Epilepsy & Behavior Reports 25 (2024) 100637

Contents lists available at ScienceDirect

Epilepsy & Behavior Reports

journal homepage: www.elsevier.com/locate/ebcr

Multifocal drug-resistant epilepsy in a patient with a newly discovered mutation in tuberous sclerosis complex 1 gene treated by deep brain stimulation in the anterior thalamic nucleus

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ARTICLE INFO

Keywords:
Multifocal drug-resistant epilepsy
Anterior nucleus of the thalamus
Deep brain stimulation
Tuberous sclerosis complex

ABSTRACT

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder caused by mutations in the tumor suppressor genes TSC1 or TSC2. TSC is characterized by the formation of multiple tumors in various organs. The most common neurological manifestation of the disorder is epilepsy present in 79–90% of cases. At least one-third of TSC patients develop drug-resistant epilepsy (DRE) which remains a great challenge for clinicians. Neuromodulation is an option in cases of multifocal epilepsy, epilepsy originating in eloquent areas, or the inability to identify the ictal onset zone. Deep brain stimulation of the anterior thalamic nucleus (ANT-DBS) may be used in the treatment of multifocal DRE. Here, we present a case of a patient with multifocal DRE caused by TSC, who was treated with ANT-DBS. A follow-up period of eight months showed that the patient's multifocal DRE was successfully treated by ANT-DBS.

Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder characterized by the formation of multiple tumors in various organs, mainly in the central nervous system, causing epilepsy in 79–90 % of cases [1]. Mutations in the tumor suppressor genes TSC1 or TSC2 cause TSC. Epilepsy is likely to be the most common and challenging clinical manifestation of TSC. At least one-third of TSC patients develop drug-resistant epilepsy (DRE) [1]. Neuromodulation is an option in cases of multifocal epilepsy, epilepsy originating in eloquent areas, or the inability to identify the ictal onset zone. In the treatment of multifocal DRE, deep brain stimulation of the anterior thalamic nucleus (ANT-DBS) has demonstrated satisfactory results [2]. Here, we present a case of multifocal DRE caused by TSC. Specifically, a mutation in the TSC 1 gene resulted in a substitution in nucleotide c.914-2A-G (NM_000368.5 (TSC1):c.914-2A > G). A follow-up period of eight months showed that the patient's multifocal DRE was successfully treated by ANT-DBS.

Case

A 48-year-old woman diagnosed with TSC 1 was referred for an ANT DBS procedure due to DRE. Since the age of two, she has been suffering from focal impaired awareness seizures (FIAS) reported as loss of awareness lasting a few minutes with postictal confusion. Thereafter she has developed two other types of focal seizures or focal to bilateral tonic-clonic (FBTCS): visual illusion "mimicking watching a 3D movie" followed by manual and oral automatisms and right-sided tonic-to-bilateral tonic-clonic seizures. All were recorded on home videos, which were reviewed by a trained epileptologist who felt that these represented epileptic seizures. Even though she has used six different antiseizure medications (ASMs) in the past, her frequency of FBTCS has increased significantly over the last three years. On average, she experienced one to four FBTCS per month, with a long post-ictal confusion period of up to 12 h and 4 to 8 FIAS. Based on magnetic resonance imaging (MRI) sequences [Fig. 1 A, B, C, D], the patient was diagnosed with TSC due to the presence of typical subependymal nodules (SENs). An MRI revealed a subcortical/cortical tuber in the right postcentral gyrus as well as migration lines in the white matter on both sides. A genetic test revealed a potentially pathogenic substitution for nucleotide c.914-2A-G in the TSC 1 gene (NM_000368.5(TSC1):c.914-2A > G). This mutation has been described since 2016 [3]. It is listed as a pathogenic variant because "the c.914–2 A > G splice site variant in the TSC1 gene destroys the canonical splice acceptor site in intron 9. It is predicted to cause abnormal gene splicing, either leading to an abnormal message that is

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https://doi.org/10.1016/j.ebr.2023.100637
Received 24 June 2023; Received in revised form 30 November 2023; Accepted 30 November 2023
Available online 1 December 2023

subject to nonsense-mediated mRNA decay, or an abnormal protein product if the message is used for protein translation.

