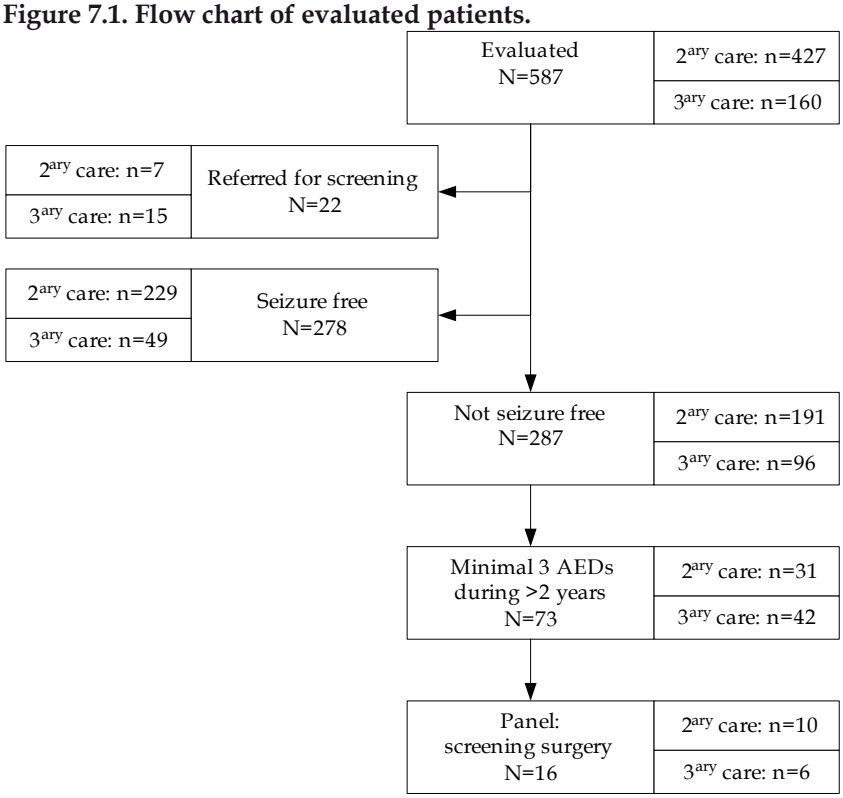
Methods

We collected two samples of adult patients who were diagnosed with, and medically treated for, epilepsy, one from a general hospital and one from a tertiary epilepsy clinic. In each center, we took a random sample of the files of patients treated for epilepsy in 2005, excluding patients who had been referred for presurgical evaluation and patients who had been seizure free for at least six months at the time of their last visit. The files of patients who had not been previously referred for presurgical evaluation, who had not been seizure free, and who had been treated for at least two consecutive years with three or more antiepileptic drugs were evaluated by an expert panel of two independent epileptologists (FL and PV) who are participants in the national presurgical evaluation program for epilepsy surgery. The expert panel determined whether patients were candidates for the presurgical evaluation program or whether they were potential candidates, i.e., whether additional diagnostic tests (MRI according to special epilepsy protocol, video EEG monitoring) were needed to determine candidacy for presurgical evaluation. The attending physicians of these potential candidates were asked why presurgical evaluation had not been considered.

Results

Figure 7.1 shows the flow chart of the random sample of 587 patients, 427 from the general hospital and 160 from the epilepsy center. Of these, 22 patients (4%) had previously been referred to the presurgical evaluation program and 278 patients (47%) had been seizure free for at least six months. In the general hospital, 191 of 427 patients (45%) had not been seizure free and in the epilepsy center 96 of 160 patients (60%). Of these 287 (191+96) patients, 73 (25%) had had seizures for at least two years and had been treated in this period with at least three antiepileptic drugs. The expert panel evaluated these 73 patients and concluded that 4 (2 in secondary and 2 in tertiary care) were candidates for presurgical evaluation. Another 12 patients were considered potential candidates, pending relevant additional tests.

Figure 7.1. Flow chart of evaluated patients.



The other 57 (78% of the 73) patients were ineligible for surgery due to type of epilepsy (40%), low seizure frequency or only nocturnal seizures (32%), contraindications (18%), age (7%), or rejection of surgery by the patient (3%).

