A new method for intraoperative localization of epilepsy focus by means of a gamma probe*

Um novo método para a localização intraoperatoria de foco de epilepsia mediante utilização de gamaprobe

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Abstract

Objective: To evaluate the utility of a new multimodal image-guided intervention technique to detect epileptogenic areas with a gamma probe as compared with intraoperative electrocorticography.

Materials and Methods: Two symptomatic patients with refractory epilepsy underwent magnetic resonance imaging, video-electroencephalography, brain SPECT scan, neuropsychological evaluation and were submitted to gamma probe-assisted surgery.

Results: In patient 1, maximum radioactive count was initially observed on the temporal gyrus at about 3.5 cm posteriorly to the tip of the left temporal lobe. After corticotomy, the gamma probe indicated maximum count at the head of the hippocampus, in agreement with the findings of intraoperative electrocorticography. In patient 2, maximum count was observed in the occipital region at the transition between the temporal and parietal lobes (right hemisphere). During the surgery, the area of epileptogenic activity mapped at electrocorticography was also delimited, demarcated, and compared with the gamma probe findings. After lesionectomy, new radioactive counts were performed both in the patients and on the surgical specimens (ex-vivo).

Conclusion: The comparison between intraoperative electrocorticography and gamma probe-assisted surgery showed similarity of both methods. The advantages of gamma probe include: noninvasiveness, low cost and capacity to demonstrate decrease in the radioactive activity at the site of excision after lesionectomy.

Keywords: Radioguided surgery; Epilepsy; Gamma probe; Electrocorticography; Brain SPECT.

Resumo

Objetivo: Avaliar a utilidade de um novo método de intervenção multimodal guiado por imagem, permitindo a detecção de áreas epileptogênicas mediante utilização de gamaprobe em comparação à eletrocorticografia intraoperatoria.

Materiais e Métodos: Dois pacientes sintomáticos com epilepsia refratária realizaram ressonância magnética, videoeletroencefalograma, SPECT cerebral, avaliação neuropsicológica e foram submetidos a neurocirurgia usando gamaprobe.

Resultados: No paciente 1 as contagens radioativas inicialmente estavam no máximo no giro temporal, cerca de 3,5 cm posterior à ponta do lobo temporal esquerdo. Após corticotomia, o gamaprobe apontou o ponto máximo na cabeça do hipocampo, de acordo com os achados de eletrocorticografia intraoperatoria. No paciente 2 as contagens foram máximas na região occipital em sua transição com os lobos temporal e parietal (hemisfério direito). Na cirurgia, a área mapeada da atividade epileptogênica na eletrocorticografia foi também delimitada, demarcada e comparada aos dados do gamaprobe. Após a lesionectomia, procedeu-se uma nova radiocountagem no paciente e na peça cirúrgica (ex-vivo).

Conclusão: A comparação entre os métodos mostrou acurácia praticamente similar. As vantagens do gamaprobe incluem: não invasividade, baixo custo e capacidade de demonstrar redução da atividade radioativa no local da exérese.

Unitermos: Cirurgia radioguiada; Epilepsia; Gamaprobe; Eletrocorticografia; SPECT cerebral.

INTRODUCTION

Epilepsy is one of the most prevalent chronic neurological disorders, affecting 1–2% of the population worldwide.(1,2) Notwithstanding the wide variety of currently available anticonvulsant drugs, 25–30% of patients remain refractory to the optimized conservative treatment. Such a refractoriness, that is generally greater in cases of partial epilepsy than in cases of generalized epilepsy, causes significant loss in quality of life and self-esteem, suggesting that, in such cases, the surgical treatment should be considered as a therapeutic alternative.(3)

Not all patients with refractory epilepsy, but only some of them, are candidates for surgery.(4) Typically, patients with
partial epilepsy are most frequently candidates for surgery than those with generalized epilepsy\(^5\).

The definition as regards surgical indication and surgical technique of choice depends on the location and number of epileptogenic foci (EFs), besides the type of epilepsy\(^6\).

In cases of generalized epilepsy, EFs are generally bilateral and multiple. Thus the foci resection is poorly feasible, and an option is made for either disconnectional (corpus callosotomy) or neuromodulatory (left vagus nerve stimulation or deep cerebral stimulation of the ventromedial nucleus of thalamus) techniques. On the other hand, in cases of partial epilepsy (either simple or complex), the foci are unilateral and frequently located in a limited area of the brain. In such cases, option is made for EF resection. In cases where resection is unfeasible due to EF location in eloquent cerebral areas, one may opt for treatment with neuromodulatory techniques, such as deep brain stimulation of the anterior nucleus of the thalamus or hippocampus.

Thus, one may conclude that the EF identification is a *sine qua non* condition for the surgical indication, requiring a careful diagnostic work-up to describe the convulsive seizure, including neuropsychological evaluation; electroencephalography (EEG); video EEG (for electroclinical correlation), either with or without invasive electrodes (foramen ovale, subdural or intracerebral); magnetic resonance imaging (MRI) to identify structural epileptogenic lesions, if applicable, by means of localization of temporal mesial sclerosis and small areas of cortical dysplasia; interictal or ictal single photon emission computed tomography (SPECT) to allow the identification of functionally abnormal areas corresponding to EFs.

In case of resection surgeries, particularly in extratemporal epilepsy where invasive monitoring has not been employed, intraoperative confirmation of the EF is required. Electrocorticography is indicated in such cases and once the EF is identified, it is intraoperatively resected\(^6,7\).

The question that is proposed by the authors is the following: could an epileptogenic focus be interoperatively identified by any other mean?

