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Deep brain stimulation of the subiculum in the treatment for refractory temporal lobe epilepsy due to unilateral mesial temporal lobe sclerosis

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ABSTRACT

Temporal lobe epilepsy (TLE) is the most common form of drug-resistant epilepsy. The main pathological changes primarily involve hippocampal sclerosis (HS). Early resective surgery of the sclerotic hippocampus is typically associated with favorable clinical outcomes. However, not all patients are suitable candidates for resective surgery of mesial temporal lobe structures. Therefore, alternative treatment modalities should be considered. We present the case of a 50-year-old right-handed woman with left HS who underwent unilateral subiculum stimulation for drug-resistant epilepsy (DRE). Since the age of 10, the patient had been experiencing focal to bilateral tonic-clonic seizures (FBTCS). Despite multiple antiseizure medications, she experienced 12 to 17 FBTCS per month in the last two years. Due to concerns about potential memory decline and personal preferences, she refused resective surgery. As an alternative, the patient underwent left unilateral subiculum stimulation. The stimulation resulted in a nearly 67 % reduction in seizure frequency at the last follow-up (20 months after surgery). This case highlights that drug-resistant epilepsy may be effectively treated with subicular stimulation in patients with HS.

Introduction

Temporal lobe epilepsy (TLE) is the most common cause of focal onset seizures, affecting 40 % of adolescents and adults with epilepsy. TLE is also one of the most common drug-resistant forms of epilepsy [1]. The underlying pathological changes predominantly involve hippocampal sclerosis (HS), which has been associated with increased drug resistance [2]. Surgical resection of HS remains the treatment of choice, but not all patients with TLE are suitable candidates for resective neurosurgery [3]. For patients with bilaterally located epileptic foci, imprecise seizure area onset localization, concerns about memory decline, and personal preferences, alternative treatment modalities should be considered. These patients remain intractable due to persistent drug-resistant epilepsy (DRE) and are potential candidates for non-resective, adjustable, and reversible neuromodulatory techniques, such as direct hippocampal deep brain stimulation (DBS) or responsive neurostimulation (RNS) [4].

The hippocampus is a highly epileptogenic structure in patients with HS and non-lesional TLE. In cases where resective surgery is not an option, direct hippocampal DBS remains the available treatment modality for both groups of patients (those with lesions due to HS and those without) [4]. Another neuromodulation technique is RNS, which has recently emerged as a safe and effective treatment for some patients with medically refractory focal epilepsy who are not candidates for surgical resection. RNS was approved in the United States in 2013 and, as of now, approximately 1800 patients worldwide have been treated with this approach [5]. This technique involves an implanted neurostimulator and intracranial leads that detect incipient seizures and respond with electrical counterstimulation [5]. However, RNS is not available in many countries. Unlike thalamic or hippocampal DBS, which involve predetermined electrode locations, RNS involves intracranial strip and/or depth electrodes that can be flexibly configured based on knowledge

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of the seizure onset zone [5,6]. Clinical studies have shown that RNS is a well-tolerated treatment option for patients with mesial temporal lobe epilepsy (MTLE) who are not candidates for temporal lobe resection [5–8]. Seizure reductions were not dependent on any clinical characteristics, including mesial temporal sclerosis (MTS), bilateral onsets, prior resection, or prior vagus nerve stimulation (VNS). Moreover, seizure reductions were similar in patients with depth leads placed within or adjacent to the hippocampus [6].

Patients with HS, as opposed to those with non-lesional TLE, generally have worse outcome and may require higher stimulation settings [4,6]. These clinical observations may indicate that sclerotic hippocampal tissue could be resistant to stimulation. HS typically involves the hippocampus proper and dentate gyrus (DG) while sparing the subiculum. The subiculum is a critical brain region in TLE. Its position as the output gate of the hippocampus allows it to modulate epileptic discharges as they exit the hippocampus [9,10]. Furthermore, evidence suggests that the subiculum mediates the generalization rather than the genesis of mesial temporal lobe seizures [11]. Limited clinical experience suggests that DBS of the subiculum is associated with good control of focal to bilateral tonic-clonic seizures (FBTCS) in patients with HS [10].

The aim of this case report was to present a 50-year-old patient with left HS and drug-resistant FBTCS who underwent left-sided subiculum DBS.

