

The Role of Invasive Electrodes in the Presurgical Evaluation for Epilepsy

Doctoral thesis

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INTRODUCTION

50 Million people around the World lives with epilepsy. The incidence of the disease is 50-70/100.000/year. Global prevalence is 4-8/1000 person, this means 1% of the 40 year old population. The prognosis of the disease is good for most of the affected people. The prognosis is also strongly influenced by the underlying etiology. 70% of the patients can be seizure free with medication. The proportion of the so called drug resistant epileptic patients is between 30-40%. In the international praxis the general consensus is that after failure of 2 monotherapeutic trials and one combination therapy the patient has to be referred to an epilepsy surgical center for presurgical evaluation. One third of the drug resistant patients can be treated with surgery. If during the presurgical evaluation the non-invasive data is not enough concordant to plan the surgery, semi-invasive or invasive investigations are needed. The development of the imaging techniques in the last 20 years on finding lesions behind focal epilepsies, made possible to reduce the number of semi-invasive or invasive investigations. However up until today there is still no such morphological investigation which could proof the epileptogenicity of a lesion. Therefore in such cases invasive EEG monitoring is still crucial for the presurgical evaluation. The development of neurosurgical methods, keeping minimal invasivity in front of our eyes, introduced semi invasive electrodes and minimal invasive surgical techniques to the field.

The goal of this thesis is – based on experience collected in epilepsy surgery in the last 15 years – to summarize the surgical observations gained with presurgical invasive

evaluations and also to present some of the epileptological experiences gained with the semi-invasive EEG technique.

Thus this PhD thesis shows the chronology of the given answers to the upcoming questions which arose through the years of development of superimposable methods and thru this it shows the evolution of our epilepsy surgical program.

Major part of the essay focuses on the review of the foramen ovale EEG (FO) technique and the analysis of our experiences gained with this technique. The reason to that is that in Hungary the only center uses this technique is ours, and it is also rarely used abroad, so we think it is necessary to summarize the gained experiences.

AIMS OF THE THESIS

1. To review the practice of the FO technique in Hungary, which was initiated by our group:
 - 1.1. To review the introduction of the semi-invasive FO-EEG technique to the armamentarium of the presurgical evaluation of epilepsies in Hungary.
 - 1.2. To analyze the specialties and potentials of the FO-EEG method in the course of the presurgical evaluation and to summarize the gained clinical benefits with this investigation.
 - 1.3. To describe the indications we established for using the FO electrodes.
 - 1.4. To write down the technical specifications of our own developed and manufactured FO electrode.
2. To retrospectively analyze the seizure spread on the mesial temporal lobe epileptic (MTLE) patients, who were monitored with scalp and foramen ovale electrodes during the presurgical evaluation.

- 2.1. Describe the specialties of contralateral seizure spread.
- 2.2. To find correlation between the pattern and time of the interhemispheric seizure spread, and also between the structural abnormalities and the clinical outcome.
3. Neurosurgical methods:
 - 3.1. Innovation of an intraoperative localization technique: for intracranial localization of subdural electrodes during surgical implantation using minimal invasive techniques.
 - 3.2. On the basis of the invasive video-EEG monitoring data, creation of a semiology specific implantation protocol of subdural electrodes.
 - 3.3. Exposition of the complications associated with intracranial electrode implantation.
 - 3.4. Review of the surgical techniques used for avoiding complications during subdural electrode implantation

METHODS

From the 97 patients who underwent intracranial video-EEG monitoring in the last 15 years, 64 had FO electrodes implanted. In twelve cases we could not collect sufficient data, therefore these patients were left out from the investigation. We had 52 patients, who were involved in the retrospective investigation on the clinical benefits of the FO electrodes.

1. The implantation method of the FO electrode

The electrode with the help of a hollow needle has to penetrate the skin of the face first then guided thru the foramen ovale and the Gasser ganglion to the temporomedial cisterns, according to

the Härtel coordinates, under fluoroscopic control. In most of the cases man can feel the penetration thru the dura and than usually cerebrospinal fluid is dripping from the lumen of the needle. After that the 0.9mm diameter 4 contact electrode is guided thru the needle to the ambiens cistern and anchored to the skin of the face with 3 stitches.

