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Seizure outcome after hippocampal deep brain stimulation in a prospective cohort of patients with refractory temporal lobe epilepsy

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ABSTRACT

Purpose: In this study, we present the results obtained from a series of patients with refractory temporal lobe epilepsy (r-TLE) who underwent hippocampal deep brain stimulation (Hip-DBS).
Methods: Nine consecutive adult patients were studied. Low-frequency and high-frequency stimulation was carried out immediately after the insertion of each electrode. Chronic continuous high-frequency stimulation was used during treatment. The mean follow-up time was 30.1 months. The mean age of the patients was 37.2 years. The MRI scan was normal in three patients; four patients had bilateral mesial temporal sclerosis (MTS), and two had unilateral MTS.
Results: The patients with unilateral MTS received unilateral implantation and experienced a 76% and an 80% reduction in seizure frequency after Hip-DBS. All patients with normal MRI scans were implanted bilaterally. Two of these patients received unilateral activation of the electrodes and experienced a 97% and an 80% reduction in seizure frequency; the third patient had bilateral activation of the device and was a non-responder. All patients with bilateral MTS were implanted bilaterally. Three of these patients received unilateral activation of the device and experienced a 66%, a 66% and a 100% reduction in seizure frequency after Hip-DBS; one patient had bilateral electrode activation, and was a non-responder. Whenever present, generalised tonic–clonic seizures disappeared completely after Hip-DBS.
Conclusions: Although performed on a relatively small number of patients, Hip-DBS was safe and effective in our patients with r-TLE. Seven of the nine patients were considered responders. Hip-DBS might represent a useful therapeutic option in patients with refractory temporal lobe epilepsy who were not candidates for resective surgery or have had previous failed procedures.

1. Introduction

Deep brain stimulation (DBS) has been used with an increasing frequency to treat patients with refractory epilepsy who were not good candidates for conventional resective surgery. Two large randomised clinical trials showed that DBS was safe and effective in the treatment of refractory epilepsy. Fisher et al.[1] reported the effectiveness of intermittent anterior thalamic stimulation, while Morrell et al.[2] studied the outcome after responsive DBS, in a study that included a significant number of patients with temporal lobe epilepsy.

Hippocampal DBS (Hip-DBS) has been rarely reported in the literature. The rationale for Hip-DBS was based on the relevant role played by the hippocampus in both seizure generation and spread, as frequently seen during invasive neurophysiologic monitoring and surgery. Presently, all series included a relatively small number of patients, used different stimulation paradigms and recruited heterogeneous patient populations.[3–8]

We present the results obtained from a series of patients with refractory temporal lobe epilepsy who underwent Hip-DBS.

2. Methods

Nine consecutive adult patients (seven men) with TLE who were surgically treated between 2009 and 2011 at the Hospital Brigadeiro Epilepsy Surgery Program were studied. The pre-operative work-up consisted of clinical history, neurological examination, interictal and ictal EEG, and MRI.

Preoperative patient characteristics such as sex, age at seizure onset, age at presentation, seizure type and frequency, and antiepileptic drug (AED) regimen were recorded.

The clinical diagnosis was based on the International Classification of Seizures (1981) and Epileptic Syndromes (1989). The following clinical characteristics were considered diagnostic for TLE: simple partial seizures (SPS) of the *déjà vu* or *jamais vu* type, or SPS including epigastric or psychic manifestations (i.e., fear)

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followed by complex partial seizures (CPS) characterised by staring and masticatory automatisms, which may be accompanied by superior limb automatisms or contralateral superior limb dystonia.

All patients had 32-channel interictal and ictal EEG recordings (10–20 system; at least three seizures recorded) including zygomatic electrodes. The presence of temporal lobe interictal spiking and the absence of extra-temporal discharges were considered findings related to TLE.

All patients had MRI examinations including sequences that allowed the adequate study of the hippocampal formation: 1 mm thick (0.3 mm interval) FLAIR, T2 and IR coronal slices perpendicular to the hippocampal axis; 3 mm thick T1, T2, gradient echo, FLAIR and IR axial slices and T1 sagittal slices. Images were visually reviewed by two members of the epilepsy team independently.

Patients underwent Hip-DBS under general anaesthesia and intra-operative scalp EEG monitoring. Electrodes (Kinetra system, 3387 Electrodes, Medtronic Inc., Minneapolis) were inserted with the patient in a prone position, through occipital burr holes. Planning was based on stereotactic CT/MRI fusion; the distal contact of the electrode was aimed at the anterior hippocampal head and inserted through the occipital burr hole along the axis of the hippocampus proper, as determined by the fused CT/MRI datasets. Intra-operative neuronavigation was used during electrode insertion. Intra-operative low frequency (6 Hz; 4 V; 300 μs) and high frequency (130 Hz; 4 V; 300 μs) stimulation was carried out immediately after the insertion of each electrode. The generator was turned off after this intra-operative neurophysiological study and programmed on an out-patient basis after the skin stitches were removed. A post-operative volumetric CT scan documented the exact position of the electrode.