The attending physicians of the 16 (4+12) patients identified as candidates or potential candidates (22% of 73, 3% of 578) for presurgical evaluation had not considered the possibility of such an evaluation for their patients. The mean time since failure of a third drug was 5.7 years (standard deviation 5.7; median 4.3; range 0.3 to 19.6) and the mean time since the onset of seizures was 18.9 years (standard deviation 12.3; median 18.1, range 5.1 to 47.6). In 7 patients, the physicians considered the burden of seizures to be low and they had not discussed surgery with the patient. Another 6 patients – all treated in secondary care - had been referred to tertiary care in the past, but the issue of epilepsy surgery had not been raised. No reasons were given for the other three patients.

In the sample of patients treated in secondary care, 7 patients had previously been referred to presurgical evaluation, and according to the expert evaluation 10 more patients (2 candidates and another 8 potential candidates) were eligible for referral. This means that referral should be considered 1.3 to 2.4 times more often than is currently the case in secondary care; i.e., in (7+2)/7 to (7+10)/7 times as many patients. In tertiary care, 15 patients had previously been referred and according to the expert evaluation 6 more patients (2 candidates and 4 potential candidates) were eligible for referral, leading to (15+2)/15 to (15+6)/15 or 1.1 to 1.4 times as many patients who should be referred for presurgical evaluation than is currently the case. Overall, we found that presurgical evaluation was needed in 26 (22 previously referred + 4 candidates) to 38 (22 previously referred + 16 potential candidates) of 578 patients, or in 4% to 7% of our patient sample, which is slightly higher than the estimate of 3% by Lathoo et al. for the UK.[136]

Conclusion

In interpreting our results, it is apparent that there is a "pool" of patients that has not been referred for presurgical evaluation during the preceding years, even though such referral would seem appropriate. For this reason, it is not possible to give an indication of the expected increase in the number of patients that should be referred for presurgical evaluation for epilepsy surgery.

We confirm that there is a substantial underutilization of epilepsy surgery and that epilepsy surgery as a treatment should receive more emphasis in secondary as well as tertiary care. Physicians should adhere more strictly to current guidelines for referral to the presurgical evaluation program for epilepsy surgery and make better use of available non-invasive diagnostic techniques. Moreover, they should always discuss surgery with their patients if seizures persist after at least 2 years of medical treatment and failure of a third antiepileptic drug.

CHAPTER 8

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General discussion

General discussion

The aim of the presurgical work-up in patients with temporal lobe epilepsy is to assess whether epilepsy surgery is indeed a treatment option, with freedom from seizures as ultimate treatment goal.[26] We found that during the presurgical diagnostic work-up of these patients, results from MRI and video EEG monitoring appeared to contribute strongly to the decision whether or not to perform epilepsy surgery.[137] If MRI and EEG monitoring results are inconclusive, FDG-PET should be performed as the next step.[130] In the Netherlands, patients considered eligible for surgery undergo a Wada procedure. We found that this can be restricted to a unilateral procedure in most patients.[138] The use of the Wada procedure in the presurgical work-up has been debated in recent years,[139] and functional MRI may provide a non-invasive replacement for this procedure to assess language lateralization. However, the possibilities of functional MRI to assess memory function are still unclear.[140]

Diagnostic test results that independently contribute to the decision concerning temporal lobe epilepsy surgery in patients referred for the presurgical work-up are not necessarily also predictors of postoperative freedom from seizures.[130;137;141] Interictal and ictal EEG results both contribute to the diagnostic decision for or against surgery, but have no value in predicting postsurgical freedom from seizures. In contrast, age, absence of tonic clonic seizures, absence of status epilepticus in the patient history, and absence of ictal limb dystonia during the seizure are all predictors of postoperative seizure freedom but have no added value in the presurgical work-up regarding the decision whether or not to perform surgery.[137;141] Absence of ictal limb dystonia as a predictor of postoperative seizure freedom is remarkable, because the occurrence of ictal limb dystonia is generally considered a reliable localizing and lateralizing sign in the presurgical work-up.[59-61] MRI results and unilateral temporal abnormalities on FDG-PET both appear to contribute to surgical decision-making and to postoperative freedom from seizures, although MRI findings are interpreted somewhat differently for both

purposes.[130;137;141]