Case

The female right-handed patient, aged 50 years, has been diagnosed with DRE according to the ILAE criteria, with an unknown etiology. According to her medical history, the patient has been experiencing focal onset seizures with impaired consciousness (FIAS) progressing to bilateral tonic-clonic seizures (BTCS) since the age of 10. Ever since, seizures occurred every 10–15 days in a series of 2–3 seizures per day, clustered over 2–4 days. A typical seizure episode in the patient involved no preceding aura, sudden behavioral changes such as cursing or slowed movements, often followed by lack of awareness of the patient's surroundings and staring, with occasional lip smacking. After the seizure, the patient remained confused for a period of 2–3 min and experienced difficulty speaking. Following the seizure, the patient was prone to injuries due to falls and burns from hot beverages. Most FIAS episodes quickly progressed to BTCS. At that time, the patient underwent a computed tomography (CT) scan, which revealed no abnormalities. Despite numerous antiseizure medications (ASMs), the patient's seizures became frequent and generalized. The patient did not report any chronic diseases and denied taking any other medications regularly. No signs of focal damage to the central nervous system were identified following a thorough neurological examination. Numerous scars resulting from past injuries were noted, including a healed wound in the occipital area of the head and burns on the right forearm and the hands of both upper limbs.

Despite three repeated video-EEG recordings during the investigation, a habitual clinical seizure could not be captured. The EEG examination revealed normal background activity characterized by posteriorly dominant symmetrical and reactive alpha rhythm at 9–10 Hz with amplitudes up to 60 uV, along with more evident beta rhythm anteriorly. Focal changes were noted, including irregular theta waves and less frequent sharp waves observed in the left temporal region (with phase reversal on F7) (Fig. 1). Considering the clinical presentation suggesting the possibility of a structural alteration in the left temporal region (as indicated by focal EEG changes and focal seizures with temporal morphology), a head MRI with epilepsy protocol was performed with intravenous contrast administration. This examination revealed left hippocampal atrophy (Fig. 2A), hyperintensity of the left hippocampus (Fig. 2B), and hippocampal architectural malformation with MRI signs consistent with mesial temporal sclerosis (Fig. 2C, D, E). The diagnostic workup was expanded to include a lumbar puncture to rule out inflammatory and autoimmune causes of DRE. The cerebrospinal fluid analysis showed no abnormalities. Further tests, including the determination of oligoclonal bands, IgG index, MRZ-reaction (MRZR), and the presence of anti-herpes type 1 (anti-HSV-1) antibodies and neural autoantibodies, yielded negative results. Neuropsychological assessment did not reveal any cognitive dysfunction, and the patient's clinical profile in the MMPI test fell within the range of average results. The patient was evaluated by a neurosurgeon who recommended

