Chronic deep brain stimulation in mesial temporal lobe epilepsy

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Abstract
The objective of this study was to evaluate the efficiency and the effects of changes in parameters of chronic amygdala-hippocampal deep brain stimulation (AH-DBS) in mesial temporal lobe epilepsy (TLE). Eight pharmacoresistant patients, not candidates for ablative surgery, received chronic AH-DBS (130 Hz, follow-up 12-24 months): two patients with hippocampal sclerosis (HS) and six patients with non-lesional mesial TLE (NLES). The effects of stepwise increases in intensity (0-Off to 2 V) and stimulation configuration (quadripolar and bipolar), on seizure frequency and neuropsychological performance were studied. The two HS patients obtained a significant decrease (65-75%) in seizure frequency with high voltage bipolar DBS (≥1 V) or with quadripolar stimulation. Two out of six NLES patients became seizure-free, one of them without stimulation, suggesting a microlesional effect. Two NLES patients experienced reductions of seizure frequency (65-70%), whereas the remaining two showed no significant seizure reduction. Neuropsychological evaluations showed reversible memory impairments in two patients under strong [...]
Introduction

About 20% of epileptic patients suffer from a pharmacologically intractable epilepsy. A surgical intervention is not possible in many cases because seizures arise from several brain regions and/or a resective surgery would produce unacceptable neurological or cognitive impairments. Hence, alternative treatment possibilities are required.

Encouraged by the success of deep brain stimulation (DBS) for movement disorders, this technique has been recently investigated for different intractable epileptic syndromes. Different sites of stimulation have been investigated targeting the amygdalo-hippocampal complex (AH), the cerebellum, the thalamic anterior nucleus, the thalamic centro-median nucleus, the subthalamic nucleus and the caudate nucleus. So far, AH stimulation has been applied in approximately 40 patients worldwide. Long-term observations in various studies conducted on patients implanted for receiving chronic high frequency stimulation (HFS, 130–190 pulses per second, pps; 5,8,11,12) showed a complete seizure control in 2 of 22 patients, a reduction of seizure rates of more than 45% in 13 patients, a moderate reduction of below 30% in 5 patients, no changes in 1 patient and 1 patient experienced an
increase of seizure frequency of 114%. Thus, the effect of HFS is very variable, and despite good response in some patients, it may not be the optimal stimulation frequency for all patients.

On the other hand, a single human study reported a beneficial effect of LFS on temporal lobe mesial-basal epileptic foci.6

Since there are very few data on LFS in human, and given that the effect of HFS does not have a consistently beneficial effect, we undertook the present study to compare the effects of high (130 pps) versus low frequency (5 pps) stimulation of the epileptic focus on the interictal spike activity.

Methods

Patients

Three subjects, all suffering from mesial temporal epilepsy, were enrolled in the present study. Due to the presence of conflicting scalp EEG data and the fact that the MRI was negative, invasive evaluation with depth electrodes was proposed (for patient details see Table 1). All 3 patients were implanted with depth electrodes (SD-BPX, Ad-Tech Instruments, Racine, Wis., USA) containing eight contacts each under stereotactic conditions. The amygdala, anterior hippocampus and posterior hippocampus were targeted bilaterally through an orthogonal approach. The dorsal frontal cortex was also implanted bilaterally, targeting the supplementary motor cortex and the anterior cingulated gyrus in patient S3 through the same approach. In addition, electrodes into the orbito-frontal lobe were implanted on the left in patient S1 and bilaterally in patients S2 and S3 through an oblique approach in the coronal plane. Reconstruction of post-implantation high-resolution CT scans with pre-operative MRI allowed assessment of the position of the depth electrode contacts.13

Drug treatment was tapered in all patients 2–5 days before study enrollment and kept constant during the study period (Table 2).

The research protocol describing this study was approved by the Ethics Committee of the University Hospital of Geneva. All subjects gave their informed consent.

Electrical stimulation

A head computed tomography (CT) was performed with 1 mm slices after the implantation. Co-registration with the patient’s MRI using a six parameters rigid body algorithm enabled inter-modality registration in order to precisely assess the location of the depth electrode contacts.13
Bipolar electrical stimulation was applied to the two contacts that showed the earliest ictal involvement (Table 2). We used an external Medtronic M3625 stimulator (Medtronic Inc., Minnesota, USA). High (130 pps) and low frequency (5 pps) stimulations were applied (450 μs/phase, 1V). Stimulation was carried out during wakefulness, i.e. starting between 10 and 11 a.m. and lasting for 3–6 h. Additional technical details of the stimulation used for each patient are given in Table 2.