As postoperative outcome, we used postoperative seizure freedom, defined as Engel class 1, one year after surgery.[141] Since the goal of epilepsy surgery is to improve functioning and well-being, quality of life also is a meaningful outcome.[142] Postoperative seizure freedom is strongly related to an improved quality of life,[143-145] and in seizure-free patients the absence of auras is independently associated with quality of life.[143] While patients consider the distinction between Engel class 1A (absence of both auras and seizures) and Engel class 1 (absence of disabling seizures) to be highly relevant, clinicians appear to be satisfied when Engel class 1 is attained. This is why most studies, including ours, use Engel class 1 as outcome.[129;141] Although we did not systematically determine quality of life in our study population, we found similar results when we used Engel class 1A as outcome in the prediction of postoperative seizure freedom as when we used Engel class 1 as outcome.[141] It might be interesting and clinically relevant to assess specifically whether postoperative quality of life (e.g., at one year) can be predicted using diagnostic test results and surgical variables.

Considering the utilization of epilepsy surgery in general, we found that more patients who have been treated unsuccessfully in secondary and tertiary care centers should be referred for presurgical work-up for epilepsy surgery, namely, 1.3 to 2.4 times more patients treated in secondary care and 1.1 to 1.4 times more patients treated in tertiary care.[146]

International comparison

The Dutch presurgical evaluation program for epilepsy patients is national and includes all patients referred in the Netherlands. The Dutch program is as effective as programs in other countries, as reflected by similar percentages of surgery and postoperative seizure freedom.[16] With respect to the use of MRI and video EEG monitoring, the presurgical work-up itself also seems similar to that used in

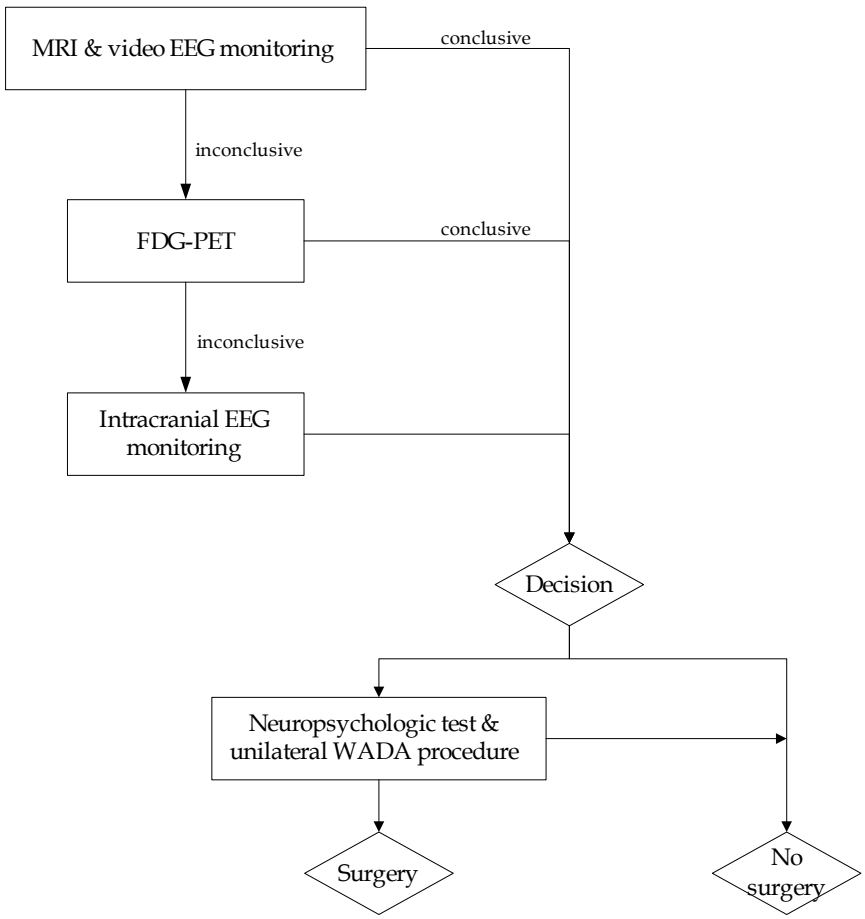
programs in other countries.[16] However, the use of other ancillary tests may differ considerably between countries, for example, the Wada test, which is standard in some countries but not in others.[139] Furthermore, the use of intracranial EEG monitoring differs considerably between countries. In the Netherlands, only 19 of 469 consecutive patients (4%) referred for the presurgical work-up of temporal lobe epilepsy surgery in the last decade underwent intracranial EEG monitoring, while in other countries this percentage is much higher, namely, 25% in the USA and 50% in France.[147;148] Furthermore, the techniques used differ (subdural or intracerebral monitoring). The Dutch program is focused on reaching an accurate decision about whether to perform surgery on the basis of the least invasive diagnostic tests.