Cerebral perfusion scintigraphy or brain SPECT is a recognized complementary method for the diagnosis of a range of diseases. The intravenously administered radiotracer remains concentrated in the normal and abnormal areas of the cortex for many hours, differently from the other regions of the body which demonstrate a physiological washout. The idea of intraoperatively utilizing a portable gamma ray detector (gamma probe) is based on such a concept. The gamma probe is generally utilized to identify sentinel lymph nodes or primary lesions in cancer patients.

The use of gamma probe in brain surgery that is known as gamma probe-assisted surgery was first introduced into the clinical practice to guide the resection of brain tumors\(^8\).

Considering that ictal brain SPECT can detect EFs and that the radiotracer remains in the abnormal cortical area for many hours, the authors have considered the hypothesis that the gamma probe might allow the intraoperative identification of the origination point of the epileptic seizures (Figure 1)\(^9\). The present study was designed to test such hypothesis.

**Figure 1.** Gamma probe-assisted neurosurgery based on the more intense uptake quantified by gamma counting in the region of the epileptogenic focus.

**MATERIALS AND METHODS**

Two patients were enrolled in the present pilot study. Both patients presented with epilepsy refractory to optimized conservative treatment and signed a term of free and informed consent once they were informed about the objective of the present study – i.e. that the gamma probe would not be utilized to guide the surgery, but only to compare the results obtained with such instrument with those observed at electrocorticography.

Brain SPECT scans were performed at the basal state (interictal phase) and during epileptic seizure (ictal phase), some hours before surgery. Besides the conventional dose, no additional radiopharmaceutical dose was required. All the radioguided surgical procedures were performed with the standard radiopharmaceutical dose applied some hours before the surgery.

The nuclear medicine images (interictal and ictal phases) were presented to the neurosurgeons team immediately before the surgery. The other tests were performed on an inpatient basis.

The patient 1 was a 25-year-old, right-handed man who presented with complex partial seizures (Five seizures per month on average) for 16 years. Interictal EEG demonstrated intermittent epileptogenic activity in the left temporal lobe, and ictal video-EEG showed the onset of the seizure in the left zygomatic and medial temporal electrodes. At MRI, a cavernoma was observed in the ipsilateral fusiform gyrus (Figure 2), and ictal SPECT demonstrated left temporal hyperperfusion (Figure 3). The neuropsychological evaluation revealed global worsening of his memory.

The patient 2 was a 29-year-old, left-handed woman who presented with complex partial seizures and clonic seizures...
targeting the neck with rotation of the head to the left since her adolescence. Interictal EEG revealed epileptogenic activity in the T6, P4 and O2 electrodes. Ictal video-EEG demonstrated three typical seizures, but did not allow the identification or lateralization of the seizures origination point (inconclusive). MRI demonstrated posterior temporoparietal and right occipital atrophy (Figure 4), and ictal SPECT showed an extensive area of hyperperfusion surrounding a smaller area of hypoperfusion (Figure 5). The neuropsychological evaluation revealed only a slight impairment of the verbal memory.

The radiopharmaceutical utilized in the ictal SPECT scans was technetium-99m labeled ethylenediamine cysteine (EDC) manufactured by Instituto de Pesquisas Energéticas e Nucleares – Comissão Nacional de Energia Nuclear, Brazil. The patients underwent surgery few hours (less than five hours) after EDC injection (ictal phase).

The surgery was performed under general anesthesia. After craniotomy on the probable epileptogenic area, radioactivity counting was performed with the gamma probe (Neoprobe 2000; Johnson & Johnson, USA). The areas with increased or decreased (patient 2) counts were marked with a cotton thread. Subsequently, electrocorticography was performed with subdural plate and depth electrodes implanted on the head of the hippocampus and amygdala, initially under spontaneous activity and subsequently after activation with alfentanil. The left temporal hyperperfusion area (patient 1) was delineated and resected. Then, the mapped areas of epileptogenic activity (electrocorticography) were delineated and compared with those detected by the gamma probe. Once the lesionectomy was completed, a new radioactivity counting was performed at the resection site and on the surgical specimen (ex-vivo).

RESULTS

In the patient 1, the electrographic study of spontaneous activity revealed to be basically normal. After intraop-
Bayesian neural networks (BNNs) and deep ensembles (DEs) are two popular techniques for representing model uncertainty, but they can be computationally expensive. In contrast, MC dropout (MC-Dropout) is a simpler and more efficient approach that has been used in various applications. However, MC-Dropout is known to be less reliable in capturing accurate uncertainty estimates compared to BNNs and DEs. In this study, we compare the performance of MC-Dropout with BNNs and DEs on a range of datasets, including a novel dataset of electrocorticographic seizures in epilepsy. We find that MC-Dropout generally provides more accurate uncertainty estimates than BNNs and DEs, but at a fraction of the computational cost. These findings suggest that MC-Dropout could be a useful tool for improving the reliability of uncertainty estimation in neural networks.
Another additional advantage would be the capacity of demonstrating the decrease in radioactivity counts at the resection site after the removal of the epileptogenic area.

The authors conclude that possible indications for the present technique would be for extratemporal epilepsy, in cases with more than one structural lesion (dual pathology), and in cases where MRI does not demonstrate structural alterations (cryptogenic epilepsy) and where electrocorticography might have a significant difficulty in the intraoperative detection of the epileptogenic focus.

The study demonstrates that radioactivity counting by means of a gamma probe was as effective as the intraoperative electrocorticography to detect epileptogenic area in both patients. Thus the results obtained with both techniques were practically congruent.

REFERENCES