Among the 46 million patients with epilepsy in the world, focal onset seizures are most commonly associated with mesial temporal lobe epilepsy (MTLE). In patients with MTLE, 30% have drug-resistant epilepsy and are potential candidates for surgical treatments. Anterior temporal lobectomy (ATL) has been the surgical procedure of choice for these patients. However, in certain patients, including those with bilateral temporal lobe epileptic foci, those without hippocampal sclerosis (HS) who are at risk for severe cognitive deficits after ablative surgery, and those with a high surgical risk derived from comorbidities, an alternative treatment modality is deep brain stimulation (DBS) of seizure onset zone (SOZ)–related structures.

In our previous study of patients with MTLE in whom intracranial electrodes were placed to determine the location and extension of the SOZ prior to ATL, we analyzed the effects of subacute (2 week), high-frequency hippocampal or parahippocampal cortex (PHC) stimulation through contact of electrodes or grids that defined SOZs. We found reduction in seizure number and interictal paroxysmal activity, as well as a 10-fold increase in the threshold to induce after-discharges. Thereafter, a clinical trial of chronic hippocampal DBS was conducted, which ABBREVIATIONS

ATL = anterior temporal lobectomy; DBS = deep brain stimulation; FAS = focal aware seizures; FIAS = focal impaired awareness seizures; GTCS = generalized tonic clonic seizures; HS = hippocampal sclerosis; IED = interictal epileptiform discharge; MTLE = mesial temporal lobe epilepsy; PHC = parahippocampal cortex; QOLIE-89 = Quality of Life Epilepsy Inventory; SAHCS = subacute hippocampal stimulation; SEEG = stereo electroencephalography; SOZ = seizure onset zone; 18F-FDG = 2-18F-fluoro-2-deoxy-d-glucose; 18F-FFMZ = 2-18F-fluoro-flumazenil.

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confirmed a significant decrease in seizure number with this therapy.

However, while patients without HS showed an immediate and significant decrease in seizure numbers in that study, those presenting with HS showed less significant seizure reduction, with an antiseizure delay up to 7 months. Other studies have also reported the need for higher intensities of electrical stimulation to achieve seizure reduction in patients with HS.

On the other hand, in surgical specimens of stimulated patients, analysis of changes in neurotransmitter content induced by subacute electrical stimulation of the parahippocampal formation (subacute hippocampal stimulation [SAHCS]) revealed that electrical stimulation induced a significant increase in gamma-aminobutyric acid (GABA) content and in benzodiazepine receptor expression in the PHC, which may account for the observed inhibition of epileptogenic activity.

Since the subiculum and PHC escape the sclerotic process in patients with MTLE, consecutive pilot studies were performed that were directed to explore the anticonvulsive effects of subicular and PHC DBS in patients with drug-resistant MTLE. In this study we aimed to determine the antiseizure effects of DBS of the PHC as an alternative treatment in patients with MTLE and HS.

Methods
Study Design
Inclusion criteria were the following: age 18–60 years, drug-resistant temporal lobe epilepsy, and MRI or EEG results with undetermined seizure onset. These characteristics indicated the requirement of stereoelectroencephalography (SEEG). All patients had an average seizure rate of ≥ 4 clinically incapacitating seizures a month while under adequate antiseizure treatment. Included female patients received contraceptive treatment during the study. The Scientific, Research and Ethics Committees of the General Hospital of Mexico reviewed and approved the protocol. Patients and families were informed and signed a written consent form and underwent the following consecutive stages of the investigation.

Baseline
The study baseline period consisted of a 3-month follow-up prior to electrode implantation. The study protocol for the baseline period included the following procedures: 1) obtaining an accurate description of seizure numbers and types in focal seizures without impaired awareness (focal aware seizures [FAS]), focal impaired awareness seizures (FIAS), and focal seizures evolving to generalized tonic-clonic seizures (GTCS); 2) EEG confirming paroxysmal activity in the temporal leads; 3) 1.5-T MRI oriented along the hippocampal axis for axial and coronal views confirming the presence of HS; 4) PET using 18F-fluorodeoxyglucose (18F-FDG) and 18F-fluorodeoxfluoromazin (18F-FFMZ) as radiotracers for identification of SOZ through a quantitative voxel-by-voxel analysis; 5) neuropsychological evaluation, including language dominance, through use of the validated Spanish version of the dichotic listening test, as well as a test battery to evaluate attention and memory (NEUROPSI), which has been validated in a Mexican population according to age and educational level and designed to avoid learning in subsequent examinations; and 6) health-related quality of life assessed by the Quality of Life Epilepsy Inventory (QOLIE-89).