Future research

The existing differences in the use and performance of ancillary tests limit the possibility of a valid comparison of different presurgical work-up programs and to obtain an international consensus on the test results required to make a decision about whether to perform temporal lobe epilepsy surgery. More studies aimed at assessing the contribution of diagnostic tests in other presurgical work-up programs are needed. Comparison of the results of such studies with our results may be a first step toward reaching international consensus on the presurgical work-up for temporal lobe epilepsy surgery. Nevertheless, based on the results of this thesis, a protocol for reaching the decision for or against temporal lobe epilepsy surgery can be suggested (figure 8.1).

A randomized study is needed to validate the clinical value (in terms of patient outcome) of the protocol described in figure 8.1. Patients referred to the presurgical work-up should be randomized to either the current work-up or to the suggested protocol. Then both operated patients and patients rejected for surgery should be followed up, with seizure freedom being used as primary outcome variable and quality of life as secondary outcome variable.

Figure 8.1. Flow chart of suggested protocol for the presurgical work-up



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SUMMARY
&
SAMENVATTING

SUMMARY

Chapter 1

Introduction.

Surgery is an outstanding treatment option for patients with drug resistant temporal lobe epilepsy. In practice, the decision to perform surgery is a consensus decision of a multidisciplinary team, based on a stepwise process involving complex diagnostic tests. Diagnostic research, using a multivariable approach is necessary to assess the contribution of each step of this process.

Chapter 2

What is the current evidence on decision-making after referral for temporal lobe epilepsy surgery? A review of the literature.

This chapter reviews the literature on studies assessing the independent contribution of different diagnostic tests to the decision to perform temporal lobe epilepsy surgery. Most studies studied addressed prognostic factors in operated patients only. Only ten articles met our inclusion criteria, of whom inclusion of SPECT accounted for five papers. Unbiased comparison of the results was not possible. We conclude that surprisingly little research in epilepsy surgery has focused on the decision-making process as a whole.

Chapter 3

Decision-making in temporal lobe epilepsy surgery: The contribution of basic non-invasive tests.

In chapter 3, the extent to which widely used diagnostic tests contribute to the decision whether or not to perform temporal lobe epilepsy surgery in the Netherlands was studied, using a nation-wide consecutive cohort of 201 patients referred for the presurgical work-up for temporal lobe epilepsy surgery. The individual and combined contribution of findings from patient history, routine EEG recordings, MRI, and video EEG monitoring to the consensus decision to

perform surgery was investigated using multivariable logistic regression and ROC curves. After their role in the referral to the presurgical work-up, patient history and routine EEG findings were hardly contributory to decision-making, whereas a convergence of MRI with long-term interictal and ictal EEG findings correctly identified the candidates considered eligible for surgery (25% of total) without the need for further ancillary tests. Videotaped seizure semiology contributed less than expected to the final clinical decision and basic test findings alone were insufficient to exclude patients from surgery.

Chapter 4

The added value of [18F]fluor-D-deoxyglucose positron emission tomography in screening for temporal lobe epilepsy surgery.

FDG-PET is an expensive, invasive, and not widely available technique used in the presurgical evaluation of temporal lobe epilepsy. In 469 consecutive patients referred to the national presurgical work-up, we assessed its contribution to the decision to perform temporal lobe epilepsy surgery in relation to MRI and video EEG monitoring, comparing documented decisions concerning surgery before and after FDG-PET results. FDG-PET was performed in 110 patients (23%); in 78 (71%) FDG-PET findings led clinicians to change the decision based on MRI and video-EEG monitoring findings. In 17% of all referred patients, the decision regarding surgical candidacy was based on FDG-PET findings. FDG-PET was most useful when previous MRI results were normal or did not show unilateral temporal abnormalities, or when ictal EEG results were not consistent with MRI findings or videotaped seizure semiology. We conclude that in patients referred for the presurgical work-up for temporal lobe epilepsy surgery, FDG-PET findings can form the basis for deciding whether a patient is eligible for surgery, especially when MRI or video-EEG monitoring are nonlocalizing.