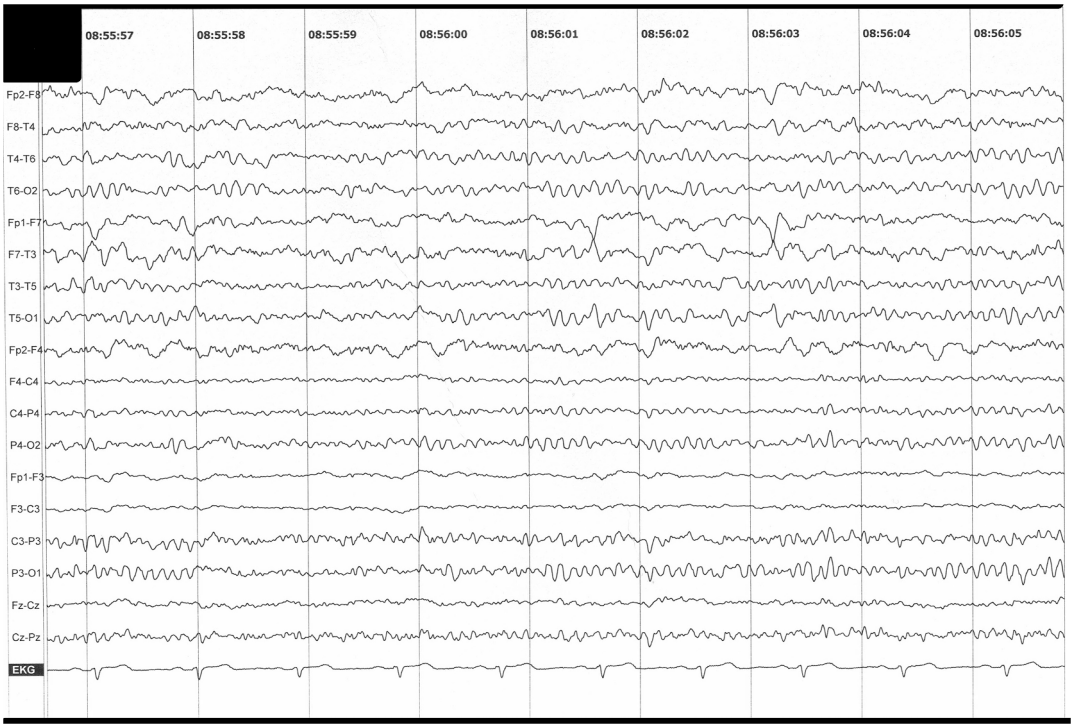

Fig. 1. The focal changes with irregular theta waves and less frequent sharp waves on the left temporal region (phase reversal on F7).

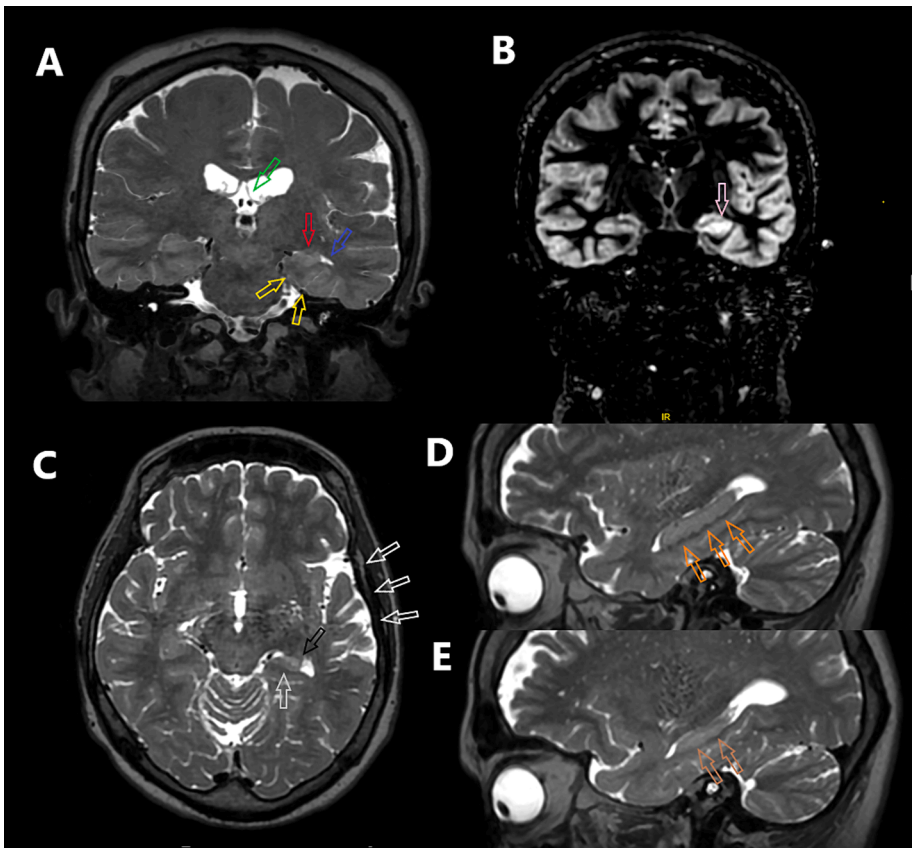

Fig. 2. (A) Coronal T2W (3D CUBE) image demonstrating left hippocampal atrophy (red arrow), temporal horn of lateral ventricle enlargement (blue arrow), elongated collateral sulcus, collateral white matter and entorhinal cortex atrophy (yellow arrow) and atrophy of the left crus of fornix (green arrow). The presented pathological features are pronounced compared to the corresponding structures on the contralateral side. (B) Coronal T2W DIR image reveals hyperintensity of the left hippocampus (pink arrow), indicative of potential sclerosis or pathological changes in this region. (C) Axial T2W (3D CUBE) image highlighting hippocampal architectural malformation on the left with its slight backward shift (black arrow), atrophic white matter in the parahippocampal gyrus (grey arrow), and atrophy of the temporal lobe (white arrow). (D) Parasagittal T2W image showing hippocampal dentation (orange arrows) on the right unaffected side. (E) Parasagittal T2W image showing loss of hippocampal dentation (orange arrows) on the left affected side indicating hippocampal sclerosis.