Electrode Implantation
Preoperative PET-CT scans were acquired with 18F-FDG and 18F-FMZ radiotracers, searching the lowest radiotracer uptake region in the PHC to define the SOZ, as described previously. On the day of surgery, MRI studies were fused to a CT scan performed with a stereotactic frame in place (Z-D Leibinger), and trajectories were planned through the use of 3A Praezis Plus software aiming to the SOZ in the PHC. Medtronic 3391 recording-stimulation electrodes, with four 3-mm contacts with a 7-mm center-to-center distance, were inserted using an occipital parasagittal burr hole and connected to a percutaneous extension for SEEG recording during subsequent days. Postoperative MRI confirmed the positioning of the electrodes. Patients were not administered anticonvulsive medications during SEEG until at least 3 seizures were recorded in each patient to identify the electrode contacts that defined the SOZ. 3D image reconstructions for electrode contact stereotactic locations were performed with Stealth planning S7 stations using Cranial 3.0 software (Medtronic Inc.) (Fig. 1). Subsequently, the entire DBS system (Activa-PC, Medtronic Inc.) was internalized.

Stimulation Parameters
Bipolar stimulation was performed through contiguous contacts in the area where the SOZ had been localized by PET scans and SEEG to confirm unilateral or bilateral onset. Stimulation parameters were 130 Hz, 450-usec pulse amplitude, 2.5–3 V, and cyclic stimulation 1 minute on and 4 minutes off.

Double-Blind Protocol
The DBS system was maintained at the off setting in all patients for the first month after implantation; thereafter, patients entered a randomized double-blind protocol by lottery number. All patients had the pulse generator programmed with the same parameters, but in 3 patients stimulation was not activated for 7 months, while in the other 3 patients DBS stimulation was activated at the beginning of the second month. The double-blind code was kept by a third party not involved in medical care or other studies, except to periodically check the stimulation parameters and status of DBS.

Quantitative Evaluation
After the double-blind period, all patients had DBS system turned on and received stimulation during the 12-month open label follow-up, with monthly consultations for collecting diaries of seizure occurrence. Anti-seizure medicine was maintained without modifications during the follow-up period. Seizure calendars for counting and logging dates and times of different seizure types separately were maintained throughout the study.
A multiple median Mann-Whitney nonparametric test was used to compare seizure occurrences between patients in whom DBS stimulation was on and those in whom it was off during the 7-month double-blind period. Thereafter, the seizure decrement in relation to baseline during the 12-month follow-up period in which all patients received DBS stimulation was evaluated for the entire group. At the 12-month follow-up for this period of stimulation in all patients, neuropsychological examinations and the QOLIE-89 were administered and scores were compared with those from the preoperative evaluation.

Interictal Spike Numbers

An automated spike count was performed using Brainstorm, an opensource application for magnetoencephalography (MEG)/EEG analysis. Custom event detection (20–150 msec, > 30 μV) was used to filter signals from artifacts. Custom event detection (20–150 msec, > 30 μV) was performed for identification of interictal epileptiform discharge (IEDs) in a 10-minute selection of 10-second epochs of the maximal paroxysmal activity from the bilateral frontal (F3, F4, C3, C4) and temporal (F7, F8, T3, T4, T5, T6) monopolar EEG leads at baseline and after 12 months of PHC stimulation. Pre- and post-PHC DBS changes in IEDs were compared using the Student t-test.

Results

Patient age ranged from 18 to 52 years (mean 29.3 ± 12.5 years), with age at seizure onset ranging from 1 to 37 years (mean 12 ± 13.2 years). Patient histories of epilepsy ranged from 11 to 25 years (mean 17.3 ± 3.9 years). Seizure frequencies ranged from 6 to 22 per month (mean 11.5 ± 9.4 per month). All patients had HS on MRI, with 2 patients showing unilateral HS (1 left, 1 right) and 4 patients showing bilateral HS. SOZ, determined by PET and SEEG studies, was unilateral in 4 patients (2 right, 2 left) and bilateral in 2 patients (Table 1).

Seizure Outcome

Electrode insertion induced a 40% reduction in seizure number during the first month after implantation. Patients who started DBS during the second month continued to show a significant reduction in seizure numbers (CI 9.1%–50%, p = 0.043), which decreased > 50% at 3 months of DBS stimulation (Fig. 2). In contrast, those patients for whom DBS stimulation was off had only a temporary reduction lasting 1 month. During the 12-month follow-up period of the open-label phase, when DBS stimulation was on in all patients, showed a reduction in seizure number. The most effective seizure control was observed during the 5th month of therapy (mean 39%, CI 18%–50%, p = 0.0002), while the least effective seizure control occurred during the 8th month of therapy. This inadequate seizure control was due to discontinuance of anticonvulsants for several days in 1 patient and the occurrence of pneumonia in another patient. Seizure frequency decreased again during the following month (Fig. 3A). The average rate of seizure decrease during the entire follow-up period was 41% (CI 25%–56%), with none of the patients being seizure free.