Chapter 5

The intracarotid amobarbital or Wada test: unilateral or bilateral?

The intracarotid amobarbital procedure (IAP or Wada test) is part of the presurgical work-up for temporal lobe epilepsy in the Netherlands. The Wada test includes two consecutive injections of amobarbital, ipsilateral and contralateral to the epileptic focus. We studied whether a bilateral procedure has added value to a unilateral, ipsilateral procedure. Using multivariable modeling, we assessed the added value of bilateral IAP on the decision for surgery, resection size, amygdalohippocampectomy, postoperative seizure freedom, memory performance, and IQ change in 183 consecutive patients referred for the presurgical work-up for temporal lobe epilepsy surgery who underwent bilateral IAP. We conclude that a bilateral IAP has added value in predicting postoperative verbal memory and IQ. A bilateral IAP is currently not used to guide surgical strategy, but may be used for this purpose when verbal capacity is of particular concern in patients with a left-sided focus. In all other cases, IAP should be performed unilaterally.

Chapter 6

Prognosis after temporal lobe epilepsy surgery:

The value of combining predictors.

Many independent predictors of seizure freedom after temporal lobe epilepsy surgery have been identified. However, the combined predictive value of these predictors is largely unknown. In 484 operated patients referred for drug resistant temporal lobe epilepsy, we assessed the combined predictive value of a multivariable model including known independent predictors. Good outcome was defined as Engel class 1, one year after surgery. All known predictors from literature were assessed and included as independent predictor when the multivariable p-value was below 0.20. The final multivariable model included

independent predictors from history (absence of tonic-clonic seizures, absence of status epilepticus), MRI (ipsilateral MTS, space occupying lesion), video EEG (absence of ictal dystonic posturing, concordance between MRI and ictal EEG), and FDG-PET (unilateral temporal abnormalities), and had an expected ROC area of 0.63 (95% confidence interval 0.57 to 0.68) for new patient populations, which means that the model has a moderate ability to discriminate between becoming seizure free or not. Furthermore, it is particularly difficult to predict not becoming seizure free after surgery.

Chapter 7

Is epilepsy surgery utilized to its full extent?

It has been stated that there is a world-wide underutilization of epilepsy surgery. We established how many patients should have been and were actually referred to the Dutch national taskforce for presurgical evaluation using two random samples of patients, one from a secondary and one from a tertiary epilepsy facility. Using international guidelines, presurgical evaluation should have been considered in 95 of 578 evaluated patients (16%), but only 22 (4%) were actually referred. An expert panel evaluated clinical data from the 73 cases who were not referred and thought that 4 of these patients (5%) were potential candidates for presurgical evaluation and diagnostic testing was insufficient in another 12 (16%). Our results show that in the Netherlands 1.3 to 2.4 times more patients treated in secondary care should be referred to presurgical evaluation and 1.1 to 1.4 times more in tertiary care. Therefore, we confirm an underutilization of epilepsy surgery in the Netherlands and conclude that treating neurologists should be more aware of current guidelines, make better use of available noninvasive diagnostic techniques, and discuss surgery with their drug resistant epilepsy patients.

Chapter 8

General discussion.

In chapter 8, the findings in preceding chapters are discussed. Diagnostic test results that contribute to the decision for or against surgery do not necessary contribute to the prediction of postoperative seizure freedom and vice versa. The Dutch presurgical work-up is only partly comparable to international programs. The use of ancillary tests may differ considerably between programs and countries. The Dutch presurgical work-up is a nation-wide program focused on reaching an accurate decision using the least invasive diagnostic tests. The differences between presurgical work-up programs across countries limit the possibilities of international comparison and of obtaining an international consensus on the decision for or against temporal lobe epilepsy surgery. Based on the findings from this thesis, a protocol for the presurgical work-up can be suggested, which should be evaluated in a randomized study, comparing the current Dutch work-up to the suggested protocol, with seizure outcome and quality of life after surgery and after the decision not to perform surgery as outcome variables.

SAMENVATTING

Hoofdstuk 1

Introductie.