resective neurosurgery (anterior temporal lobectomy with amygdalo-hippocampectomy). However, the patient declined the proposed procedure. At the age of 48, the frequency of FBTCS increased despite multiple changes in AEDs. Over the last two years, the patient experienced 12 to 17 FBTCSs per month (with a mean of 15 FBTCSs per month). These seizures occurred in clusters, and postictal confusion persisted for up to 1 to 2 days, accompanied by severe postictal headaches and drowsiness. Additionally, the patient sustained several craniofacial injuries as a result of FBTCSs.

Based on the promising results of DBS in patients with MTLE due to HS, this treatment modality was proposed to the patient. After thorough discussion of the treatment options, the patient ultimately agreed to this form of treatment. The patient was extensively informed about the effectiveness and safety of DBS for HS and provided written informed consent prior to the surgery. Before the surgical procedure, the patient was taking ASMs including levetiracetam (1500 mg), lacosamide (400 mg), and lamotrigine (200 mg). The patient's neurological assessment revealed no notable abnormalities. She diligently maintained a detailed seizure diary. Baseline seizure frequency was determined based on the average seizure count over the 3 months preceding implantation. For preoperative planning, the patient underwent a high-resolution 3 Tesla MRI scan, which included sequences such as Fluid Attenuated Inversion Recovery (FLAIR), non-contrast T2-weighted imaging, and contrast-enhanced T1-weighted MP-RAGE sequences to aid in stereotactic planning.

The surgery was conducted under general anesthesia, without invasive monitoring. A Leksell G stereotactic head frame (Leksell, Stockholm, Sweden) was securely affixed to the patient's skull, and stereotactic contrast-enhanced CT images with a slice thickness of 1.25 mm were obtained. These images were then merged with preoperative MRI images using stereotactic surgical planning software (Framelink S8, StealthStation, Medtronic, Minneapolis, MN, USA). The target for DBS electrode placement was determined to be the subiculum, located just below the sclerotic hippocampus, based solely on neuroimaging. Following target calculation, the patient underwent surgery in the semisitting position, and a posterior approach was utilized. The quadripolar electrode (Medtronic 3387, Minneapolis, MN, USA) was then implanted into the left subiculum. Immediately after DBS lead implantation, the patient underwent non-contrast-enhanced intraprocedural stereotactic CT to verify the precise position of the DBS electrode and to rule out any intracerebral hemorrhage. The intraprocedural CT images were merged with preoperative planning, confirming the accurate placement of the implanted DBS lead. Finally, during the same operative session and while the patient remained under general anesthesia, the implantable pulse generator (Activa 37603, Medtronic, Minneapolis, MN, USA) was implanted in the left subclavicular region.

The initial stimulation parameters were set at 1.6 V, 180 microseconds, and 130 Hz, with stimulation initiated on the first postoperative day. Stimulation was delivered in an intermittent mode, with 1 min of stimulation followed by 5 min off stimulation. All contacts of the implanted 3387 DBS lead (labeled as 0 most distal and 3 most proximal) were configured as cathodes, with the implantable pulse generator (IPG) serving as the anode. A soft start function was employed to gradually ramp up each stimulation set over 8 s. The patient was discharged on the

