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INVASIVE EEG MONITORING AND ITS APPLICATION IN THE SURGICAL TREATMENT OF PATIENTS WITH PHARMACORESISTANT EPILEPSY

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Epilepsy is one of the most common neurological diseases. It manifests itself as a disorder of the central nervous system that is caused by repetition of abnormal, excessive and synchronous neural discharge [1]. Such neural discharges are clinically manifested with epileptic seizures, and a diagnosis of epilepsy is made if seizures are repeated two or more times. Possible causes of epilepsy are various: genetic disorders, birth trauma, anoxia, infection, traumatic head injury, stroke, and many others, but in approximately one third of patients the cause of epilepsy is unknown. Seizures have a major impact on the health of patients - each new seizure could cause micro damage to the brain and the patients could possibly be hurt during the attack. Also, seizures affect the quality of life of patients - often people suffering from epilepsy have problems with employment and promotion opportunities. For many of them a driver's license could be denied, and also there is significant effect on the social life because of the frequent isolation from friends and constant uncertainty whether the seizure will happen.

Consequently, the main goal of treatment in patients with epilepsy is partial or complete reduction of seizures. The treatment is usually pharmacological (anti-epileptic drugs – AED), with one, two or more AEDs. However, there are great difficulties with the pharmacoresistant form of epilepsy, in which seizures continue after two years of treatment and / or after unsuccessful treatment with a combination of two to three antiepileptic drugs [2]. According to available literature, in about 50% of people with epilepsy only one AED is sufficient for complete seizure reduction, but the problem is that about 36% of patients have pharmacoresistant form of epilepsy [3].

Patients with pharmacoresistant epilepsy are treated with invasive methods, such as vagus nerve stimulation or one of neurosurgical procedures. The vagus nerve stimulation in combination with drug therapy can be very beneficial. For the purpose of stimulation, the vagus nerve stimulator is implanted in the left chest and the wire electrode is wrapped around the left vagus nerve [1]. The vagus nerve stimulator works on the assumption that stimulation of the nerve vagus sensory fibres can desynchronize cortical activity and reduce the incidence and severity of the epileptic seizures [1]. Another possibility for the treatment of pharmacoresistant epilepsy is surgical resection of epileptic regions of the brain. It is recommended to perform surgical resection as soon as it is determined that it is the only possible treatment , because the long term, frequent and severe attacks can lead to serious damage of the brain tissue and significantly affect cognitive and motor abilities of patients with epilepsy.

The result of the surgical resection is removing one part of the brain, and is of great importance that before the resection areas responsible for the generation of epileptic seizures are localized with great precision, but it is of equal importance to determine whether these areas can be removed without fatal consequences to neurological and cognitive function. For this purpose, detailed preoperative assessment designed to accurately predict the outcome of the surgery and to preserve the quality of life of patients is performed.

The preoperative assessment and invasive monitoring is being performed since 2010 at the Department of Neurology, University Hospital Center Zagreb, as part of the Referral Centre for Epilepsy of the Ministry of Health of the Republic of Croatia, led by Prof. Sanja Hajnšek. A multidisciplinary team consisting of neurologists, neurosurgeons, neuroradiologists and medical engineers participates in this extremely demanding procedure. The procedure is highly personalized. It requires a high degree of expertise and knowledge, and careful selection of patients based on a detailed preoperative evaluation (determination of the semiology of the seizures, epileptogenic lesion detection, and detection of the epileptogenic zone [4]). After the selection of patients, the preoperative evaluation is performed, which precedes the neurosurgical procedure of removing epileptic tissue.

Preoperative evaluation can be divided into two phases: Phase I - non-invasive procedures and Phase II - invasive procedures. Phase I includes: preoperative neuropsychological and neurocognitive testing, cognitive evoked potentials, EEG polygraph video recording, magnetic resonance (MR - 3T), MR volumetric analysis (particularly hippocampal sclerosis), functional MR recording with MR tractography, MR spectroscopy, and 'postprocessing' MR methods. Examples of the results of the MRI are shown in Figure 1.

Also, the functional imaging methods are performed, such as PET (positron emission tomography), SPECT (single-photon emission computed tomography) and SISCOM (Subtraction ictal SPECT co-registered to the MR) which presents comparison of ictal and interictal SPECT co-registered to MR (Figure 2).

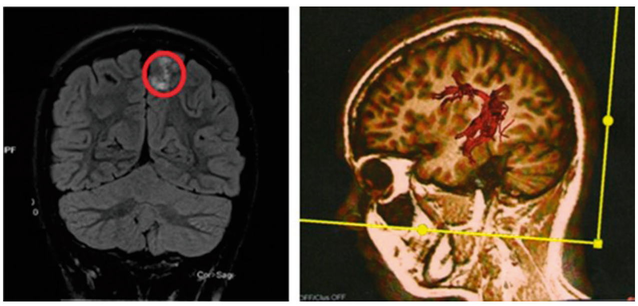

Fig. 1: a) MR-3T with marked area of the lesion and b) functional MRI with a location of *Fasciculus arcuatus*