Bij mensen met medicamenteus onbehandelbare temporaalkwab epilepsie is epilepsie chirurgie een zeer goede behandelmogelijkheid. Het besluit om iemand wel of niet te opereren is een consensus besluit, genomen door een multidisciplinair team, gebaseerd op een stapsgewijs proces bestaande uit verschillende diagnostische testen. Om de bijdrage van iedere stap van dit proces te onderzoeken is multivariaat diagnostisch onderzoek noodzakelijk.

Hoofdstuk 2

Wat is de huidige onderbouwing voor de besluitvorming na verwijzing voor temporaalkwab epilepsie? Een overzicht van de literatuur.

In dit hoofdstuk worden de studies beschreven waarin onderzoek naar de onafhankelijke bijdrage van verschillende diagnostische testen op de besluitvorming bij epilepsie chirurgie van de temporaalkwab wordt gepresenteerd. De meeste studies betroffen de prognostische waarde bij patiënten die geopereerd waren. Slechts tien artikelen voldeden aan onze inclusiecriteria, waarvan vijf over de bijdrage van SPECT gingen. Het was niet mogelijk om de resultaten van de verschillende studies te vergelijken. We concluderen dat verrassend weinig onderzoek binnen de epilepsie chirurgie zich heeft gericht op het besluitvormingsproces.

Hoofdstuk 3

Besluitvorming bij epilepsie chirurgie van de temporaalkwab: de bijdrage van niet invasieve basis testen.

In hoofdstuk 3 hebben we onderzocht in welke mate de meest gebruikte niet invasieve diagnostische tests bijdragen tot de besluitvorming bij epilepsie chirurgie

van de temporaalkwab in Nederland. Hierbij werden 201 patiënten bestudeerd die verwezen waren naar het nationale programma voor beoordeling van epilepsie chirurgie van de temporal kwab. We onderzochten de individuele en gecombineerde bijdrage aan de consensus besluitvorming voor chirurgie van anamnese, routine EEG registraties, MRI en video EEG registraties met behulp van multivariabele logistische regressie analyse en ROC curven. Naast hun rol in de verwijzing naar het beoordelingsprogramma, bleken anamnese en routine EEG bevindingen weinig bij te dragen aan het besluitvormingsproces na verwijzing. Patiënten met concordante resultaten bij MRI-, interictaal EEG- en ictaal EEG-onderzoek bleken allen kandidaten voor chirurgie (25% van alle operatiekandidaten), zonder dat aanvullende testen nodig waren. De aanvalssemiologie, beoordeeld middels de video registratie, droeg minder dan verwacht bij aan de uiteindelijke beslissing voor chirurgie en de resultaten van de onderzochte basis testen alleen bleken onvoldoende om patiënten af te wijzen voor chirurgie.

Hoofdstuk 4

De toegevoegde waarde van [18F]fluor-D-deoxyglucose positron emission tomography bij de beoordeling voor epilepsie chirurgie van de temporaalkwab

FDG-PET is een kostbare, invasieve techniek, die gebruikt wordt bij de beoordeling voor epilepsie chirurgie van de temporaalkwab. Bij 469 patiënten, verwezen voor beoordeling voor chirurgie, hebben we de bijdrage van FDG-PET aan de besluitvorming voor epilepsie chirurgie van de temporaalkwab onderzocht, gegeven de resultaten van MRI en video EEG registratie, door gedocumenteerde beslissingen voor en na de uitvoering van FDG-PET met elkaar te vergelijken. FDG-PET was uitgevoerd bij 110 patiënten (23%). Bij 78 (71%) van alle verwezen patiënten veranderden de clinici het besluit voor chirurgie, genomen na MRI en video EEG registratie, op basis van de FDG-PET resultaten. FDG-PET was vooral geschikt als MRI geen afwijkingen of geen unilaterale temporale afwijkingen toonde of als de ictale EEG registraties niet consistent waren met de MRI resultaten

en de aanvalssemiologie van de video registratie. We concluderen dat FDG-PET een basis voor de beslissing tot operatie kan vormen bij mensen die verwezen zijn voor beoordeling voor epilepsie chirurgie van de temporaalkwab, met name als MRI en video EEG registratie niet localiserend zijn.

Hoofdstuk 5

De intracarotide amobarbital of Wada test: unilateraal of bilateraal?