fifth postoperative day. Notably, the unilateral subicular stimulation resulted in a reduction in seizure frequency, evident at the 2-month follow-up. Scheduled follow-up visits occurred monthly during the initial 3 months post-implantation, during which the stimulation voltage was gradually increased to 2.4 V. Postoperative MRI was conducted to confirm the location of the implanted DBS lead. Utilizing the SureTune™ 3 software, preoperative MRI, intraprocedural CT, and postoperative MRI images were fused with intraprocedural CT scans to visualize patient-specific anatomy and the DBS lead location, including visible contacts in relation to the hippocampal formation (Fig. 3A, B, C). Additionally, EEG recordings were performed according to the international 10–20 system, with six additional electrodes in the inferior temporal chain. Those electrodes, derived from 10 to 10 system, included: F9/F10, T9/T10 and P9/P10. EEG was recorded during both the intermittent left hippocampal deep brain stimulation (DBS phase-on) and after 12 h of stimulation being switched off (DBS phase-off). Visual analysis revealed sharp wave discharges in the left temporal region, often exhibiting a pseudoperiodic pattern, along with breech rhythm in this region (Fig. 4A). Sharp waves were slightly, but insignificantly, more frequent in EEG recordings during the off-DBS phase compared to the on-DBS phase (Fig. 4B).

After 20 months of unilateral subicular DBS, there was a 67 % reduction in FBTCS (5 versus 15 baseline FBTCS). The patient reported milder and shorter-lasting postictal confusion and headaches. Notably, over the entire 20-month follow-up period, the patient experienced only 3 craniofacial injuries compared to 1 or 2 injuries each month before surgery. There were no hardware-related complications observed in this patient, and both the patient and her family members reported satisfactory treatment outcomes.

Discussion

We present a case of a patient with longstanding DRE attributed to left HS who underwent successful unilateral subicular DBS. The patient declined resective neurosurgical therapy due to concerns regarding postoperative verbal memory decline and personal preference. Despite nearly 40 years of epilepsy duration and multiple ASMs, her FBTCSs increased over the last 2 years, becoming intractable and resulting in severe craniofacial injuries. Ultimately, due to the fear of the consequences of these injuries, the patient opted for non-resective, adjustable therapy and consented to undergo a DBS procedure.

Taking into account the long-standing DRE and the findings from EEG and MRI scans, which indicate severe HS, we opted to target the subiculum for DBS. Several factors guided this decision. Firstly, the sclerotic process primarily affects the hippocampus proper and dentate gyrus while sparing the subiculum [10]. Our decision was also influenced by the clinical observations reported by Velasco et al., who noted a 50–70 % reduction in total seizure frequency (including FIAS and FBTCS) at 18 months in four patients with HS compared to over 95 % seizure reduction in five patients with non-lesional TLE [4]. This discrepancy suggests that sclerotic hippocampal tissue (the hippocampus proper and DG) may be less affected by DBS than in non-lesional MTLE patients. Additionally, there is a possibility of worse outcomes in patients with HS due to the higher impedance of sclerotic tissue, which may require higher stimulation settings [9]. Boex et al. reported based on 8 patients (2 with HS and 6 non-lesional TLE epilepsy) that quadripolar stimulation was necessary to achieve a 65–75 % reduction in seizures in HS patients, whereas bipolar stimulation was sufficient in non-lesional TLE epilepsy patients [9]. These findings suggest that a larger zone of stimulation may be necessary in HS patients compared to non-lesional MTLE patients, where a limited zone of stimulation or even a microlesional effect could be sufficient [9]. Considering these observations, we opted for monopolar stimulation mode in our patient due to pronounced mesial temporal lobe sclerosis visible in Fig. 2. All active contacts of the implanted DBS lead (Model 3387, Medtronic Minneapolis, USA) were set as cathodes to influence a larger volume of brain tissue. This stimulation mode resulted in a significant 67 % reduction in seizure frequency at 20 months postoperatively, consistent with the findings of other authors [9].