ASMs were administered at daily doses of topiramate (TPX) 500 mg, lacosamide (LCM) 400 mg, vigabatrin (VGB) 3000 mg, and lamotrigine (LTG) 800 mg. The plasma concentrations of lamotrigine and topiramate were therapeutic. Despite taking four different ASMs, her seizure frequency increased to 10 per month in the six months before the DBS implantation. In EEG recordings, sharp theta waves or slow wave discharges were observed either in the left or less clearly distinguished in the right temporal areas or nearly simultaneous on both sides. The typical EEG tracing recorded or provided by the patient is presented in Fig. 2. During the 58 h of video-EEG monitoring, no seizure was detected. ACE II (Addenbrooke's Cognitive Examination III) and CVLT (California Verbal Learning Test) demonstrated good cognitive performance. Although the majority of seizures seemed to be of temporal origin, the patient reported several other types of focal seizures (visual illusion, right-sided tonic seizures), which suggested multifocal DRE due to TSC, and she wished to have more effective treatment. To treat her DRE, she was recommended ANT DBS. The patient signed an informed consent form. The presented patient is a participant in the study approved by the Ethics Committee of the Institute of Psychiatry and Neurology, Warsaw.

Preoperative 3 Tesla MRI was done (scanner: SIGNA™ 3.0 T MRI Scanners GE Healthcare, United States) using the following sequences three-dimensional axial BRAVO (white-matter-nulled – WMn), contrast-enhanced 3D axial T1 rapid gradient-echo (MP-RAGE) sequences, 3D T2 Cube sequences, and axial T2 short tau inversion recovery (STIR). The ANT DBS procedure for bilateral electrode implantation began with the placement of the stereotactic frame (Leksell G, Stockholm, Sweden) under general anesthesia. After the attachment of the CT localizer, the preoperative CT images were obtained (scanner: Light Speed VCT 64 Slice CT Scanner GE Healthcare, United States). Surgical planning was achieved using the Stealth Station S8 frame-based DBS software (Medtronic, Minneapolis, Minn., United States) by fusing the preoperative MRI with stereotactic CT images. The targeting was done directly and adjusted to the individual patient's anatomy. The endpoint of the mammillothalamic tract (MTT) was chosen as a stereotactic target. The trajectory to the ANT was transventricular. The position of the implanted DBS leads (Medtronic 3389, Minneapolis, Minn., United States) was checked by intraprocedural CT with the Leksell G frame on.