De intracarotide amobarbital procedure (IAP of Wada test) is onderdeel van de beoordeling voor epilepsie chirurgie van de temporaalkwab in Nederland. De IAP bestaat uit twee achtereenvolgende injecties met amobarbital, ipsilateraal en contralateraal aan het epileptisch focus. We onderzochten of de bilaterale procedure toegevoegde waarde heeft ten opzichte van een unilaterale procedure, bestaande uit een injectie ipsilateraal aan het focus. Met gebruik van multivariabele modellen hebben we de toegevoegde waarde van een bilaterale IAP onderzocht voor de beslissing tot chirurgie, resectiegrootte, amygdalahippocampectomie, postoperatieve aanvalsvrijheid, geheugen en IQ veranderingen bij 183 patiënten verwezen voor beoordeling voor epilepsie chirurgie van de temporaalkwab, die een bilaterale IAP ondergaan hebben. We concluderen dat de bilaterale IAP toegevoegde waarde heeft bij het voorspellen van postoperatief verbaal geheugen en IQ. Momenteel wordt de bilaterale IAP niet gebruikt om de chirurgie strategie te bepalen, maar deze kan voor dit doel gebruikt worden als de verbale capaciteit in het geding is bij patiënten met een focus links temporaal. In alle andere gevallen kan IAP unilateraal uitgevoerd worden.

Hoofdstuk 6

De predictie van aanvalsvrijheid na epilepsie chirurgie van de temporaalkwab: de prognostische waarde van een combinatie van predictoren.

Er is een groot aantal onafhankelijke predictoren van aanvalsvrijheid na epilepsie chirurgie van de temporaalkwab geïdentificeerd. De gecombineerde predictieve waarde van deze predictoren is grotendeels onbekend. In 484 geopereerde

patiënten, verwezen vanwege therapieresistente temporaal kwab epilepsie hebben we de gecombineerde predictieve waarde onderzocht van een multivariabel model van alle bekende onafhankelijke predictoren. Een positieve uitkomst werd gedefinieerd als Engel klasse 1, één jaar na operatie. Alle bekende predictoren, beschreven in de literatuur werden onderzocht en geïncludeerd als onafhankelijke predictor mits de multivariabele p-waarde kleiner dan 0.20 was. Het uiteindelijke multivariabele model bevatte onafhankelijke predictoren met betrekking tot de anamnese (afwezigheid van tonisch-clonische aanvallen, afwezigheid van status epilepticus), de MRI (ipsilaterale MTS, ruimte-innemende laesie), de video EEG registratie (afwezigheid van ictale dystonie, concordantie tussen MRI en ictaal EEG) en de FDG-PET scan (unilaterale temporale afwijkingen). Het model had een verwacht gebied onder de ROC curve van 0.63 (95% betrouwbaarheidsinterval 0.57 tot 0.68) voor nieuwe patiëntenpopulaties, wat betekent dat het model een matig vermogen heeft om te onderscheiden of iemand wel of niet aanvalsvrij wordt. Verder bleek dat het vooral moeilijk was om te voorspellen of iemand niet aanvalsvrij wordt na operatie.

Hoofdstuk 7

Wordt epilepsie chirurgie volledig benut?

Er is beschreven dat epilepsie chirurgie als behandeling wereldwijd onvoldoende gebruikt wordt. Wij hebben onderzocht hoeveel patiënten verwezen zijn en verwezen zouden moeten worden naar het Nederlandse programma voor beoordeling van de mogelijkheden van epilepsie chirurgie, gebruik makend van twee aselecte steekproeven van patiënten, één in een tweedelijns en één in een derdelijns epilepsie kliniek. Volgens internationale richtlijnen zouden 95 van de 578 onderzochte patiënten (16%) voor beoordeling voor chirurgie in aanmerking moeten komen, terwijl slechts 22 (4%) daadwerkelijk verwezen zijn. Een groep van experts evalueerde de klinische gegevens van de 73 niet verwezen patiënten en beoordeelde dat 4 van deze patiënten (5%) kandidaten zijn voor verwijzing en dat 12 anderen (16%) mogelijke kandidaten zijn, maar dat er bij deze 12 patiënten

onvoldoende diagnostische testresultaten beschikbaar waren. Onze resultaten laten zien dat in Nederland 1,3 tot 2,4 maal zoveel patiënten vanuit de tweedelijn verwezen zouden moeten worden voor beoordeling voor epilepsie chirurgie en 1,1 tot 1,4 maal zo veel vanuit de derde lijn. Aldus bevestigen we dat in Nederland onvoldoende gebruik gemaakt wordt van epilepsie chirurgie en we concluderen dat behandelend neurologen zich beter bewust moeten zijn van de vigerende richtlijnen, meer gebruik zouden kunnen maken van beschikbare niet invasieve diagnostische testen en chirurgie met hun therapieresistente patiënten zouden moeten bespreken.