2. Method of investigating interhemispheric propagation of seizures in mesial temporal lobe epilepsy

From the 64 patients evaluated with FO electrodes, we analyzed 47 and 20 of them has matched our inclusion criterias.

Inclusion criteria for patients:

1. Having exclusively mesiotemporal onset seizures
2. Having seizures that predominantly do not remain localized but propagate to contralateral mesiotemporal regions
3. Absence of any extratemporal epileptogenic lesions, proved with MRI

Exclusion criteria for patients:

1. Having seizures with simultaneous onset in ipsilateral FO and scalp electrodes
2. Having seizures with simultaneous onset in right and left FO electrodes
3. Having seizures where onset cannot be clearly defined

We carefully inspected all seizures recorded for the included patients and excluded those seizures that matched the following criteria:

1. Seizures where the time points of seizure onset or subsequent propagation to contralateral scalp or FO channels could not be precisely defined
2. Seizures where the scalp electrode involvement could not be precisely defined

Patients' mean \pm SD age at epilepsy onset was 19 \pm 6.8 years, epilepsy duration was 16.9 \pm 8.7 years and mean age was 36 \pm 7.7 years. Surgical outcome was based on a 2-year follow-up. Of the 20 patients 13 with unilateral mesiotemporal seizure onset underwent surgery (standard anterior temporal lobectomy). Out of them seven patients have been seizure-free (Engel I) at a 2-year follow-up whereas six patients continued to have seizures after surgery (Engel II, III or IV). Seven patients exhibited independent bilateral mesiotemporal seizure onset and therefore surgery was not indicated. Mesiotemporal structural alteration evident on high-resolution MRI scans was present in 13 patients. Out of them nine had hippocampal sclerosis (HS) and four had mesiotemporal dysgenesis. Seven patients had normal MRI.

EEG recording

EEG monitoring with combined scalp and FO electrodes was carried out using Brain Quick System 2 or 98 (Micromed, Mogliano Veneto, Italy). The exact location of FO electrodes was confirmed by X-ray scan and in some cases by MRI. Additionally, 16 Ag/AgCl scalp electrodes (Fp1, Fp2, F3, F4, F7, F8, T3, T4, C3, C4, T5, T6, P3, P4, O1, and O2) according to the 10-20 International System as well as EOG, EMG and ECG electrodes were placed. All signals were recorded to a vertex reference and neighboring channels were re-referenced for bipolar montages.

Seizure analysis

The analysis of the seizures was done according to the consensus of more experienced electroencephalographers. They were first reviewed for matching inclusion and exclusion criteria. Then we designated ictal onset in the initiating FO channel, in the contralateral FO channel, in the ipsilateral scalp and in the contralateral scalp. Among FO and scalp channels on the same side those channels with the earliest ictal onset were designated. Ictal onset was defined by the first unequivocal sign of localized rhythmic activity clearly distinguishable from preceding and background activity. For each seizure an inter-FO electrode propagation time (IFPT) was calculated which was defined as a time delay between time points of ictal onset in the initiating and in the contralateral FO channel. For each patient an individual average of IFPT was calculated across seizures.

Based on the temporal sequence of contralateral scalp and FO channel recruitment, seizures were assigned into one of the two categories such as Type I and Type II. Type I correspond to those seizures where the ictal pattern propagated to the contralateral FO channels before the contralateral scalp channels. Seizures were also assigned as Type I if no contralateral scalp spread occurred following initial contralateral FO channel recruitment. Type II corresponds to seizures where contralateral scalp channels were recruited earlier or simultaneously with contralateral FO channels. Based on their predominant seizure propagation types, patients were also classified as Type I or Type II.

Statistical methods

T-test was used to statistically compare IFPT for Type I and Type II seizures and patients. MRI data were classified to two

categories: normal and positive MRI. Positive MRI included HS and mesiotemporal dysgenesis. To compare average IFPT for patients with normal and positive MRI, t-test was used. To evaluate surgical outcome, patients with seizure-free outcome were compared with those patients who did not become seizure-free after surgery or surgery was not indicated because of independent bilateral seizure onset. The interaction between surgical outcome and patient type (Type I vs. Type II) was tested using the Fisher's exact test according to a 2x2 design. To test the interaction between patient type and MRI categories, we also used Fisher's exact test according to a 2x2 design.