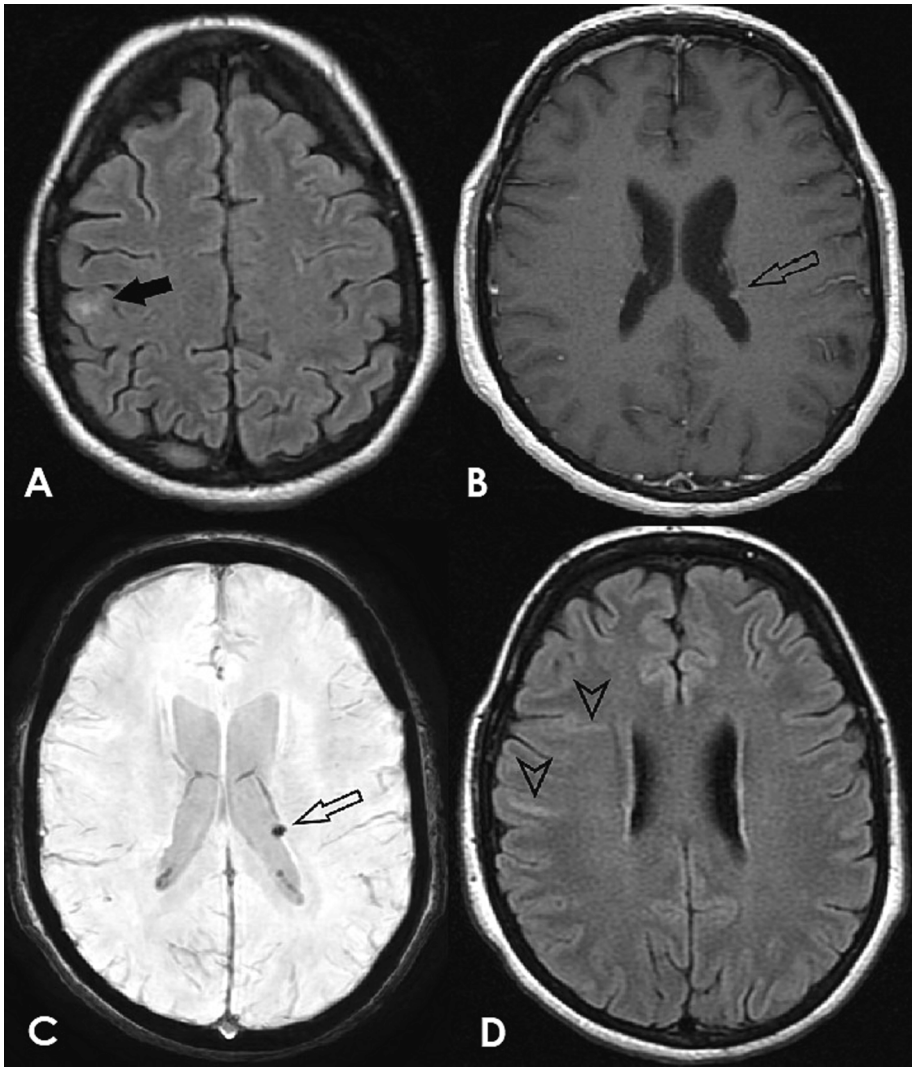

Fig. 1. Selected radiological features of the characteristic cerebral manifestations of tuberous sclerosis in the presented patient visible on MRI. The thick black arrow indicates a hyperintense focal lesion with poorly defined margins in the FLAIR sequence (A), corresponding to cortical/subcortical tuber. The thin black arrows portray a small round lesion in T1-weighted, located subependymally in the third ventricle with visible vivid enhancement following contrast administration (B) and the presence of calcifications in SWI (C), consistent with subependymal hamartoma. In the FLAIR sequence, the linear hyperintense marks corresponding to radial bands (indicated by black arrowheads) are visible within the white matter (D). Abbreviations: MRI- magnetic resonance imaging; FLAIR- fluid-attenuated inversion recovery; SWI- Susceptibility weighted imaging.