The ideal target within the mesial temporal structures for DRE in non-lesional patients or patients with HS is not known [4,9,10]. This uncertainty stems from the limited clinical experience with hippocampal DBS in the treatment of TLE. Nonetheless, there is ample evidence suggesting that TLE originates from and spreads through the hippocampal formation, which includes the hippocampus proper, DG, and the subiculum. Clinical evidence indicates that ictal and interictal epileptiform EEG activity primarily arises in the hippocampus [12], and temporal lobectomies involving the hippocampus are more effective in reducing seizures compared to those sparing the hippocampus [13]. These observations paved the way for hippocampal DBS for TLE in the early 21st century [4–10,14]. Recent studies have also highlighted the active role of the subiculum and parahippocampal gyrus in the propagation of temporal lobe seizures [10,15]. Bondallaz et al. conducted a study involving eight patients with refractory MTLE who underwent invasive recordings to place a permanent DBS lead near the ictal focus [7]. In six patients who experienced over 50 % reduction in seizure frequency, all had active contacts located less than 3 mm from the subiculum [7]. This finding suggests that the efficacy of hippocampal DBS may be linked to the involvement of the subiculum, which serves as the main output pathway of the hippocampal formation [7]. Supporting this notion, Vazquez-Baron et al. initiated subicular DBS in patients with MTLE secondary to HS and found it to be highly effective, with a mean reduction of 67.93 % in FBTCS reported in six patients at a 24-month follow-up [10]. Aside from its intrinsic functions, the subiculum is considered as an input and output gateway between hippocampus and cortical and subcortical structures. Velasco et al. compared the role of the subiculum to that of the centromedian nucleus (CMN) for the treatment of FBTCS [6]. The above mentioned clinical evidence suggests

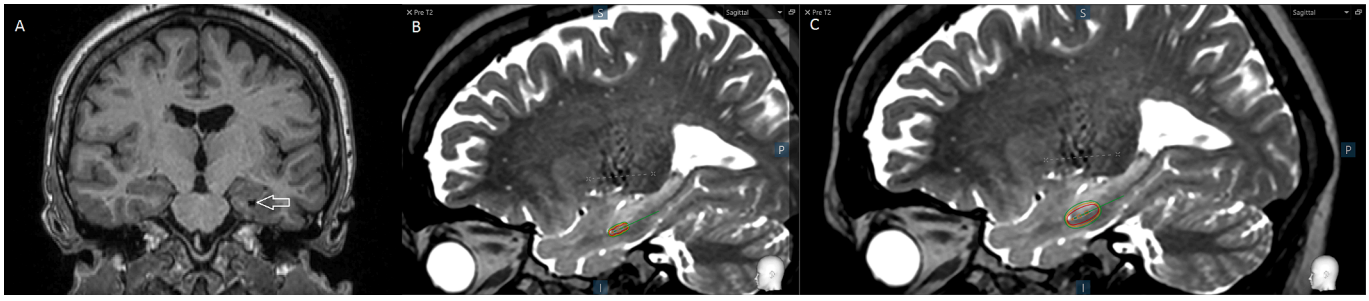

Fig. 3. (A) Postoperative T1 weighted coronal image showing the implanted DBS lead in the left subiculum (white arrow). (B) Preoperative and postoperative MRI, CT images were fused with using the SureTune™ 3 software with visualization of the implanted DBS lead on sagittal T2 weighted sequence. (C) Preoperative and postoperative MRI, CT images were fused with using the SureTune™ 3 software which enabled the creation of patient-specific anatomy and DBS lead location with volume of tissue activated (VTA).