3. Method of neuronavigation and fluoroscopy assisted subdural strip electrode implantation

We introduce our method by using the data obtained during the implantation of 24 subdural electrodes in 8 patients. For neuronavigation a Brain Lab Vector Vision neuronavigation system (Brain LAB Med. Computersystem GmbH, Germany) was used. The intraoperative fluoroscopy images were taken with a Siemens Siremobil 2000 X-ray machine. MR compatible fiducial markers were placed onto the patient's head before surgery. High resolution MRI was performed (Siemens Somatom Symphony, 1.5T) and Digital Imaging and Communication Images (DICOM) were transferred to the navigation workstation in the operating room via local network. The patient's head was fixed in a Mayfield head-holder. After standard registration procedure the projection of the cortical surface anatomy could be perfectly visualized using the navigation probe even on closed skull. The entry point and the target point were located, than a burr hole was made over

the entry point. After opening the dura the strips were inserted to the subdural space towards the target point defined by the navigation probe. The stainless steel radiopaque navigation probe was visualized with fluoroscopy (Siemens, Siremobil 2000) until the desired radiopaque stainless steel or platinum electrode contact of the strip did not reach the tip of the navigation probe. This way we could control the real position of the electrode during the procedure.

The key instrument is the navigation probe which is visible for the infrared cameras of the navigation system and for the fluoroscopy as well. Therefore the position of a metallic object, e.g. a strip electrode, co-registered to the navigation probe is locatable in the skull even if the electrode disappears from our eyes under the bone and dura by using a small craniotomy as a minimally invasive approach. After surgery a routine postoperative X-ray was done to document the final position of the electrodes. By the end of the long term video-EEG monitoring session the X-rays were repeated to monitor any dislocations of the electrodes. We also performed a routine brain MRI to localize the electrode contacts on the brain surface. The platinum electrodes give less, the stainless steel electrodes give more noise signal on the MRI images, therefore they appeared better on the pictures. A 3D reconstruction was created from the images to better visualize each contact and to plan the surgery.

RESULTS

Between 1996 and 2009 our team has performed 242 epilepsy surgical interventions on 190 patients. 145 epilepsy surgeries were performed in this time period. Among them 71 anterior temporal lobectomies, 3 selectiv amygdalo-hippocampectomies

and 39 topectomies or epilepsy indicated lesionectomy, 3 calloso-commisurotomies and 29 VNS implants.

We performed invasive intracranial monitoring in 97 cases, in 64 cases with foramen ovale electrodes and in 43 cases we used only subdural electrodes. In ten patients we combined FO and subdural electrodes. All together we implanted 131 FO electrodes, 104 strip electrodes and 18 grids.

1. We introduced the FO technique in Hungary in 1996 to investigate surgical amenable epilepsies.

We proofed that the direct temporomedial EEG recorded using FO electrodes makes the ictal and interictal activity of the two temporo-medial sides comparable. We confirmed that this technique is sensitive enough to differentiate between temporo-medial and –lateral, ictal and interictal activities.

Analyzing the data of 43 patients monitored with FO electrodes shows that in 42 cases a clear cut clinical decision could be made using the data obtained with the FO electrodes if there is or not an indication for resective surgery. There was only one patient who needed further investigations. In 24 cases on the basis of a unilateral seizure onset zone surgery was indicated. In one case tough bilateral seizure onset was found, due to severe semiology, progressive worsening and motivation of the patient we decided to perform a one sided anterior temporal lobectomy.

We found our best results in the patient group with bilateral HS and unilateral seizure onset, every patient in the group belongs to Engel 1 category on the 5 years follow-up.

In the patient group with unilateral HS and unilateral seizure onset, we found 80% of the patients in Engel 1 category after 5

years. Among the patients with a negative MRI, the Engel 1 outcome is 56%, but Engel 1+2 is 89%.