**Analysis**

In order to evaluate the efficacy of the electrical stimulation on the interictal activity, we computed the rate of spikes per minute, 2 h before, during, and 2 h after the stimulation periods on the contacts adjacent to the stimulation sites as well as in the contralateral homologous structures (Table 2). In order to avoid a bias due to vigilance changes related to increase or decrease of interictal discharges, analysis was restricted to awake periods. Stereotactic EEG (SEEG, CEEgraph XL system, Biologic Inc., Illinois, USA) was recorded continuously with a sampling frequency of 512 Hz. In order to remove DBS artifacts SEEG were low-pass (15 or 30 Hz) and high-pass (1.6 Hz) filtered before spikes were counted (Table 3).

We used automatic spike detection software algorithm based on spatio-temporal correlation (BESA, MEGIS Software GmbH Penzberg, Germany). To statistically compare the number of spikes per minute computed before, during and after the stimulation periods, we used the Sign Test given that the sampled data for the same patient are dependent variables and their distribution was not normal.
Results

The electrodes were correctly implanted in the targeted structures as shown as an example in Fig. 1 in patient S1. Fig. 2 describes the mean number of interictal spike per minute, before, during and after LFS period (A) and HFS period (B) in patient S1. Fig. 3 describes the mean number of interictal spike per minute, computed over periods of about 2 h, before, during and after HFS and LFS periods in all three patients.

High frequency stimulation (HFS)

HFS of the amygdala-hippocampal structures resulted in a reduction of the interictal spike rate at the stimulated site shortly after the beginning of the stimulation for S1 ($p < 0.001$) and S3 (trend) and after a few hours of stimulation for S2 ($p < 0.01$). Spike reduction extended to the contralateral mesial temporal lobe in S1 and S3.

When the HFS was turned off, a significant increase of the spike rate in the stimulated site was observed in two out of 3 patients. This rebound effect extended to the contralateral mesial temporal lobe in patient S3. In all 3 patients, no seizure occurred during the stimulation and post-stimulation periods (i.e. 18 h).

Low frequency stimulation (LFS)

Important variations, resulting in overall increases of the interictal spike rates, in the ipsilateral and in the contralateral amygdala, were observed in 2 subjects (S1, S3) with LFS. LFS did not produce any significant changes in S2.

Habitual seizures occurred in patients S1 and S3 during and after LFS, similar to their baseline frequency.

Discussion

This study reports the short-term effects of HFS (130 pps) and LFS (5 pps) in non-lesional temporal epilepsy. Stimulation with 130 pps, but not with 5 pps, was associated with a reduction of interictal spike discharges and absence of any clinical or subclinical seizures during and after the stimulation periods. While the analyzed periods were too short to allow definite conclusion on the clinical efficacy of chronic DBS in these patients, our study provides preliminary evidence that HFS is more useful than LFS for the treatment of this epilepsy syndrome. In recent years, studies have shown that MRI-negative temporal lobe epilepsy does not necessarily represents a contraindication to surgical treatment, especially if the PET provides evidence of unilateral onset. However, many patients have bilateral seizure onset, and intact memory functions. In these cases, surgery is unlikely to provide complete seizure control, but instead may create major neuropsychological deficits.

Even if it can be argued that the rate of interictal epileptic discharges might not be a valid measurement of the epileptogenic activity, our study adds further evidence to the effect of DBS applied on the epileptogenic focus in temporal lobe epilepsy. Our observations are in agreement with other studies showing the reduction of interictal spike rates observed after HFS of the amygdala-hippocampal complex measured during short off stimulation periods during invasive explorations. Studies...
of chronic mesial temporal HFS studies conducted with implanted devices showed an increase of the beneficial effect of DBS over time in the responder patients. Long-term follow-up of patients implanted DBS devices are required to determine if such a progressive antiepileptogenic effect can be predicted by short-term evaluation through intracranial electrodes.

The effect of DBS in the contralateral mesial temporal lobe observed in two patients suggests that DBS might not only act at site of the stimulation but also at distant sites through inhibitory/excitatory connectivity. This effect illustrates the strong connectivity between bilateral limbic structures and is consistent with usual findings in temporal lobe epilepsy: contralateral propagation of the epileptogenic activity and frequent bilateral abnormalities seen on PET, SPECT as well as MR volumetry and MR spectroscopy. This close functional relationship between both temporal lobes could make DBS a valuable tool for patients with bilateral temporal lobe epilepsy.

The LFS of the amygdala-hippocampal complex increased the epileptogenic interictal activity in 2 out of 3 patients, although it was not associated with any increase in the usual frequency or the duration of the seizures. Chkhenkeli et al. used LFS (1—20 pps) in patients with mesiobasal temporal lobe foci and observed that stimulation with 1—3 pps, but not 5—20 pps, suppresses interictal discharges. LFS was also found to be beneficial in other brain structures of epileptic patients, notably the anterior thalamus, the caudate nucleus, cerebellum and neocortex, with stimulation of several seconds or minutes, and was found to be beneficial for these sites. Further studies are needed investigating the effects of LFS with even lower frequencies in non-lesional temporal lobe epilepsy or other epilepsy syndromes, not amenable to surgery.

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References