Different seizure types showed different degrees of improvement. The best seizure control was achieved for GTCS, which decreased in frequency by over 80% (p < 0.0001) after 2 months of DBS stimulation (Fig. 3B). FIAS decreased by over 50% after the 1st month of DBS stimulation (mean 13%, CI 0%–44%, p < 0.001) (Fig. 3C). In contrast, FAS decrements were not significant at any time point and even demonstrated a higher seizure frequency than baseline during some months (CI 67%–164%) (Fig. 3D).

Interictal Spike Changes on Scalp EEG

IEDs significantly decreased after PHC DBS in both the bilateral temporal (CI 6%–54%) and frontal regions (CI 9%–54%), p < 0.0001, even in patients with unilateral DBS. In fact, the contralateral region to DBS had a greater decrease than the ipsilateral region, though this difference was not statistically significant (Fig. 4A and B).

Neuropsychological Performance

None of the patients had normal baseline memory
scores, which is a common finding in our epileptic population, probably resulting from long seizure histories and resistance to medical treatment. After 12 months of PHC DBS, there was a trend toward improvement in all tests, although it did not reach statistical significance.

Side Effects and Quality of Life
No patients had complications related to the surgical procedures. The range of therapeutic stimulation parameters used in this study had no side effects on 4 patients. Two patients reported nonpainful paresthesia over the V2 branch of the trigeminal nerve territory on the stimulated side during the on period of cycling DBS stimulation, probably due to current spread to the neighboring ganglion, which prevented the desired increase in pulse amplitudes. There were no other reported side effects. None of the patients showed significant differences in the QOLIE-89 general score between baseline (mean score 66, CI 53–79) and after 12 months of DBS stimulation (mean 68, CI 60–76). Two patients who had been unemployed returned to work during the follow-up period.

Discussion
The present study had the following aims: 1) to define a surgical target for the treatment of MTLE in patients with HS that, in our experience, show a lower and delayed antiseizure effect of DBS in the sclerotic hippocampus (the proposal to use PHC DBS was based on information derived from previous studies); 2) to standardize the surgical procedure and thereby make it simpler and safer; 3) to determine the effects of PHC DBS on different seizure types as well as the latency of the antiepileptic effect; 4) to study the mechanisms involved in the antiepileptic effect of PHC-DBS; and 5) to determine if PHC DBS induces cognitive deterioration.

Surgical Approach
In patients subjected to subacute stimulation of the hippocampus prior to anterior temporal lobectomy, the best antiepileptic responses are correlated with higher numbers of neuronal cells in surgical specimens of the hippocampus, particularly the cells in the CA1 and CA4 regions. On the other hand, PHC has been assigned critical roles in the generation and propagation of temporal lobe–onset seizures, and this structure escapes from sclerosis in cases where seizures originate from the mesial temporal lobe. Therefore, we decided to test the effects of PHC DBS for treatment of MTLE in patients with hippocampal sclerosis.

The intrinsic connectivity between the hippocampal formation and the PHC may play an essential role in neuromodulation of this target. The PHC sends projections to all hippocampal formation subfields. These projections originate from neurons in the II and III layers of the PHC, with a few projections from deeper layers that are likely part of a feedback inhibitory system. On the other hand, previous studies on PHC subacute electrical stimulation through subdural grid placement for defining SOZs had demonstrated that high-frequency subacute stimulation of SOZ decreased IEDs, increased postdischarge thresholds, and decreased regional blood flow. Therefore, in patients with HS and possible neuronal cell loss in the CA1 and CA4 regions, DBS of the PHC seemed promising. The present results confirm that PHC DBS induced a faster and more adequate control of FIAS and GTCS than hippocampal stimulation in patients with HS.

Defining the Parahippocampal SOZ as a Target
Determination of the hippocampal areas related to SOZ using a quantitative analysis of minimal hippocampal metabolism of \(^{18}\)F-FDG and decreased potential bind-
ing of 18F-FMZ PET, allowed direct placement of electrodes in parts of the PHC likely to be related to seizure onset or spreading.13 In addition, tetrapolar electrodes spaced 7 mm between contacts (Medtronic Inc.) can be used for EEG recording via a percutaneous extension cable and then connected to an internalized pulse generator (IPG) for DBS, which reduces intracranial electrode placement to a single procedure, thereby saving time and cost of surgical procedures and reducing the risk of possible complications. In addition, the PHC seemed to be a safer target because the electrodes were placed away from the cerebral blood vessels of the Sylvian fissure and the carotid cistern.