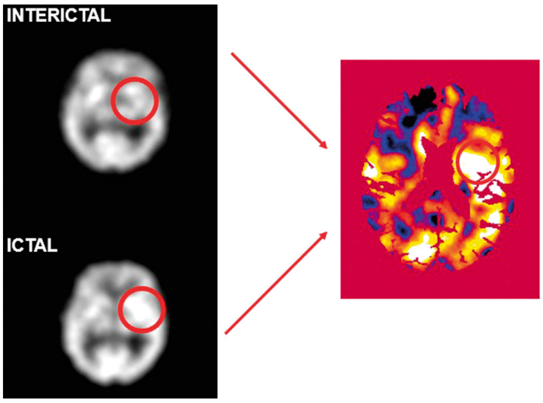

Fig. 2: SISCOM – subtraction of ictal from interictal SPECT and correlation with MRI; the connection between functional and morphological information, the area of the epileptogenic activity is marked

Based on the results obtained in the Phase I of the preoperative evaluation, the more detailed location of the area of interest is known, which is necessary for the Phase II. The Phase II consists of invasive procedures that will provide detailed information about the exact location of the epileptogenic tissue that has to be removed. Also, the Phase II emphasizes the value of the invasive monitoring, because it shows what would happen if the epileptic tissue is removed and what impact it will have on the patient's quality of life.

Invasive stage of the preoperative evaluation consists of the Wada test and invasive EEG monitoring. In the Wada test one hemisphere of the brain is temporarily anesthetized with certain amount of anaesthetic in order to see what impact the absence of one hemisphere would have on motor and cognitive functions of patients [5]. Although the Wada test is the golden rule of lateralisation of speech function, it is important to assess for each patient the ratio between risks and complications related to this method and the postoperative benefit.

Invasive EEG monitoring is a procedure that determines the exact location of the epileptic zone for the neurosurgical resection, but also at the same time maps areas of the cortex responsible for speech, cognitive, motor and sensory functions. Special electrodes for invasive monitoring are implanted into the patient, and EEG activity is monitored over several days (24 hour a day) with a 128-channel EEG amplifier. Based on the data obtained from methods in Phase I, for each patient it is determined which electrodes are required for invasive monitoring and precise location where electrodes should be implanted. There are several types of electrodes, they can vary in their form and way of implantation (surface electrodes or deep electrodes). Figure 3 shows a schematic view of the location of the electrodes (a) and a realistic view of the location (b). From the data obtained from invasive monitoring about the location of the epileptogenic zone, neurosurgeons determine the trajectory of the neurosurgical resection.

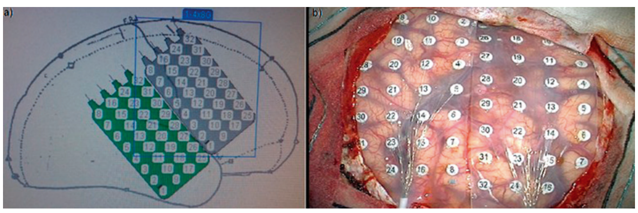

Fig. 3: Electrode scheme (a) and realistic representation (b)

Anatomy of the brain (gyrus and sulci) and the organization of brain functions are specific for each person. Therefore it is necessary to determine whether the area of the epileptogenic zone, which is planned for neurosurgical resection, also contains areas of the brain associated with motor control, sensors, and cognitive functions or speech. The "brain mapping", whose main role is to preserve the quality of life of the patient after surgery, should be performed for every patient. "Brain mapping" is performed with the cortical stimulator and a battery of tests, where electrical stimulation of individual electrodes simulates the disabling brain tissue beneath these electrodes to determine what would happen if that piece of brain tissue is removed. The battery of tests is very carefully selected with the purpose to examine cognitive, motor and sensory functions. During the procedure, the stimulation is performed with two by two electrodes and the intensity of the stimulation is gradually increased. During the test, it is important to record all the changes that the patient feels regarding the motor, sensory, and cognitive functions and speech.

Based on the results of the testing, for each patient the functional brain map is defined (shown in Figure 4). The functional brain map is very important for the planning of the neurosurgical resection because it provides insight into which motor, sensory or cognitive functions are related to the area of the epileptogenic zone, and which part of the brain tissue could be removed without adverse consequences for the patient.

Based on the information obtained from the invasive monitoring, the neurosurgical removal of epileptic tissue is performed.

The success of the procedure is evaluated according to the quality of life of the patient after the surgery, measured with a degree of the reduction of epileptic seizures while preserving all motor, sensory and cognitive functions.

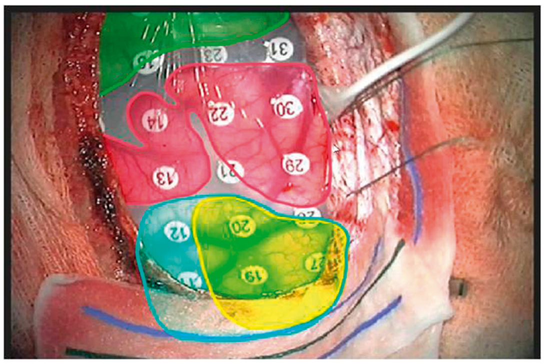

Fig. 4: The functional brain map: individual presentation of sensory and motor areas related to the epileptogenic zone; red line – primary sensor area, green line – primary motor area, yellow line – area of lesion, blue line – epileptogenic area

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