Hoofdstuk 8

Algemene discussie.

In hoofdstuk 8 worden de bevindingen van voorgaande hoofdstukken bediscussieerd. Diagnostische test resultaten met een bijdrage tot de besluitvorming voor operatie hoeven niet persé een bijdrage te leveren aan de voorspelling van postoperatieve aanvalsvrijheid en andersom. Het Nederlandse beoordelingsprogramma voor epilepsie chirurgie is maar gedeeltelijk vergelijkbaar met internationale programma's. De toepassing van aanvullende diagnostische testen verschilt aanzienlijk in de verschillende programma's en landen. Het Nederlandse programma is een nationaal programma wat gericht is op het nemen van een juiste beslissing met zo min mogelijk invasieve testen. Door de verschillen in internationale programma's is een vergelijking moeilijk, evenals het komen tot een internationale consensus over de besluitvorming voor epilepsie chirurgie van de temporaalkwab. Gebaseerd op de resultaten van dit proefschrift is het mogelijk om een protocol voor de beoordeling voor epilepsie chirurgie van de temporaalkwab op te stellen. Dit protocol kan geëvalueerd worden in een gerandomiseerde studie, waarin het huidige beoordelingsprogramma vergeleken wordt met het voorgestelde protocol, met postoperatieve aanvalsvrijheid en kwaliteit van leven als uitkomst variabelen.

DANKWOORD

DANKWOORD

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LIST OF PUBLICATIONS
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CURRICULUM VITAE

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CURRICULUM VITAE

Sabine Uijl werd geboren op 28 maart 1971 in Voorburg. Na afronding van het VWO in Den Haag in 1989 heeft zij de opleiding tot fysiotherapeut gevolgd aan de Haagse Academie voor Fysiotherapie. Direct aansluitend deed zij van 1993 tot 1996 de studie Biomedische Gezondheidswetenschappen aan de Katholieke Universiteit Nijmegen, tegenwoordig de Radboud Universiteit Nijmegen.
Het afstudeerproject bij de afdeling fysiologie van de Katholieke Universiteit Nijmegen onder begeleiding van prof. dr. M. Hopman resulteerde in de eerste wetenschappelijke publicatie. Haar wetenschappelijke carrière werd vervolgd met een aantal onderzoeksprojecten op het gebied van fysiologie en longfunctie.
In 1998 verhuisde zij naar Groningen, waar zij onder begeleiding van prof. dr. R. Sanderman (Noordelijk Centrum voor Gezondheidsvraagstukken, Rijksuniversiteit Groningen) twee jaar aan een studie naar de patiëntentevredenheid bij mensen met kanker werkte. In 2000 maakte zij de stap naar beleidsonderzoek bij het College voor Zorgverzekeringen in Amstelveen. Vanaf 2002 is zij bezig met wetenschappelijk onderzoek op het gebied van epilepsie binnen de afdeling klinische neurofysiologie van het UMC Utrecht en het Rudolf Magnus Instituut voor Neurowetenschappen. Hier heeft zij onder begeleiding van prof. dr. A.C. van Huffelen en prof. dr. K.G.M. Moons (Julius Centrum voor gezondheidswetenschappen en eerstelijns geneeskunde, UMC Utrecht) het onderzoeksproject uitgevoerd naar de diagnostiek leidend tot een operatie beslissing bij mensen met epilepsie van de temporaalkwab, wat geleid heeft tot dit proefschrift. Tevens heeft zij onder begeleiding van prof. dr. C.A. van Donselaar een onderzoeksproject gedaan naar het optreden van bijwerkingen bij mensen met epilepsie die goed onder controle is met medicatie. In 2007 heeft zij daarnaast haar masters graad Klinische Epidemiologie aan de Universiteit Utrecht behaald. Momenteel voert zij onder begeleiding van prof. dr. K.G.M. Moons en dr. F.S.S. Leijten onderzoek uit naar de grootte van en redenen voor onderverwijzing van patiënten met epilepsie naar het prechirurgisch beoordelingsprogramma.