PHC DBS Effects on Different Seizure Types

An insertional antiepileptic effect was seen during the first month after electrode implantation in all patients, which has already been reported by others.31,32 In our patients, the antiepileptic effects of electrode insertion did not last beyond 1 month in patients whose DBS stimulators remained off during the double-blind period. Moreover, no correlation was found between the seizure reduction by implantation and that during the follow-up after the 12-month period with DBS stimulation on. In patients who started DBS stimulation during the 2nd month of the double-blind period, seizures had a tendency to decrease even more (Fig. 2). Significant decreases in seizure frequency occurred after the first month of DBS stimulation during the open-label phase for incapacitating FIAS (IQR 19%–20%) and GTCS (IQR 0%–16%). In contrast, FAS increased up to 200% during the first 2 months of DBS stimulation (IQR 67%–236%). However, FAS occurrence

![FIG. 2. Seizure occurrence during the double-blind period. A: Total number of seizures in patients with DBS stimulation on (dark trapezoids) and off (clear trapezoids). B: FAS with DBS stimulation on (dark squares) and off (clear squares). C: FIAS with DBS stimulation on (dark circles) and off (clear circles). D: Focal evolving to GTCS in with DBS stimulation on (dark triangles) and off (clear triangles). There were nonsignificant differences in FAS and FIAS occurrence between patients with DBS stimulation on and those with DBS stimulation off, probably due to the small number of patients in each group. BL = baseline.]
was difficult to assess during our study, as has been observed in other studies.\(^9\),\(^{12,32}\) In 2 patients who reported an unusual increase in this seizure type, extended video-EEG recordings of several clinical seizures did not identify EEG correlations during clinical seizures. Therefore, increases in the number of FAS type seizures should be closely monitored.

### Antiepileptic PHC DBS Mechanisms

On the other hand, the persistence of FAS may indicate that PHC DBS interferes with the propagation rather than the genesis of seizures. In this regard, scalp EEGs obtained before stimulation showed a higher number of IEDs ipsilateral to the SOZ in cases with unilateral seizure onset. After 1 year of PHC DBS, a bilateral reduction in IEDs occurred in the frontal and temporal regions, being more prominent in the hemisphere contralateral to unilateral DBS, perhaps related to a reduction in bilateral synchronous discharges, which results from propagation of seizures with focal onset. Therefore, PHC DBS may be interfering with the propagation rather than the genesis of hippocampal-onset seizures. A quantitative analysis of the changes induced by PHC DBS on PET-MRI with \(^{18}\)F-FDG and \(^{18}\)F-FFMZ at the end of the follow-up period provided further information on the antiepileptic mechanisms and will be the subject of a future report.

### Cognitive Outcome After PHC DBS

No neuropsychological deterioration was observed after 12 to 18 months of PHC DBS, and a slight improvement in performance was observed, which indicates that this therapy achieved neuropsychological preservation. Due to the memory decline reported after hippocampectomy in patients without HS, PHC DBS might be an alternative for those cases.\(^6\)
Latency of Antiepileptic PHC DBS Effects

Antiepileptic effects were observed beginning with the 1st month of DBS stimulation, as shown by comparison of DBS patients in the on- and off-stimulation groups during the double-blind period, particularly for patients with incapacitating seizures. The antiepileptic effect occurred immediately after the onset of PHC DBS stimulation, in contrast with our own series of hippocampal DBS in patients with severe sclerosis, in whom the antiepileptic effect started after 7 months. In recent years, brain stimulation long-term results have been auspicious. In 2017, in a group of 111 adult patients with a 6-year follow-up, Geller et al. observed that patients reached a 53% median seizure reduction at year 2 and up to 66% at year 6. Meanwhile, our pilot group had a 63% median reduction during the 1st year and also faster antiepileptic effects than with DBS of the anterior thalamic nucleus (ATN). However, PHC DBS studies with longer follow-up are needed for comparison.

Future Trends

This study should be extended to a larger number of patients, particularly after bilateral SOZ confirmation with SEEG, in patients with a posterior SOZ in the PHC, particularly those with severe hippocampal sclerosis, and major surgical risks which, in our experience, derive from the toxic effects of antiseizure drugs.

Conclusions

PHC stimulation produces an important antiseizure effect on incapacitating seizures in patients with drug-resistant MTLE and HS. Use of larger interspace contact DBS electrodes facilitates reduction of the surgical procedure to a single intracranial step. Preoperative planning can be assisted by quantitative PET imaging using metabolic and specific radiotracers to define the SOZ. The PHC target is safely positioned away from vascular structures that could be damaged during electrode implantation, and PHC DBS does not seem to induce cognitive deterioration.

Highlights

- PHC DBS has a better and faster seizure response control than other targets.
- Due to its size and position, away from vascular structures, this target is safer.
- PHC DBS might interrupt seizure propagation, rather than seizure generation itself.

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Disclosures
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