Chronic continuous high frequency stimulation was used during treatment (1–3.5 V; 130 Hz; 300 μs). Bipolar continuous stimulation between the contacts of the more distal and the more proximal electrodes was carried out, aiming to stimulate the entire implanted area. The voltage was increased in 0.2 V increments in 2-week intervals, to a maximum of 3.5 V, or until the patient was rendered seizure-free or adverse effects appeared.

The reduction in seizure frequency was studied in each patient after Hip-DBS. Follow-up time ranged from 15 to 50 months (mean = 30.1 months). Medications were kept stable during the study. Patients with at least a 50% reduction in seizure frequency were considered responders.

In this sample, age ranged from 23 to 53 years (mean = 37.2). Age of seizure onset ranged from 0.5 to 22 years (mean = 11.7 years).

Interictal EEG showed bilateral temporal lobe spiking in seven patients (Patients I, II, III, VI, VII, and VIII), and unilateral temporal lobe spiking in the other two (Patients IV and V). Ictal recordings showed seizures arising mainly from the left temporal lobe in five patients (Patients I, II, III, V and VI) and from the right temporal lobe in four patients (Patients IV, VII, VIII, and IX).

The MRI was normal in three patients (Patients III, VI, and VIII). Four patients had bilateral mesial temporal sclerosis (Patients II, V, VII, and IX) and two had unilateral mesial temporal sclerosis (Patients I and IV; one left, and one right). (Table 1)

Patients were included if they were not good candidates for resection (i.e., presence of bilateral MTS, left temporal lobe epilepsy with normal MRI) or declined to undergo resective surgery (i.e., unilateral MTS).

The Student's *t*-test was used for statistical analyses ($p < 0.05$ was considered significant).

3. Results

In six patients (Patients I, II, III, V, VIII, and IX), an increase in temporal lobe spiking was observed unilaterally at the time of electrode insertion, as noted in a previous study[13]; in two patients (Patients IV and VIII), a bilateral spiking increase was noted. In all patients, an ipsilateral temporal lobe recruiting response (time-locked spike-like activity) was noted during low frequency acute stimulation. In six patients (Patients I, II, III, VI, VII, and VIII), high frequency intra-operative hippocampal stimulation reduced or abolished interictal spiking. We did not observe any increase in spike frequency after high-frequency intra-operative Hip-DBS or any after-discharges after low-frequency intra-operative stimulation.

Hip-DBS was able to reduce seizure frequency in this series ($p < 0.05$). Six patients were implanted bilaterally (Patients II, III, V, VI, VII, VIII and IX) and two unilaterally (Patients I and IV). The side defined by the surface ictal recordings was initially activated in those patients who received bilateral implantation; the second side was activated only after stimulation of the first side failed to provide seizure frequency reduction or disappearance. The two patients with unilateral mesial temporal sclerosis, Patients I and IV, received unilateral implantation and experienced a 76% and an 80% reduction in seizure frequency after Hip-DBS, respectively. In one of these patients (Patient I), generalised tonic–clonic seizures disappeared completely. All three patients with a normal MRI (Patients III, VI, and VIII) were implanted bilaterally. Two of these patients, Patients III and VIII, had unilateral activation of the electrodes and experienced a 97% and an 80% reduction in seizure frequency, respectively; the third patient (Patient VI) had bilateral activation of the device and was a non-responder (12% reduction in seizure frequency). All four patients with bilateral mesial temporal sclerosis (Patients II, V, VII, and IX) were implanted bilaterally. Three of these patients, Patients II, VII and IX, had unilateral activation of the device and experienced a 66%, a 66% and a 100% reduction in seizure frequency after Hip-DBS, respectively; one

Table 1
Patient demographics and pre-operative data.

Patient	Sex	Age at surgery	Age seizure onset	Video-EEG interictal	Video-EEG ictal	MRI	Sz type	SzF/month
I	M	27	15	Bitemporal	Left temporal	Left MTS	CPS	3
							GTCS	1
II	M	29	22	Bitemporal	Left temporal	Bilateral MTS	SPS-CPS	30
III	M	23	11	Bitemporal	Left temporal	Normal	CPS	180
IV	F	28	0.5	Right temporal	Right temporal	Right MTS	CPS	5
V	M	46	12	Left temporal	Left temporal	Bilateral MTS	SPS-CPS	8
VI	F	45	18	Bitemporal	Left temporal	Normal	SPS-CPS	8
							GTCS	1
VII	M	36	1	Bitemporal	Right temporal	Bilateral MTS	CPS	3
VIII	M	46	18	Bitemporal	Right temporal	Normal	SPS-CPS	5
IX	M	55	8	Bitemporal	Right temporal	Bilateral MTS	CPS	30
							GTCS	1

Sz, seizure; SzF, seizure frequency, CPS, complex partial seizure; GTCS, generalised tonic–clonic seizure; SPS, simple partial seizure; MTS, mesial temporal sclerosis; M, male; F, female.