In the bilateral seizure onset group, with a unilateral resection the number of seizures could be reduced, but this improved their quality of life only a little.

In twenty patients the electrodes were beside lateralization also used for localization. In ten cases we needed to differentiate between temporo- medial versus lateral epilepsy. We found unilateral seizure onset in 9 cases and out of them in 8 patients surgery was indicated and performed. Two patients belong to Engel 1 category, four patients to Engel 2, and one patient to Engel 3 after 5 years, we lost one patient for follow up.

We also used the FO electrodes in ten patients for differentiating between extratemporal and temporal epilepsies. We found 9 patients with unilateral seizure onset and we were able to operate on seven of them. In four patients we performed temporal, in two extratemporal resection and in one patient we performed an awake surgery for localizing the Wernicke region behind the vein of Labbé with electrical stimulation and then performed a topectomy with subpial transection according to Morell. The outcome was Engel 2 in five cases, Engel 1 in one case, and Engel 3 by the patient with awake surgery. Thus in that group the seizure outcome for Engel1+2 is 71.1%, which is not bad if we take in account how complex and complicated these epilepsies are.

For using the FO electrodes we defined the following indications:

1. In mesial temporal lobe epilepsy for lateralizing the seizure onset side
2. For localizing the seizure onset zone within the temporal lobe (temporomedial vs. temporolateral)

3. Within the temporomedial structures defining if anterior or posterior seizure onset zone is present
4. Proofing independent bilateral seizure onset zones
5. Clarifying the role of the temporobasal structures in the seizure spreading mechanisms in temporal and extratemporal epilepsies
6. Differentiating between temporomedial and extratemporal epilepsies

We planed and manufactured new FO electrodes for reducing the costs of the investigation.

The new electrodes were successfully used in investigating temporomedial epilepsies.

2. The studies for investigating the interhemispheric seizure spread on MTLE patients were partially done using the electrodes manufactured by our group. We analyzed 65 seizures of 20 patients. The inter FO propagation time was significantly lower in Type I (average: 8.2s) than in Type II (average: 13.2s) seizures. Twelve patients had only Type I and six patients had only Type 2 seizures. Two patients had both seizure types. 90% of the patients had only one seizure type and only 10% had both seizure spreading mechanisms. We found correlation between the seizure type and the MRI defined lesions: 85% of the patients with Type I seizures had a temporomedial lesion and only 28.5% of the patients with Type II seizures.

The seizure spread showed another correlation with the clinical outcome of the patients: the surgical prognosis is better for patients with Type I seizures than with Type II seizures, where

surgery is less indicated or if surgery is performed the chance for seizure freedom is lower.

3. For the first time nationally and internationally we describe an intraoperative localizing method using neuronavigation and fluoroscopy parallelly for minimal invasive strip electrode implantation. This method allows us to see the electrode and the cortical surface in the same time in the real, and detected in the virtual space of the navigation system. This method makes possible to implant the subdural strip electrodes with great precision.

We elaborated the epilepsy type specific implantation protocol for intracerebral grid and strip electrodes for our epilepsy surgical team using our surgical and epileptological experiences.

We described the complications in our practice and developed our own implantation protocol for reducing the complication of large subdural grid electrode implantations.

CONCLUSIONS

1. The FO electrode is a safe, semi-invasive technique, which is sensitive enough for recording the electrical events starting or propagating in the temporomedial region.

2. We defined two separate contralateral seizure spreading mechanisms of the MTLE patient population. Type I, which first involves the contralateral FO electrode before reaching the scalp electrodes, secures a faster spread and more frequent incidence among MTLE patients than Type II. The faster contralateral spread and dominance of Type I seizures suggests the possibility of using a direct mesiotemporal tract. According

to our hypothesis this could be the same dorsal hippocampal commissure as proposed by Gloor (1993)

3. Based on the simultaneous use of neuronavigation and fluoroscopy in localizing subdural electrodes intraoperatively, resulting in precise electrode positioning, this technique serves the better understanding and defining of epileptological zones, describing seizure spreading mechanisms and mapping eloquent cortical regions.

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