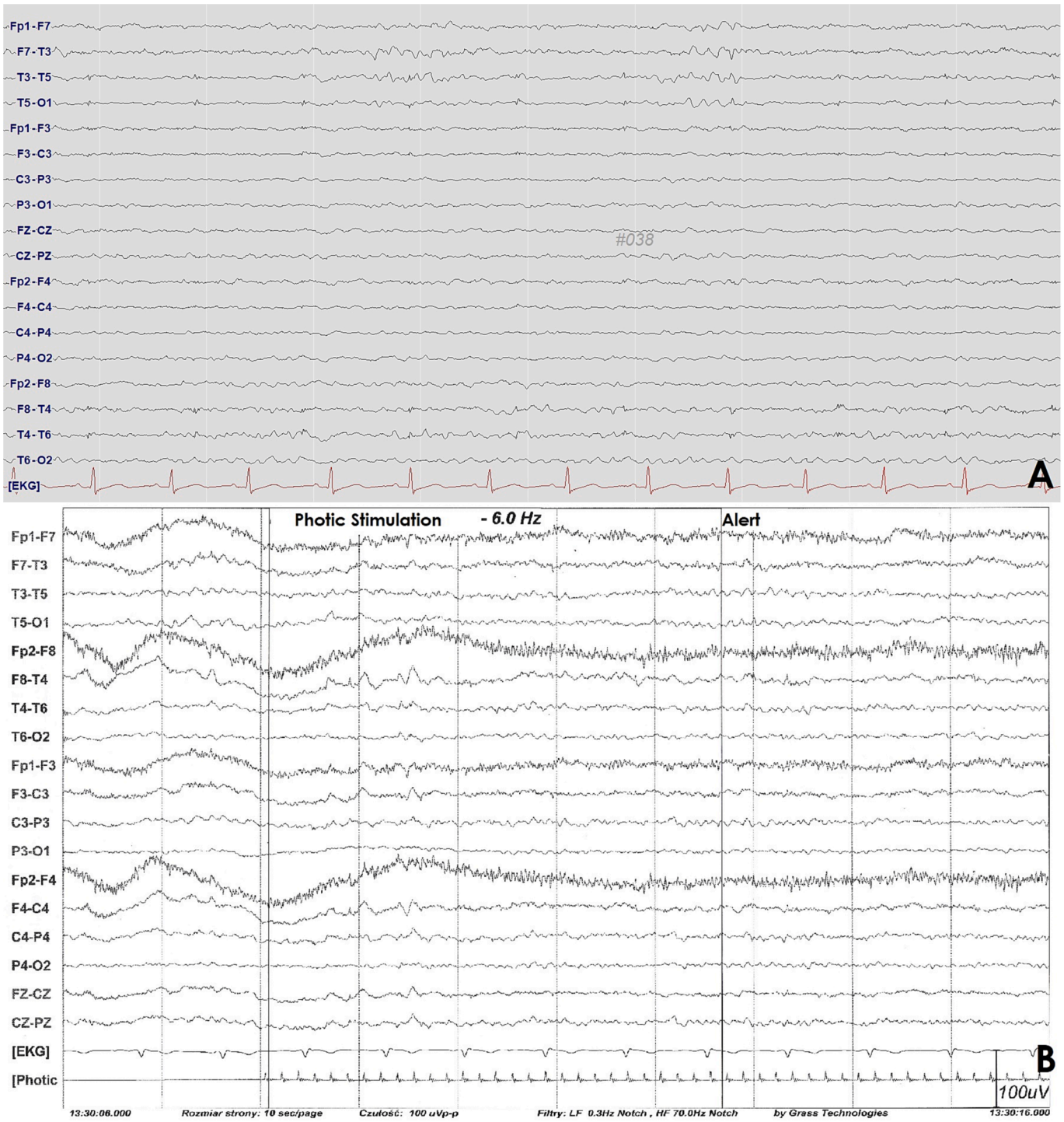

Fig. 2. EEG recording with theta and slow waves visible over the left temporal region (A) and sharp theta waves in the right temporal area (B) propagating to the right central region. Abbreviations: EEG- electroencephalogram.

After returning from the CT suite, the head frame was removed, and a dual channel implantable pulse generator – (Activa PC 37601 Medtronic, Minneapolis, Minn., United States) was implanted during the same procedure. The general anesthesia in this patient was complicated by the development of pneumothorax. The pleural drainage was done urgently by the general surgeon. She made a full recovery and further postoperative course was uneventful.

She recovered fully and the postoperative course was uneventful. The stimulation parameters were 3 V, 145 Hz, 90 ms, and intermittent stimulation mode ("on" 1 min, and "off" 5 min). The SureTune™ 3 DBS software visualized the implanted leads [Fig. 3]. The stimulation was monopolar by activating two middle contacts of the implanted 3389 DBS leads.