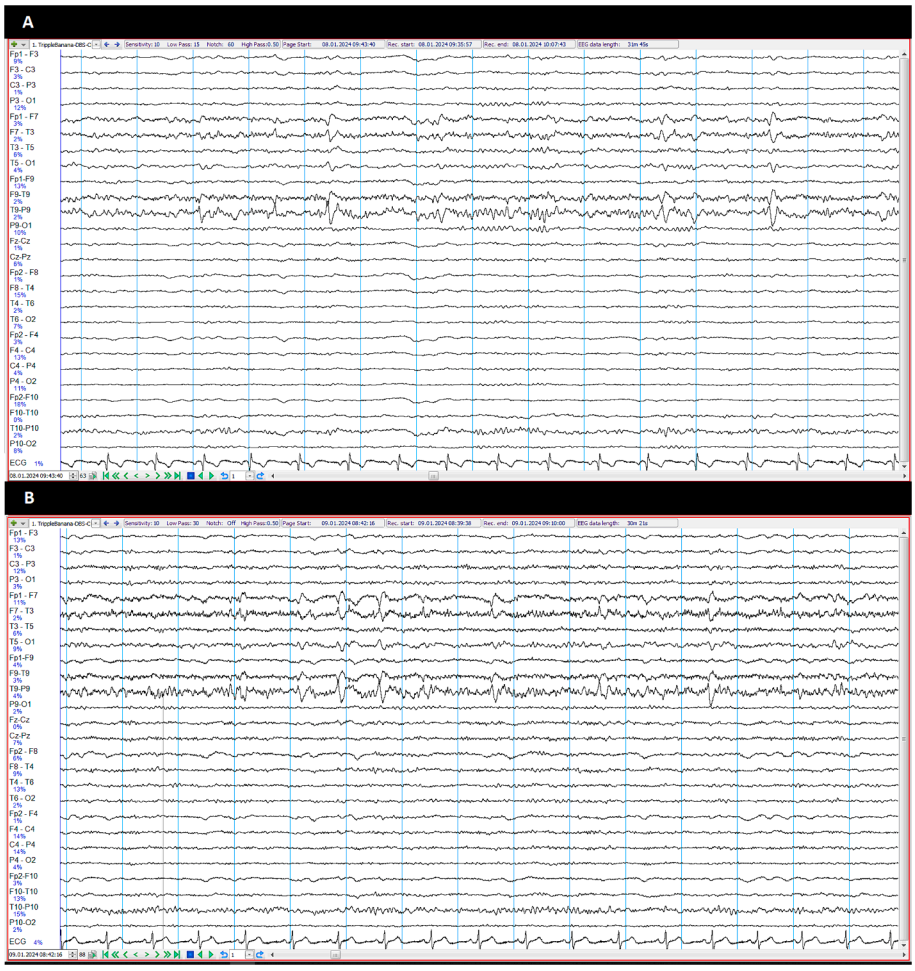

Fig. 4. EEG was recorded twice: during the intermittent left hippocampal deep brain stimulation (phase on-DBS) and after 12-hour of switched off stimulation (phase off-DBS). (A) Visual analysis revealed sharp waves in left temporal region, frequently with pseudoperiodic pattern. Breach rhythm is seen in this region. (B). Sharp waves were slightly, but insignificantly more frequent in EEG during off-DBS in comparison to on-DBS phase.

that the subiculum may be also involved in seizure propagation [9,10,13,14]. Moreover, not only subiculum but also the parahippocampal cortex may be targeted in patients with severe HS and MTLE [15]. In the largest study of hippocampal DBS for MTLE, Cukiert et al. found no correlation between the locations of active contacts and seizure reduction [16]. Contacts located in the hippocampus proper (42 of all 160 contacts), below the hippocampus in the subiculum (19 contacts), or in the parahippocampus (3 contacts) were similarly effective. Among 25 patients, 15 patients were stimulated bilaterally and 10 unilaterally. In this study 19 patients had HS (11 unilateral HS, and 8 bilateral HS) and only 6 non-lesional MTLE [16]. The relatively large stimulating parameters used for permanent DBS may have obscured the correlation between the exact location of active contacts and clinical outcomes [16]. Interestingly, Geller et al. found that seizure reductions were comparable in patients with depth leads placed within or adjacent to the hippocampus [6]. The median percent seizure reduction in their study was 70 %, with 29 % of subjects experiencing at least one seizure-free period of six months or longer, and 15 % experiencing at least one seizure-free period of one year or longer [6]. Cukiert et al. also reported promising results regarding hippocampal DBS, with a 91 % reduction in FIAS and a 66 % reduction in focal aware seizures (FAS) [16]. FIAS were significantly more reduced than FAS [16].

Theoretically, patients with non-lesional MTLE may benefit from hippocampal stimulation with leads implanted within the hippocampus proper, and those with lesional TLE may benefit from subicular or parahippocampal stimulation [10,15]. The subicular stimulation provided a significant reduction in FBTCS for our patient. However, further studies are needed to confirm the results obtained in this single case report and in other patients reported in the literature [10,15].

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Ethical statement

The research conducted for this manuscript adhered to all relevant ethical guidelines and regulations.

CRediT authorship contribution statement

Michał Sobstyl: Writing – original draft, Supervision, Methodology, Conceptualization. **Magdalena Kowalska:** Writing – original draft. **Magdalena Konopko:** Writing – original draft. **Aleksandra Wierzbicka:** Writing – review & editing, Visualization. **Karol Karamon:** Visualization. **Ewa Nagańska:** Writing – review & editing, Writing – original draft, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

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