A diary was given to the patient and her husband to record her seizures. At the last follow-up, 8 months after surgery, the patient reported only two FIAS (possibly with right-sided tonic phase) and four FIAS lasting a few minutes. None of the reported seizures were connected with automatisms or clonic. The postictal time was shortened and lasted 30 min to 3 h without preoperative debilitating headaches. Vigabatrin (the cause of blurred and decreased vision in the patient) was

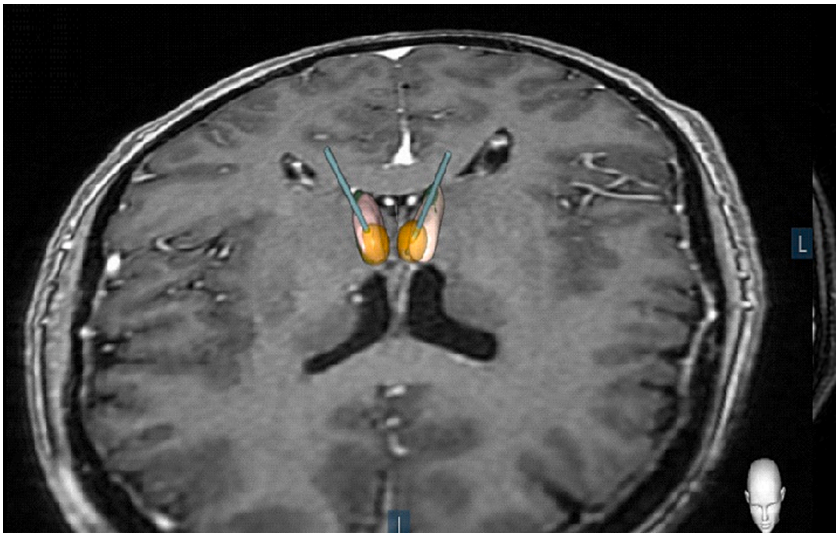

Fig. 3. The registration of intraprocedural CT scan and preoperative MRI T1-weighted images showing both electrodes were placed in ANT. The SureTune™ 3 software was used to visualize the implanted DBS leads and the VTA. Abbreviations: CT- computed tomography; MRI- magnetic resonance imaging; DBS- deep brain stimulation; VTA- volume of tissue activated.

withdrawn. Treatment results were satisfactory to the patient and her family.

Discussion

We report a patient diagnosed with a novel mutation in the TSC 1 gene and DRE who was treated with ANT-DBS. We are aware of only one case of DRE in a TSC patient treated efficiently with ANT-DBS by Zheng et al [4]. This patient's frequency of seizure was reduced by about 90 % [4]. Our patient, after 8 months of follow-up, experienced a 90 % reduction in seizure frequency and reported complete recovery from previous FBTCS and focal automatism seizure. The follow-up period in the Zheng et al. case report was 15 months [4]. In both cases, DBS hardware and stimulation parameters were similar. The VTA's (volume of tissue activated) in our patient showed that the anteromedial parts of the ANT were stimulated. The exact location of the best stimulation part of ANT is still debated [5]. The statement made by Zheng et al. that ANT DBS is a reasonable neuromodulation option for patients with TSC who suffer from multifocal DRE is supported by our experience. It should be emphasized that patients with TSC may suffer from many complications of this disease affecting not only the brain and lungs but also the heart, kidneys, skin, liver, spleen, pancreas, bones, and eyes [6]. As this group of patients tends to use many drugs, including ASMs that are not free from some potential side effects, neuromodulation which often enables the reduction of ASMs seems to be a preferable treatment option. In the future, patients with multifocal DRE caused by TSC may benefit from ANT DBS. This is only a preliminary assumption but ANT DBS may be most effective in ameliorating DRE due to multifocal epilepsy in TSC patients.

Conclusions

In our case, bilateral ANT-DBS proved to be a safe and effective way to treat multifocal DRE caused by TSC. It is only a case report with a relatively short follow-up period. More studies involving more individuals with TSC and multifocal DRE with longer follow-up periods are needed to confirm the promising results achieved in this study.

CRediT authorship contribution statement

Michał Sobstyl: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Paweł Jezierski:** Data curation, Investigation, Writing – original draft, Writing – review & editing. **Magdalena Konopko:** Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Angelika Stapińska-Syniec:** .

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.

Acknowledgments

none

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